



Our STN: BL 125734/0

LATE-CYCLE
MEETING MEMORANDUM
April 29, 2021

CellTrans, Inc.
Attention: Jose Oberholzer, MD, MHCM, FACS
2201 W. Campbell Park Drive, Ste 23
Chicago, IL 60612

Dear Dr. Oberholzer:

Attached is a copy of the memorandum summarizing your April 1, 2021, Late-Cycle 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 in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in 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

Late-Cycle Meeting Summary

Meeting Date and Time: April 1, 2021 at 3 pm (Eastern Time)
Meeting Call-In Information: Teleconference
(b) (4)
Application number: BLA STN 125734/0
Product name: Donislecel (Purified Allogeneic Islets of Langerhans for Transplant)
Proposed Indication: indicated to treat Brittle type I diabetes mellitus
Applicant: CellTrans Inc.
Meeting date & time: October 30, 2020 at 9 AM
Committee Chair: Sukhanya Jayachandra, PhD

FDA ATTENDEES


Pankaj Amin, PhD, CBER/OCBQ/DMPQ
Patricia Beaston, MD, PhD, CBER/OTAT/DCEPT
Kimberly Benton, PhD, CBER/OTAT
Michael Brony, CBER/OCBQ/DCM/APLB
Wilson Bryan, MD, CBER/OTAT
Dennis Cato, CBER/OCBQ/DIS/BMB
Christine Drabick, CBER/OCBQ/DIS/BMB
Melanie Eacho, PhD, CBER/OTAT/DCGT
John Eltermann, RPh, MS, CBER/OCBQ/DMPQ
Varsha Garnepudi, PhD, CBER/OCBQ/DBSQC
Andrea Gray, PhD, CBER/OTAT/DCGT
Christine Harman, PhD, OCBQ/DMPQ
Elizabeth Hart, MD, CBER/OTAT/DCEPT
Ilan Irony, MD, CBER/OTAT/DCEPT
Sukhanya Jayachandra, PhD, CBER/OTAT/DCGT
Safa Karandish, BS, MT, CBER/OTAT/DHT
Wei Liang, PhD, CBER/OTAT
Anthony Lorenzo, CBER/OCBQ/DMPQ
Narayan Nair, MD, CBER/OBE/DE
Tyree Newman, MDiv, CBER/OTAT/DRPM
Steven Oh, PhD, CBER/OTAT/DCGT
Tejashri Purohit-Sheth, MD, CBER/OTAT/DCEPT
Renee Rees, PhD, CBER/OBE/DB
Laura Ricles, PhD, CBER/OTAT/DCGT
Theodore Stevens, MS, RAC, CBER/OTAT
Lisa Stockbridge, PhD, CBER/OCBQ/DCM/APLB
Million Tegenge, PhD, CBER/OTAT/DCEPT
Edward Thompson, OTAT/DRPM/BII
Irina Tiper, PhD, CBER/OTAT/DCGT
Lori Tull, CBER/OTAT/DRPM
Prajakta Varadkar, PhD, CBER/OTAT/DCGT

Debra Vause, OCBQ/DMPQ
Yongjie Zhou, PhD, MD, CBER/OTAT/DCEPT

APPLICANT ATTENDEES

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

(b) (4)



BACKGROUND

BLA STN 125734/0 was submitted on May 19, 2020, for Donislecel (Purified Allogeneic Islets of Langerhans for Transplant).

Proposed indication: to treat Brittle type I diabetes mellitus

PDUFA goal date: August 18, 2021

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on March 19, 2021, and issued Advisory Committee Briefing Materials on April 14, 2021.

DISCUSSION

1. Discussion of Substantive Review Issues

Chemistry, Manufacturing, and Control

At this time, we have substantive review issues regarding the following:

- a. There are outstanding issues related to analytical in vitro potency assay for final product lot release, specifically pertaining to Glucose Stimulation Index (GSI) assay sample and sampling points. The Applicant proposes to sample just the “top” fraction of the pre-culture islets for the potency assay, even though the final product may also include (b) (4) fractions of the pre-culture islets. The Applicant is not sampling the final drug product post-culture and we are unable to assess the potency of the final drug product.
- b. There are outstanding issues with the Applicant’s proposed labeling regarding the delivery devices used to administer the final product. The Applicant proposed a general label for donislecel (product) infusion into the hepatic portal vein using sheaths/introducers or catheters with certain dimensional specifications. The use of sheaths/introducers alone to infuse a therapeutic agent is an off-label use of these devices; however, use of intravascular catheters that are intended for targeted delivery of drugs or therapeutic agents/fluids would be on-label use. A teleconference was held with the Applicant on March 5, 2021 to discuss the Applicant’s response to an FDA information request dated February 4, 2021. The Applicant noted during the teleconference that some sheaths/introducers were used in conjunction with catheters and additional information will be provided to the agency. This issue is still under review and needs to be resolved.
- c. Lack of identity testing on critical raw materials per 21 CFR 211.84 was communicated to the Applicant at midcycle meeting. A teleconference was held with the Applicant on March 5, 2021 to provide further clarifications and expectations for identity testing of critical raw materials used in the manufacturing process to meet regulatory requirements. The Applicant acknowledged FDA response.

Meeting Discussion for Chemistry, Manufacturing, and Control Issues:

The Applicant reiterated their reasoning for not assessing GSI from the (b) (4) (b) (4) preculture fractions. Due to the limited shelf-life of the final product, the Applicant also reiterated that a potency assay on the final product could not be performed prior to lot release. FDA explained that potency assay on the final product in the final container closure system would still be important to perform, even if the results would be available post-transplant. The Applicant agreed that performing potency testing (e.g., GSI) on final product could be included with results available post-transplant. In addition, the Applicant stated that they are

willing to develop and incorporate better potency assays during the postmarketing period.

There was no discussion of items b. and c. during the meeting.

Clinical

- d. We are unable to agree on the indication being sought “Donislecel is an allogeneic pancreatic islet cellular therapy indicated for the treatment of brittle Type 1 diabetes (labile diabetes) in adults whose symptoms are not well controlled despite intensive insulin therapy.” We are concerned with the proposed indication because “brittle” or “labile” diabetes is not a clearly defined clinical condition, and the term “symptoms” is non-specific. The appropriate patient population for whom donislecel may be indicated will be a topic of discussion for the Advisory Committee.
- e. Based on the data provided in your BLA, we are unable to agree that your primary composite endpoint, $HbA_{1c} \leq 6.5\%$ and absence of SHE 1-year after the last transplant, can be used to provide evidence of effectiveness. You did not provide baseline data for SHE events for 6 (60%) of subjects in UIH-001 and 8 (42%) of subjects in UIH-002. This issue was previously raised in our July 6, 2017 teleconference with you regarding the previous submission of your BLA, and still has not been adequately addressed in your Application. Through the interactive review process, we have attempted to get these data. In your October 19, 2020 response to our October 5, 2020 request for additional information regarding the missing SHE data, you provided “verbatim descriptions of individual SHE events”. However, these “verbatim descriptions” did not conform to your stated objectives. Based on the data provided, we believe that 25 (83%) of the subjects did not meet accepted criteria for SHE, severe cognitive impairment requiring third party assistance, during the year prior to transplant. We also note that 1 (3%) subject did not have baseline HbA_{1c} and 6 (20%) subjects had a HbA_{1c} <6.5% during the 3 months prior to first transplant. Therefore, we do not believe your composite endpoint is interpretable. However, we do believe that your data demonstrate that your product leads to insulin independence as 21/30 (70%) of subjects achieved insulin independence for at least 1 year. We will ask the AC to consider the duration of insulin independence and risks from your product, the procedure to administer them and immunosuppression during the entire follow-up period, in evaluating the benefit-risk profile of donislecel.

Meeting Discussion for Clinical Issues:

The Applicant reiterated that they began their study in 2004, and the technology to manage diabetes was different then. The Applicant stated that they relied on the endocrinologist assessment for eligibility and they did not collect data on neurocognitive symptoms for SHE. The Applicant agreed with the Agency that insulin independence was a benefit for patients with T1D. The Applicant

expressed willingness to modify the indication and to narrow the target population to identify a population that will have a favorable benefit-risk profile.

2. Additional Applicant Data - Inspection

Meeting Discussion:

CellTrans Inc. expressed concern with the upcoming inspection and provided options to the inspectors:

- a. Actual organ/tissue process is a 12-hour process and the availability of the donation is limited due to COVID-19 pandemic and availability of culture media.
- b. Use of research organ for the process inspection. The product would be safe, but not of quality for use in humans.
- c. Final alternative is a mock isolation.

FDA expressed that a suitable surrogate in lieu of a donor pancreata could be used. If mock isolation were used during inspections, the actual manufacturing steps and processing times for manipulations should be similar to manufacturing process proposed in the BLA submission. FDA noted they are aware of the limitations for this choice and are willing to work with CellTrans Inc, for the inspection. FDA provided a date range of late May to mid-June 2021 for the inspection.

3. Information Requests

There are currently no outstanding responses to any information requests by the agency for this application. The FDA may have additional information requests in the future.

Meeting Discussion:

There was no discussion of this item during the meeting.

4. Discussion of Upcoming Advisory Committee Meeting

An Advisory Committee meeting is planned for April 15, 2021.

The topics for discussion at the Advisory Committee Meeting include:

- Characterization and critical quality attributes of donislecel as they relate to product comparability in the context of consistent product quality and clinical effectiveness
- Primary composite efficacy endpoint
- Indication “Treatment of Brittle Type 1 Diabetes” for the application.

Meeting Discussion:

There was no discussion of this item during the meeting.

5. Risk Management Actions (e.g., REMS)

Your risk management plan is focused on mitigating risks of the administration of safe use of donislecel at “hospitals and clinics that administer donislecel.” However, your BLA provides clinical and manufacturing information only for the CellTrans manufacturing facility located at the UI Health in Chicago, IL. You have not provided data to support the use of your product at other sites. Please revise your risk management plans to be consistent with this as a “center-specific” product.

Meeting Discussion:

There was no discussion of this item during the meeting.

6. Postmarketing Requirements/Postmarketing Commitments

No PMRs/PMCs have been identified at this time.

Meeting Discussion:

There was no discussion of this item during the meeting.

7. Major Labeling Issues

- a. Potential labeling concerns for product administration related to item 1.b above.
- b. In your application, you have provided clinical and manufacturing information only for the CellTrans manufacturing facility located at the UI Health in Chicago, IL. Therefore, that is the only site that may be supported during this application cycle and references to other laboratories and other sites are not acceptable.

Meeting Discussion:

The applicant clarified that the BLA is only for UI Health in Chicago, IL manufacturing facility and clinical site.

8. Review Plans

Review is ongoing and issues may be added, expanded upon, or modified as we continue to review this application.

Meeting Discussion:

There was no discussion of this item during the meeting.

9. Applicant Questions

Meeting Discussion:

There was no discussion of this item during the meeting.

10. Wrap-up and Action Items

Meeting Discussion:

There was no actions items presented and informed the CellTrans Inc. to expect the final summary for this discussion within 30-days of this meeting.

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.

End