Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Tissues and Advanced Therapies
Cellular, Tissue and Gene Therapies Advisory Committee Meeting April 15, 2021
69th Meeting
Summary Minutes
OPEN Session

Committee Members
Lisa Butterfield, Ph.D. (Chair)
Kenneth Berns, M.D., Ph.D.
Christopher Breuer, M.D.
Bernard Fox, Ph.D.
Jeannette Yen Lee, Ph.D.
Sean Morrison, Ph.D.
Mark Walters, M.D.
Joseph Wu, M.D., Ph.D.
John Zaia, M.D.

Temporary Voting Members
Sandy Feng, M.D. Ph.D.
Lawrence Goldstein, S.B., Ph.D.
David Harlan, M.D.
Ellen Leschek, M.D.
Bashoo Naziruddin, M.D.
Emmanuel Opara, M.D.
Raymond Roos, M.D.

Industry Representative
Geoffrey Martin Nichol, M.B., Ch.B.***

Consumer Representative
Randy Hawkins, M.D. **

**Consumer Representative
*** Industry Representative

Speakers and Guest Speakers
Patricia Beaston, M.D., Ph.D. (FDA)
Wilson Bryan, M.D. (FDA)
Elizabeth Hart, M.D. (FDA)
Betul Hatipoglu, M.D. (Applicant)
Sukhanya Jayachandra, Ph.D. (FDA)
James McGarrigle, Ph.D. (Applicant)
Jose Oberholzer, M.D. (Applicant)
Klearchos Papas, M.D. (Guest)
James Shapiro, M.D. (Applicant)

FDA Participants
Rachael Anatol, Ph.D.
Melanie Eacho, Ph.D.
Ilan Irony, M.D.
Peter Marks, M.D., Ph.D.
Steven Oh, Ph.D.
Raj Puri, M.D., Ph.D.
Tejashri Purohit-Sheth, M.D.
Laura Ricles, Ph.D.
Irina Tiper, Ph.D.
Celia Witten, Ph.D., M.D.

Designated Federal Officers (DFO)
Jarrod Collier, M.S.
Christina Vert, M.S.

Committee Management Specialist(s)
Joanne Lipkind, M.S.

Director
Prabhakara Atreya, Ph.D.

These summary minutes for the April 15, 2021 meeting of the Cellular, Tissue and Gene Therapies Advisory Committee were approved on May 10, 2021.

I certify that I participated in the April 15, 2021 meeting of the Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC) meeting and that these minutes accurately reflect what transpired.

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_____/S/_____
Jarrod Collier, M.S.
Designated Federal Officer

_____/S/_____
Lisa H. Butterfield, Ph.D.
Chair

On April 15, 2021 at 10:00 a.m. Eastern Standard Time (EST), the 69th meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) took place in open session to discuss biologics license application (BLA) 125734 for donislecel (purified allogeneic deceased donor pancreas derived Islets of Langerhans). Given the topic of this meeting, it was determined to be a Particular Matter Involving Specific Parties (PMISP).

Dr. Lisa Butterfield, the Chair, called the meeting to order. The DFO, Mr. Jarrod Collier, made administrative remarks, conducted roll call and invited the committee members to introduce themselves, and read the Conflict of Interest (COI) statement into the public record and announced no conflict of interest waivers issued under 18 U.S. Code Section 208 in connection with this meeting. During the open session, CTGTAC members, consultants, FDA speakers, Applicant, staff, and the public speakers all participated via the Adobe Connect web conference.

Dr. Wilson Bryan, Director of the Office of Tissues and Advanced Therapies, provided FDA Opening Remarks. This was followed by the Guest Speaker, Dr. Klearchos Papas, giving a presentation on "Assessment of Islet Quality Pre-Transplant". Immediately following this presentation, there was a 15-minute Q & A session for the Guest Speaker.

After the Guest Speaker Q & A session, during the Chemistry, Manufacturing, and Control (CMC) section of the agenda, the Applicant, CellTrans, Inc., made joint presentations given by Dr. James McGarrigle and Dr. Jose Oberholzer on the topics of "Introduction and Manufacturing Process" and "Potency and Purity Assays and Relationships to Clinical Outcomes", respectively. Immediately following the Applicant presentation, Dr. Sukhanya Jayachandra provided an FDA presentation titled "AM Session Product Characterization". Following these presentations, there was a CMC Clarifying Questions and Answers session with the Presenters.

During the CMC Questions to the Committee for discussion, the following Discussion questions were presented to the committee:

Discussion Question 1:

a. What is the contribution of endocrine, exocrine, or other cell types expected to be in the final drug product to the clinical outcomes and product potency?

b. How might the relative proportions of endocrine, exocrine, or other cell types in the product play a role in clinical outcomes and product potency?
c. What are the specific types of non-β cells that the Applicant should characterize and/or, possibly, control for in the product?

Discussion Question 2:

a. Are the product quality attributes of purity and potency sufficient to evaluate lot-to-lot consistency in manufacturing, product quality, and product strength?
b. If not, what additional product characteristics, not previously identified as CQAs for donislecel, would provide more meaningful measures to assess lot-to-lot product consistency?

Summary of Discussion:

CMC Question #1: The Committee acknowledged that there was great variability in the final product and raised concerns regarding the presence of ductal and non-beta cells in the final product. The ductal cells present in the final drug product could differentiate into beta cells and could damage other cells via inflammatory actions. Retrospective evaluation of ductal cells and non-beta cells in the final product could be informative to determine if the ratio of endocrine versus exocrine cells affects the clinical outcomes. The Committee suggested rapid testing methods, such as flow cytometry and measurement of oxygen consumption rate, to characterize the final product and potentially be implemented post-approval.

CMC Question #2: The Committee discussed that it is difficult to have consistent product lots because each lot is derived from a different donor pancreas. In addition, the committee noted that it would be good to have better quality control of the product to avoid administration of multiple doses. The committee suggested adding rapid quality control assays to aid in controlling lot-to-lot variability. Committee members also discussed the issue of human leukocyte antigen (HLA) desensitization and suggested retrospective HLA analysis.

After FDA CMC committee discussion concluded, the Committee was released to a 45-minute lunch break.

Once the Committee returned from lunch, a 60-minute Open Public Hearing (OPH) session was held from 1:45 p.m. to 2:45 p.m. in which 4 pre-registered public speakers made presentations and oral comments. The names of OPH speakers and their oral

remarks may be obtained from the transcript posted on the website.

Following the OPH session the meeting transitioned to the Clinical session in which Dr. Elizabeth Hart, Branch Chief for the Division of Clinical Evaluation and Pharmacology/Toxicology, provided a presentation titled "FDA Clinical Introductory Remarks". This presentation was immediately followed by the second set of Applicant presentations on clinical aspects as listed below:

Dr. Jose Oberholzer - Introduction, Agenda, Executive Summary
Dr. Betul Hatipoglu - Introduction to Diabetes and Unmet Clinical Need
Dr. James Shapiro - Introduction to Islet Cell Transplantation
Dr. Jose Oberholzer - Efficacy, Safety, and Risk-Benefit Assessment

After a 10-minute break, Dr. Patricia Beaston from FDA gave a presentation on "Clinical Considerations". This presentation was followed by a "Clarifying Questions and Answers" session by the Presenters and Committee Members.

Immediately following Clarifying Questions and Answers session, the Committee moved to "Questions to the Committee" and "Committee Discussions" session, during which the following Discussion Questions were presented to the Committee:

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 1 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:

a. 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 2 endocrinologists on the panel, Drs. David Harlan and Ellen Leschek 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 patients 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 that Donislecel would be appropriate for patients who are not surgical candidates, but would otherwise be candidates for whole pancreas transplant.

Following the Committee Discussion, the Committee was asked to take a vote on the following voting question:

- Does donislecel delivered by intraportal administration have an overall favorable benefit-risk profile for some patients 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 in the biologics license application (BLA) 125734.

Following the vote, the Chair asked that all voting members provide an explanation for their individual voting decisions, which they provided.

After the voting was completed Dr. Peter Marks, Director of CBER, thanked the committee and provided Closing Remarks.

The meeting was then adjourned on April 15, 2021 at 6:03 PM EST.

Additional information and details may be obtained from the transcript and the recording of the webcast of the meeting that may be viewed at: https://youtu.be/qufQ5NO2aYE