PUBLICCITIZEN

1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

April 30, 2021

Janet Woodcock, M.D.
Acting Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Peter Marks, M.D., Ph.D.
Director, Center for Biologics Evaluation and Research
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Wilson Bryan, M.D.
Director, Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Biologics license application for donislecel transplants (BLA 125734) as treatment for "brittle" type 1 diabetes

Dear Drs. Woodcock, Marks, and Bryan:

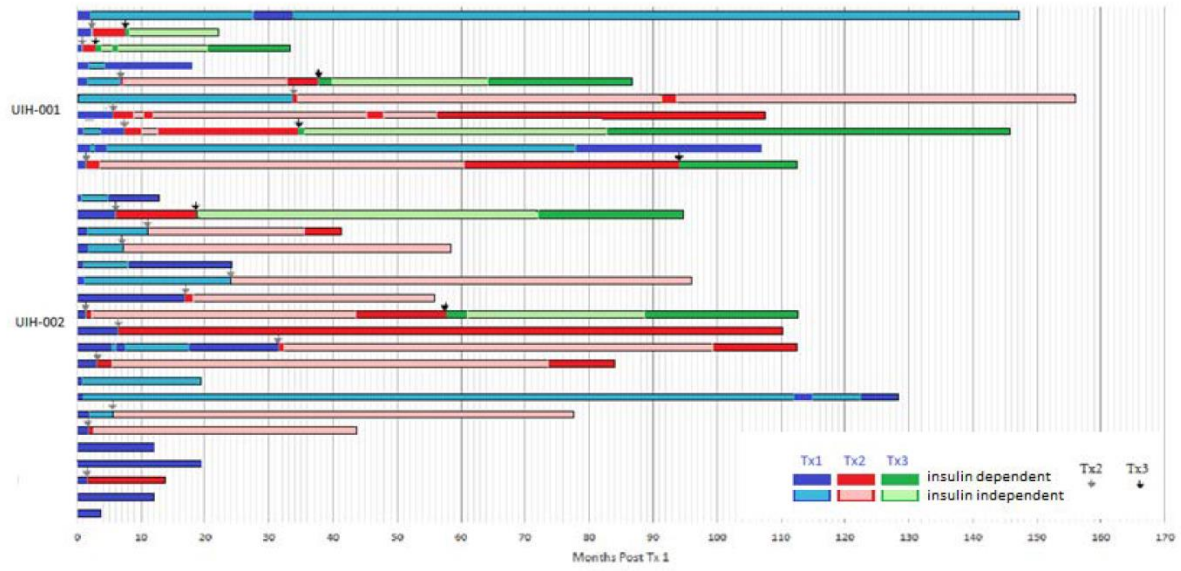
Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, strongly opposes Food and Drug Administration (FDA) approval of biologics license application (BLA) 125734 for donislecel (purified allogeneic deceased donor pancreas derived Islets of Langerhans) for the treatment of "brittle" type 1 diabetes mellitus. This BLA was the subject of a Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) meeting on April 15, 2021.

Public Citizen strongly opposes the approval of donislecel because clinical trials of the product failed to provide substantial evidence that it has a favorable benefit-risk profile and because the quality control of the pancreatic cellular extracts that comprise this biological product remains uncertain.

According to the FDA's briefing document for the April 15, 2021, CTGTAC meeting, the safety and efficacy of donislecel was assessed in a Phase 1/2 study (UIH-001; 10 subjects) and a Phase 3 study (UIH-002; 20 subjects). Subjects received one to three donislecel transplants. Remarkably, these two small trials represented the totality of the evidence the Applicant submitted to support approval of donislecel.

With respect to the benefits of donislecel transplants, four subjects (13.3%) were insulin-independent for less than one year, 11 subjects (36.7%) for one to five years, and 10 subjects (33.3%) for longer than five years.[1] The figure below, excerpted from the FDA briefing document for the April 15, 2021, CTGTAC meeting, provides the duration of insulin dependence or independence following every transplant for each of the 30 subjects.[2]

Figure 4. Duration of Insulin Dependence or Independence by Transplant for Each Subject.



All 30 subjects received a donislecel transplant at time 0 (the x-axis shows the number of months after the initial transplant), and many subjects received up to two additional transplants before the studies were terminated. The tiny arrows above each bar on the graph show if and when a specific subject received an additional transplant.

The figure shows marked heterogeneity in the study follow-up period, number of treatments, and the achievement of insulin independence. Specifically, the mean follow-up for study UIH-001 was 7.8 years with a substantial range of 1.5 to 13 years, and for study UIH-002 the mean follow-up was 4.7 years with a range of 0.3 to 10.7 years.[3] Regarding the number of transplants, 37% of all subjects received only a single transplant, 40% received two transplants, and 23%

[1] Food and Drug Administration. FDA Briefing Document; Cellular, Tissue, and Gene Therapies Advisory Committee Meeting, April 15, 2021, BLA 125734 Donislecel. https://www.fda.gov/media/147525/download. Accessed April 30, 2021. Page 35.
[2] *Ibid*. Page 36.
[3] *Ibid*. Page 29.

received three transplants.[4] Finally, the mean duration of insulin independence was 5.1 years (range 0.24 to 12.8 years) for the study UIH-001 and 3.2 years (range 0 to 9.9 years) for the study UIH-002.[5] For the 25 subjects who became insulin-independent at some point after one of their transplantations, four (16%) maintained that status for less than one year, 11 (44%) for one to five years, and ten (40%) for longer than five years.[6]

Based on these results, the FDA reviewers concluded that donislecel transplantation has the ability to provide prolonged insulin independence for a subset of patients with type 1 diabetes.[7] Unfortunately, that response was highly variable and was accompanied by a large number of dangerous adverse effects.

With respect to risks, FDA reviewers noted that the Applicant's safety evaluation, which was limited to one year after the last donislecel transplant, was insufficient "[g]iven the potential risks associated with the donislecel and the immunosuppression required to maintain the viability of donislecel." The FDA therefore performed its own safety assessment based on all adverse events that occurred after the first transplant through the last date reviewed for each subject.[8] The agency assessment revealed that a large proportion of subjects experienced life-threatening or severe adverse events, including:

- The following procedural complications: a liver laceration requiring emergency surgery in one subject (3.3%), hepatic hematomas in two subjects (6.7%), and severe anemia requiring transfusions in three subjects (10%);[9]
- Eighty-three life-threatening or severe adverse events that occurred during the first year after the first transplantation with donislecel;[10]
- Thirty-one life-threatening or severe adverse events that occurred during the second through fifth years after the first transplant, including one death at post-transplant day 592 due to sepsis-related multi-organ failure;[11]
- A second death that occurred nine years after the subject's first transplant.[12] The Applicant stated that the decedent had severe and repeated hypoglycemia events prior to transplantation, which are presumed to have been the main cause of the subject's progressive dementia and death, but that conclusion was not confirmed with an autopsy. The FDA clinical reviewer noted that this subject had experienced only four days of insulin independence during the entire duration of follow-up despite much longer

[4] *Ibid*. Page 28.
[5] *Ibid*. Page 35.
[6] *Ibid.* Page 35.
[7] *Ibid*. Page 37.
[8] *Ibid*. Page 38.
[9] *Ibid*. Page 46.
[10] *Ibid*. Page 38.
[11] *Ibid*. Page 38.
[12] Cell Trans. Cellullar, Tissue, and Gene Therapies Advisory Committee briefing document. Lantidra (donislecel) for the treatment of brittle type 1 diabetes mellitus. Meeting Date: 15 April 2021. https://www.fda.gov/media/147529/download. Accessed April 30, 2021. Page 78.

immunosuppressive therapy and had had "a very complex medical history." The cause of death for this subject remains undetermined;[13]

- Twenty-three life-threatening or severe adverse events that occurred five or more years after the first transplant; and[14]
- Six subjects (20%) experienced a total of 11 life-threatening adverse events including: neutropenia (four events), anemia, breast cancer, papillary thyroid cancer, hyperlipidemia, pancytopenia, post-transplant lymphoproliferative disease, and urosepsis.[15]

The FDA safety review concluded that these life-threatening and severe adverse effects and many other less severe adverse effects were expected with the immunosuppression therapy necessary to maintain the viability of the transplanted islet cells.[16] Given the lack of control groups in the donislecel clinical trials, it is uncertain whether the observed adverse-event rates were higher or lower than those seen with full pancreas transplants.

We believe these adverse-event data demonstrate that the risks of donislecel are unacceptably high compared with its benefits.

The case for not approving this biological product is further strengthened by two other serious problems with this application. The first involved the clinical profiles of the subjects who were enrolled, and the second involved the FDA-identified concerns regarding the quality controls for ensuring the potency and purity of each specific lot of donislecel.

First, prior to enrollment in the clinical trials, a substantial proportion of the subjects already had achieved reasonable glycemic control prior to their donislecel transplants, as evidenced by the following observations:

- A hemoglobin A1C (HbA1c) level > 7% had been documented in only 19 of 30 subjects in the year prior to their first transplant.
- A severe hypoglycemic event had been documented in only five of 30 subjects in the year prior to their first transplant.[17]

These indicators suggest the trials included many subjects who would not have been considered to have had "brittle" type 1 diabetes. Thus, many of the subjects studied may have had similar, or perhaps even better, outcomes had they received standard-of-care insulin treatment. Inclusion of control arms in the clinical trials would have allowed for a better assessment of the efficacy and safety of donislecel.

---

[13] Food and Drug Administration. Cellular, Tissue, and Gene Therapies Advisory Committee, April 15, 2021 meeting recording. https://www.youtube.com/watch?v=qufQ5NO2aYE. Accessed April 30, 2021. Time: approximately 6:12:32 to 6:15:49.

[14] Food and Drug Administration. FDA Briefing Document; Cellular, Tissue, and Gene Therapies Advisory Committee Meeting, April 15, 2021, BLA 125734 Donislecel. https://www.fda.gov/media/147525/download. Accessed April 30, 2021. Page 39.

[15] *Ibid*. Page 38.

[16] *Ibid*. Page 45.

[17] *Ibid*. Page 8.

During the April 15, 2021, CTGTAC meeting, representatives of the Applicant were asked directly about the lack of control groups in the clinical trials for donislecel. In response, they said that in 2007 they had considered adding controls to at least one of their two trials during discussions with the FDA regarding the design of the trials, but ultimately, they were dissuaded by the FDA from including such a group because persons with type 1 diabetes "never" become insulin-independent. When pressed by a CTGTAC member, however, the Applicant's representative did lament that they had not at least included a control arm composed of subjects eligible for the trial who ultimately did not receive a donislecel transplant: "In retrospect there is one thing that I do regret, that is for the patients that we turned down…I think I would offer them to enroll in an observational study."[18] The omission of a comparison group of any kind seriously undermines an assessment of how the safety and efficacy of donislecel transplants compare with other type 1 diabetes therapies.

Importantly, the FDA reviewers noted that over the 15 years when the two donislecel clinical trials were being conducted, there had been many advances in insulin monitoring and delivery devices.[19] The "inability to keep up with the rapidly developing technology-based improvements to manage [type 1 diabetes] has been identified as a major limitation of the clinical trials of donislecel."[20]

Finally, FDA reviewers appropriately raised serious concerns about quality controls for ensuring the potency and purity of each specific lot of donislecel. In particular, the FDA reviewers noted the following:

> FDA's position is that the CQAs [critical quality attributes] proposed by the Applicant for potency and purity do not have a demonstrated relationship to the clinical performance of specific lots of donislecel. Without a demonstrated relationship with clinical effectiveness and/or *in vivo* potency/activity, controlling product quality through [the] two proposed CQAs may not be sufficient to ensure the manufacturing process consistently produces donislecel lots of acceptable safety and quality to provide the intended clinical benefit…[21]
>
> Given [the] mechanism of action, controlling the composition of the product is crucial to maintaining consistent product quality. Although use of DTZ [dithizone] staining (purity and EIN/IEQ [Equivalent Islet Number/Quotient]), determination of viability, and evaluation of insulin secretion is consistent with the hypothesized mechanism of action of

[18] Food and Drug Administration. Cellular, Tissue, and Gene Therapies Advisory Committee, April 15, 2021 meeting recording. https://www.youtube.com/watch?v=qufQ5NO2aYE. Accessed April 30, 2021. Time: approximately 6:32:53 to 6:35:20.

[19] Food and Drug Administration. FDA Briefing Document; Cellular, Tissue, and Gene Therapies Advisory Committee Meeting, April 15, 2021, BLA 125734 Donislecel. https://www.fda.gov/media/147525/download. Accessed April 30, 2021. Page 11.

[20] Harlan DM. Islet transplantation for hypoglycemia unawareness/severe hypoglycemia: Caveat emptor. *Diabetes Care*. 2016;39(7):1072-1074.

[21] Food and Drug Administration. FDA Briefing Document; Cellular, Tissue, and Gene Therapies Advisory Committee Meeting, April 15, 2021, BLA 125734 Donislecel. https://www.fda.gov/media/147524/download. Accessed April 30, 2021. Pages 4-5.

> hormone-secreting activity, this approach does not evaluate the contribution of other cells present in the islets to hormone-secreting activity… It is not clear whether the same ratio of exocrine and endocrine tissue that is present in the pancreas is maintained in donislecel because the Applicant does not evaluate the presence of other cell types…[22]
>
> Considering the available data, FDA's position is that while the CQAs identified by the Applicant and controlled in the product by *in vitro* lot release assays may have some value in assuring a consistent manufacturing process, these CQAs may not be adequate to ensure that the consistent quality of the product can be provided to all patients and may not represent specific ability or capacity of the product to effect a given result (e.g., therapeutic effect).[23]

Thus, the FDA reviewers observed from the Applicant's documentation that donislecel preparations are heterogeneous enough to raise significant concerns about product purity, quality, and potency. This heterogeneity and the lack of adequate critical quality controls is a serious deficiency and plausibly means that no two transplants with donislecel are alike, thereby adding to the uncertainty of donislecel's benefits and risks.

At the April 15, 2021, CTGTAC meeting, committee members voted 14 yes, 4 no, with 1 abstention in response to the following "Question 1:"

> Does donislecel delivered by intraportal administration have an overall favorable benefit-risk profile for some patients with Type 1 diabetes?

Although the majority of CTGTAC members voted "yes" to this question, most of them also noted the very rare, imprecisely defined indication proposed by the Applicant for the BLA for donislecel and voiced concern about the substantial risks of immunosuppressive therapy required to maintain the transplants.

CTGTAC temporary voting member David Harlan, M.D., from the Diabetes Center of Excellence at the University of Massachusetts voted "no" and said the following in explaining his vote:

> The question being so narrowly focused that it was a difficult one for me … Could someone in the United States benefit from this?… There may be a few, but it's a few. There's only [about] 100 pancreas transplants done in this country every year and that's very effective. So we are talking about patients that are not candidates for pancreas transplants that might get this. And I voted "no" because I too take care of patients with diabetes, and I've transplanted islets before. I've done both, and I've seen them both pre- and post-transplant. And I've seen the awful things that can happen in post-transplant recipients, that it's really hard to get that informed consent from someone when you're asking them to consider a future that they don't know. When it works, it's great. When it doesn't work, it can be catastrophic. So I just was worried about opening Pandora's

[22] *Ibid*. Pages 9-10.
[23] *Ibid*. Page 10.

> box… And I think it was very telling that very few of the patients even in these trials truly had severe hypoglycemia unawareness.[24]

Immediately after Dr. Harlan's explanation for his vote, Ellen Leschek, M.D., from the National Institute of Diabetes and Digestive and Kidney Diseases explained her "yes" vote as follows:

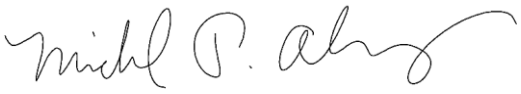
> I very reluctantly voted "yes" for exactly the same reasons that Dave [Dr. Harlan] voted "no." I voted "yes" because of the way that the question was posed. That it was, you know, could a few people benefit? Yes. There are some people that could benefit. I believe though that it is a much smaller number than maybe the company believes. I am concerned that if this agent is approved that too many people will get treated this way when in fact for a lot of those people the risks will outweigh the benefits. And so, I am very, very concerned about that. And the other thing I will say is that I am also worried that approval may hamper future studies in this area because I don't think the studies that we heard about today as being definitive, I think that a lot more studies are needed, and I worry with an approval those studies won't happen.[25]

The above comments from committee members signal substantial doubt about both the safety and effectiveness of donislecel. Indeed, careful review of the evidence presented by the Applicant and of the CTGTAC proceedings strongly suggests that donislecel transplantation for type 1 diabetes should continue only as a rarely used but experimental intervention, if at all.

In closing, Public Citizen urges the FDA to not approve the BLA for donislecel because there is not adequate evidence showing that this product has a favorable benefit-risk profile and there are serious concerns regarding the quality controls for ensuring the potency and purity of each specific lot of donislecel.

Thank you for considering our comments on this important public health matter.

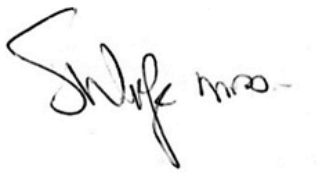
Sincerely,



Michael T. Abrams, M.P.H., Ph.D.
Health Researcher
Public Citizen's Health Research Group

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group

[24] Food and Drug Administration. Cellular, Tissue, and Gene Therapies Advisory Committee, April 15, 2021 meeting recording. https://www.youtube.com/watch?v=qufQ5NO2aYE. Accessed April 30, 2021. Time: approximately 7:59:11 to 8:01:05.
[25] *Ibid*. Time: approximately 8:01:08 to 8:02:10.



Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen's Health Research Group