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August 23, 2018

Wilson Bryan, M.D.
Food and Drug Administration
Office of Medical Products and Tobacco
Center for Biologics Evaluation and Research
Office of Tissue and Advanced Therapies
Document Control Center
10903 New Hampshire Avenue WO71, G112
Silver Spring, MD 20993-0002

Attn: *Dr. Patrick Riggins*

Type C Meeting Request: Type C Meeting: **BB-IND** 9336
Facilitating group BLA submission

Dear Dr. Bryan:

We are requesting a Type C meeting to discuss some of the key strategic matters as a group toward use of Purified Human Pancreatic Islets in the treatment of the most severe cases of Type 1 diabetes mellitus, for which every other therapeutic option has failed. **The indication for islet transplantation is to treat the most severe cases of TID, where every other attempt to correct hypoglycemia unawareness and severe hypoglycemic episodes has failed.** These complications put the patients' lives and the lives of.others at risk (for example a subject driving a vehicle at the time of the hypoglycemic episode), and in these limited cases islet transplantation can be considered a life-saving procedure.

In 2017, the number of patients in the US with TID was approximately 1.2 million (htt ps:/ / professional.diabetes.org/ con t ent / fast-facts-dat a-an d-st at ist ics-about-diabetes). Awareness of hypoglycemia is impaired in 30% of patients with TID (Gold AE, Diab Care 1994; Geddes J, Diabet Med 2008; Choudhary P Diabet Med 2010; Hopkins D, Diab care 2012) and recurrent severe hypoglycemia is reported in 66% of these patients. Assuming 1.2 million people with TID in the US, 360,000 are expected to have impaired awareness of hypoglycemia, 237,600 are expected to have recurrent severe hypoglycemia, and it is estimated that less than 30% of them would fail to improve, despite access to all possible interventions, or less than **71,280 people would not be responsive to interventions** such as hypoglycemia-focused educational and behavioral programs and diabetes technologies.

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We would like to meet to discuss and get your guidance about a possible facilitated path for islet transplantation by submitting one BLA to include five participating centers of the NIH CIT consortium.

Background information and consideration supporting our request:

- **Since September 8, 2000, the FDA began to regulate allogeneic pancreatic islet** tissue products as it did **pharmaceuticals;** i.e. requiring a full BLA application following completion of a Phase 3 trial. We recognized that these regulations may have been appropriate 10 years ago and we, as a field, have complied with every policy stipulation, and diligently initiated the NIH CIT Phase 3 multicenter trial to demonstrate that islet transplantation was an effective and safe treatment for select patients with type 1 diabetes.

- **During these past 10 years we have completed a major effort funded by the NIH, to complete a FDA Multicenter Phase 3 trial:**
  (htt p:/ / diabetes.diabetesjournals.org/ cont ent / early/ 2016/ 07/25/db16-0234.full-text.p df)
  (htt ps:/ / www.diabetesresearch.org/ fi1e/ Diabet es-Care-2016-Hering -dc15 -1988-I .pdf)
  In addition, the NIH has submitted extensive manufacturing and clinical reports to the FDA following this Phase 3 trial.

- The growing international experience as well as the results of the recently completed NIH CIT Multicenter Trial (FDA Phase 3), have dramatically changed the landscape for islet transplantation over the past decade, and **the stance of national regulatory agencies has evolved in several other countries, including Canada, UK, France, Switzerland, Italy, as well as in Asia and Australia,** with several countries now regulating and compensating islet transplantation in a manner analogous to organ transplantation rather than like pharmaceuticals. EMA (CAT), for example, decided that allogeneic islets are not ATMP and should follow the rules of organ transplant at ion . There is a strong incentive to harmonize these regulatory issues between EMA and FDA.

- Islet transplant programs in these countries can now treat hundreds of patients each year because of this facilitated regulatory path and the available reimbursement, while **we (in the US} are falling behind** other countries in this field, **and our patients are unfairly denied this potentially life-saving therapy** even if, ironically, we have developed the manufacturing processes for islet isolation and continue to train the rest of the world in this technology.

- **Considerations that resulted in this change in the stance of regulatory agencies** worldwide include:
    - Considering that in **simultaneous islet-kidney transplantation** it made no sense to handle the kidney as an organ and the islets as an ATMP, since they come from the same donor.
    - **Islet autografts** (e.g., islets obtained from surgical pancreatectomy of the patient's own pancreas for chronic pancreatitis or trauma) **are already approved and reimbursable in the USA.** The manufacturing process for these autotransplants is comparable to that used for allogeneic islet transplants, as far as enzymatic digestion and purification steps to reduce the tissue volume infused. The main reason why allogeneic islet transplants were (and in the USA still are) considered to be 'drugs' is that the **islets are subject to 48-72 hours of low-temperature in-vitro tissue culture.** It was believed that this additional in-vitro culture period somehow changed the islet preparation to "more than minimally manipulated."
    - Hematopoietic stem cell transplants are routinely maintained at 25°C for variable periods prior to transplantation, to prepare the recipient for the transplant and this is not considered manipulation of the product. Similarly, in islet transplantation **this "hibernation" period** is performed **to get the recipient ready for transplant** (induction immunosuppression), **and to improve patient safety,** to perform quality controls and assure that it is suitable for transplantation. In fact, a previous multicenter trial demonstrated that transplanting islets immediately after isolation resulted in several cases of primary non-function, thus exposing the recipient subjects to the risk of immunosuppression without the benefit of receiving a functional transplant.
    - Extensive validation studies performed during the NIH CIT Multicenter Trial have documented that **cultured human islets during this short period do not change in their biological characteristics,** do not divide, and are comparable to the islet products obtained before this short-term culture. In autografts, the islets are transplanted immediately after isolation mainly because the patient is still in the operating room and any level of functional islets that can be returned to the patient would be beneficial.

- We have started the process of gap analysis in preparation for a possible BLA submission to the FDA, but the cost required to complete this process following the same rules of pharmaceuticals is unsustainable at our academic, non-profit institutions (budget example can be provided upon request).

- The NIH and US taxpayers have already spent over $100 million over the 10 years it took to complete the multicenter Phase 3 trial (CIT consortium), which allowed standardization and validation of cGMP manufacturing and transplant

- protocols at the 8 manufacturing cGMP cell processing facilities in North America that were selected to be part ofthis unprecedented NIH collaborative effort. The NIH, however, cannot support the expenses related to BLA applications, and this, along with the financial restrictions imposed by our institutions, makes it almost certain that completion of this process and subsequent formal FDA approval of islet transplantation for treatment of the most severe cases of Type 1 Diabetes will fail.

  Based on these facts, we strongly believe that **a facilitated path for approval of islet transplantation in the US should be considered** and we are seeking your help to better guide us in this direction.

Sincerely,

Camillo Ricardi MD, FNAI
Chairperson, Steering Committee of the NIH CIT Consortium
Stacy Joy Goodman Professor of Surgery
Distinguished Professor of Medicine
Professor of Biomedical Engineering, Microbiology and Immunology
Director, Diabetes Research Institute and Cell Transplant Center, University of Miami

NIH CIT Consortium collaborators in alphabetical order:

- Rodolfo Alejandro, MD
- Xunrong Luo, MD
- James Markmann, MD, PhD
- Ali Naji , MD, PhD
- Andrew Posselt, MD, PhD
- Peter Stock, MD, PhD

Enclosure(s):

1. Meeting request information
2. Information on Phase 3 CIT Trial
3. Supplementary data on Phase 3 CIT Trial
4. http://diabetes.diabetesjournals.org/content/early/2016/07/25/db16-0234.full-text.pdf
5. https://www.diabetesresearch.org/file/Diabetes-Care-2016-Hering-dc15-1988-1.pdf

Type C Meeting Request Information

1. Product name

- *Purified Human Pancreatic Islets*

2. Product information

- Allogeneic Islets Cells (human, NIAID/DAIT) Administered via lntraportal Infusion and lmmunosuppressive Therapy

3. Proposed indication

Treatment of Type 1 diabetes mellitus.

4. Type of meeting requested.

This is a Type C Meeting Request. We request that the meeting be a GO-minute face-to-face meeting.

5. Purpose of the meeting

- *This meeting is to discuss the submission strategy coordinated among participating NIH CIT consortium members to file afacilitated group BLA application as these centers have participated collaboratively in conducting NIH funded pivotal phase 3 study.*

6. Specific objectives/outcomes expected from the meeting

The major objective is to gain a clear understanding of any issues or concerns by the Agency and the potential options in advancing our BLA submission as a

- *Facilitated group BLA submission based on CIT manufacturing and clinical reports with excel based summary reports on previous clinical activities with an emphasis on post marketing surveillance/post approval monitoring*
- *RMAT designation under The Cure Alliance as a 501c3 "sponsors" for the group BLA*

7. Preliminary Agenda

- *Introductions* *IOmin*
- *Discussion of questions submitted* *22min*
- *Discussions of issues identified by the Agency* *21 min*
- *Summary of conclusions reached at the meeting* *Imin*

8. Discussion outline

The required studies have been completed (along with literature in support of safety and efficacy). We would like to discuss facilitated BLA submission in the meeting.

9. Individuals attending the Type C meeting

University of Miami, Diabetes Research Institute	• Camillo Ricardi, M.D. Stacy Joy Goodman Professor of Surgery Distinguished Professor of Medicine Professor of Biomedical Engineering, Microbiology and Immunology Director, Diabetes Research Institute and Cell Transplant Center • Khemraj Hirani, Ph.D, RAC, CIP, CCRP, MBA Director, Regulatory Affairs and Quality Assurance Diabetes Research Institute University of Miami Miller School of Medicine • Rodolfo Alejandro, MD Professor, Division of Endocrinology, Diabetes, & Metabolism Director, Clinical Cell Transplant Program Miller School of Medicine, University of Miami • David Baidal, MD Assistant Professor Division of Endocrinology, Diabetes and Metabolism Clinical Cell Transplant Program - Diabetes Research Institute University of Miami • Elina Linetsky, Ph.D. Research Assistant Professor Director, cGMP Cell Processing Facility Cell Transplant Center Diabetes Research Institute University of Miami Miller School of Medicine • Luis A. Roque Quality Assurance Auditor Diabetes Research Institute University of Miami Miller School of Medicine
Northwestern University Feinberg School of Medicine	• Xunrong Luo, MD, PhD Professor of Medicine and Surgery Director, Human Islet Transplant Program Director, Center for Kidney Research and Therapeutics Northwestern University Feinberg School of Medicine

	• Nitin Katariya, MD Assistant Professor of Surgery Director, Pancreas Transplant Program Northwestern University Feinberg School of Medicine • Jason Wertheim, MD, PhD Associate Professor of Surgery Vice Chair for Research, Department of Surgery Northwestern University Feinberg School of Medicine • Ann LeFever, PhD Assistant Professor of Medicine Direct or, cGMP Cell Processing Facility Northwestern Memorial Hospital Northwestern Medicine
Harvard Medical School	• James F. Markmann MD, PhD Professor of Surgery Harvard Medical School Chief Division of Transplant Surgery Mass General Hospital Co -Direct or, Center for Transplantation Sciences, MGH
University of California, San Francisco	• Andrew M. Posselt, MD, PhD Professor in Residence Director, Clinical Islet Transplant Program Division of Transplantation Department of Surgery University of California, San Francisco • Peter G, Stock, MD, PhD Professor in Residence Surgical Director, Pancreas Transplant Program Co-Director, Islet Transplant Program Division of Transplantation Department of Surgery University of California, San Francisco • Greg Szot , M .S. Technical Director, Human Islet and Cellular Transplantation Facility Division of Transplantation Department of Surgery University of California, San Francisco • Florinna Dekovic CLS/MT, CQA GMP Facility Director- Lab Operations and Quality Assurance UCSF Human Islet and Cell Therapy Facility University of California, San Francisco

University of Pennsylvania, Perelman School of Medicine	• Ali Naji, MD, PhD Surgical Director, Kidney and Pancreas Transplant Program Vice Chair, Research, Department of Surgery J. William White Professor of Surgical Research

10. Agency staff requested by Sponsor to attend this meeting

Wilson Bryan, MD
Celia M. Witten, MD, PhD
Peter Marks, MD, PhD
Patrick Riggins, PhD
Bruce Schneider, MD

11. Suggested dates for the meeting

November 12, 13, 14 and 15
November 19 and 20
Dec. 5, 6, 7
Dec 12, 13, 14

Comments from International Collaborators:

From Dr. James Shapiro (University of Alberta, Edmonton, Canada):
In Canada, healthcare approvals are Province-specific. Alberta approved islet allotransplantation in April 2001, and have continued to fund as standard of care since then. The process involved multiple face-to-face interactions with the Government of Alberta, and Alberta Health Services (the hospital arm of the government) helped put the original package together.
The government of Alberta covered the costs for all out-of-province islet recipients up till 2010, then decided that out-of-province patients could only be transplanted if their reciprocal province reimbursed Alberta for the costs of care delivery. Recently Nova Scotia agreed to cover the interprovincial costs, and Ontario have in the past. Vancouver has had a more complex local funding I believe a composite of philanthropic support and BC Transplant (BC government). Quebec is going through a pilot program with limited initial funding from government, and Ontario has initiated an approval process for the center in Toronto.
Health Canada (the FDA equivalent in Canada) took over regulation of all aspects of solid organ and cellular transplantation some years ago, and audits our laboratory on a regular basis. They have always been supportive, and have never been obstructive in the process.
Happy to provide further supporting documentation in any and all aspects if it will help in any way with the FDA process.

From Dr. Phil O'Connell (President of The Transplantation Society and Head of the Australian Islet Transplant Network):
Essentially it was funded by the Australian National Funded Centre Scheme. Which is a funding mechanism set up by the state Health departments to fund high cost, low volume procedures which are emerging technologies that do not fit in an activity based funding scheme. It allows for the establishment of a highly specialized Australian service in a restricted number of centres that provide the service for the whole country. Apart from islets and example is pediatric heart transplantation.

They commission a Health Technology Assessment which is assess the feasibility
They call and evaluate tenders i.e. Sites
Commission an Economic evaluation to come up with a costing model/procedure

Overall it takes about 2 years from beginning to end
I can give you more info if you think it would be helpful.

From Dr. Thierry Berney, Head of Transplantation at the University of Geneve, CH:
In Switzerland, islet transplantation is fully covered by health insurance since July 1, 2010, in authorized centers (universities of Geneva and Zurich). All 4 modalities are covered: SIK, IAK, ITA and autotransplantation. Please see attached document {832.112.31; this is the comprehensive list of all procedures covered in Switzerland.

Islets are on page 66. This document exists in all 3 official languages in Switzerland, not English, I am attaching the Italian version for Camillo...)

To achieve this, involved centers (i.e. Roger Lehmann from Zurich and myself) worked closely with Swisstransplant (the Swiss equivalent of UNOS) to prepare and submit a document requesting reimbursement. In this document, we also included pancreas transplant alone and pancreas after kidney, which were not reimbursed at the time. We submitted the whole package in September 2009. So, it took a little less than 1 year to obtain reimbursement. I am also enclosing the document submitted by Swisstransplant.