

**FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)
Office of Tissues and Advanced Therapies (OTAT)
69th Cellular, Tissue, and Gene Therapies (CTGT)
Advisory Committee Meeting**

OPEN SESSION

Web-Conference

April 15, 2021

This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO.

ATTENDEES

COMMITTEE MEMBERS	
Lisa Butterfield, Ph.D.	University of California, San Francisco
Kenneth Berns, M.D., M.P.H.	University of Florida
Christopher Breuer, M.D.	Nationwide Children's Hospital
Bernard Fox, Jr. Ph.D.	Providence Portland Medical Center
Randy Hawkins, M.D.	Private Practice
Jeannette Yan Lee, Ph.D.	University of Arkansas for Medical Sciences
Sean J. Morrison, Ph.D.	University of Texas Southwestern Medical Center
Geoffrey M. Nichol, M.D., M.B.A.	BioMarin Pharmaceutical
Mark C. Walters, M.D.	USCF Benioff Children's Hospital Oakland
Joseph Wu, M.D. Ph.D.	Stanford University
John A. Zaia, M.D.	Beckman Research Institute of City of Hope
TEMPORARY VOTING MEMBERS	
Sandy Feng, M.D., Ph.D.	University of California, San Francisco
Lawrence Goldstein, S.B., Ph.D.	University of California San Diego School of Medicine
David Harlan, M.D.	University of Massachusetts
Ellen W. Leschek, M.D.	National Institutes of Health
Bashoo Naziruddin M.D.	Baylor University Medical Center
Emmanuel C. Opara, M.D.	Wake Forest University
Raymond Roos, M.D.	University of Chicago

SPEAKERS AND GUEST SPEAKERS	
Klearchos Papas, M.D.	University of Arizona
FDA PARTICIPANTS/SPEAKERS	
Peter W. Marks, M.D., Ph.D.	Food and Drug Administration
Wilson Bryan, M.D.	Food and Drug Administration
Tejashri Purohit-Sheth, M..D	Food and Drug Administration
Elizabeth Hart, M.D.	Food and Drug Administration
Celia M. Witten, Ph.D., M.D.	Food and Drug Administration
Rachel F. Anatol Ph.D.	Food and Drug Administration
Ilan Irony, M.D.	Food and Drug Administration
Patricia Beaston, M.D., Ph.D.	Food and Drug Administration
Raj Puri, M.D., Ph.D.	Food and Drug Administration
Melanie Eacho, Ph.D.	Food and Drug Administration
Sukhanya Jayachandra, Ph.D.	Food and Drug Administration
Steven Oh, Ph.D.	Food and Drug Administration
Laura Ricles, Ph.D.	Food and Drug Administration
FDA ADMINISTRATIVE STAFF	
Prabhakara Atreya, Ph.D.	Food and Drug Administration
Mr. Michael Kawczynski	Food and Drug Administration
Mr. Jarrod Collier, M.S.	Food and Drug Administration
Ms. Joanne Lipkind, M.S.	Food and Drug Administration

TABLE OF CONTENTS

OPENING REMARKS: CALL TO ORDER AND WELCOME	5
ADMINISTRATIVE ANNOUNCEMENTS, ROLL CALL, INTRODUCTION OF COMMITTEE, CONFLICT OF INTEREST STATEMENT	7
FDA OPENING REMARKS.....	22
ASSESSMENT OF ISLET QUALITY PRE-TRANSPLANT.....	27
Q AND A	49
APPLICANT PRESENTATIONS - INTRODUCTION AND MANUFACTURING PROCESS	62
APPLICANT PRESENTATIONS - POTENCY AND PURITY ASSAYS AND RELATIONSHIPS TO CLINICAL OUTCOMES.....	70
FDA PRESENTATION.....	78
CMC CLARIFYING QUESTIONS TO PRESENTERS	96
CMC QUESTIONS TO THE COMMITTEE/COMMITTEE DISCUSSION	112
OPEN PUBLIC HEARING.....	150
FDA CLINICAL INTRODUCTORY REMARKS	180
APPLICANT PRESENTATION: INTRODUCTION, AGENDA, EXECUTIVE SUMMARY	185
INTRODUCTION TO DIABETES AND UNMET CLINICAL NEED	190
INTRODUCTION TO ISLET CELL TRANSPLANTATION.....	193
EFFICACY, SAFETY, AND RISK-BENEFIT ASSESSMENT	202
FDA PRESENTATION.....	226
CLINICAL CONSIDERATIONS	226
CLARIFYING QUESTIONS TO PRESENTERS	258
QUESTIONS TO THE COMMITTEE/COMMITTEE DISCUSSION	297
VOTING	336
MEMBER REMARKS.....	339
CLOSING REMARKS.....	354
ADJOURNMENT.....	354

1 **OPENING REMARKS: CALL TO ORDER AND WELCOME**

2

3 **MR. MIKE KACZYNSKI:** All right. Welcome and
4 good morning. This is the 69th meeting of the
5 Cellular, Tissue, and Gene Therapies Advisory
6 Committee. I'm Mike Kaczynski, a project manager with
7 FDA, and I'll be today's meeting facilitator. This is
8 a live, virtual public meeting that's being broadcast
9 in its entirety on the FDA YouTube Channel.

10 Today's event is also being recorded and will
11 be posted on FDA's website along with other relevant
12 meeting materials. Throughout today's meeting, I will
13 be reminding speakers and our presenters, committee
14 members, sponsors, and OPH speakers as to when they are
15 close to their allotted times and possibly assist them
16 with any technical issues as well, as when needed.
17 Just a reminder everyone, that once called upon, please
18 manage your mute, activate your webcam.

19 Note to all members and participants, you
20 know, if you do encounter a technical issue, not to

1 panic, we're just going to possibly take an unscheduled
2 break if some major thing does occur. But, at this
3 time I would now like to introduce Dr. Lisa
4 Butterfield, the CTGT Committee chair, who will now
5 provide opening remarks. Dr. Butterfield, please
6 activate your camera and take it away.

7 **DR. LISA BUTTERFIELD:** Thank you very much.
8 Good morning everyone, and welcome to today's
9 proceedings. My name is Lisa Butterfield. I'm at the
10 Parker Institute for Cancer Immunotherapy and
11 University of California, San Francisco. I'm a tumor
12 immunologist, working in cellular and gene therapies,
13 and I would like to call today's proceedings to order.

14 I would like very much to welcome all of the
15 regular members, all the temporary members of the
16 Advisory Committee. I'd like to also welcome the
17 participants, the public, and the audience who are all
18 joining us through this virtual event. Always better
19 to be together, but this is where we are now, and we'll
20 have an excellent meeting and accomplish all our goals

1 today. With that, I would like to turn it over to our
2 very abled designated federal officer, Jarrod Collier.

3

4 **ADMINISTRATIVE ANNOUNCEMENTS, ROLL CALL, INTRODUCTION**
5 **OF COMMITTEE, CONFLICT OF INTEREST STATEMENT**

6

7 **MR. JARROD COLLIER:** Okay. Thank you very
8 much, Dr. Butterfield. Good morning, everyone. My
9 name is Jarrod Collier, and it is my pleasure to serve
10 as the designated federal officer for today's 69th
11 CTGTAC meeting. On behalf of the FDA, the Center of
12 Biologics Evaluation and Research, and the Committee, I
13 would like to welcome everyone to today's virtual
14 meeting.

15 The meeting for today will be to discuss the
16 biologics license application 125734 for donislecel,
17 purified allogeneic deceased donor pancreas derived
18 Islets of Langerhans. Today's meeting topic was
19 described in the federal register notice that was
20 published on February 17th, 2021.

1 I would now like to acknowledge the
2 contributions of a few other members of the Division of
3 Scientific Advisors and Consultants team including our
4 director, Dr. Prabhakara Atreya; Joanne Lipkind; Karen
5 Thomas; Christina Vert, who will also serve as the
6 backup DFO and conduct the voting portion of today's
7 meeting; and Kathleen Hayes, all of whom have assisted
8 in preparing for this meeting. I would also like to
9 express many thanks to Mr. Michael Kaczynski for
10 facilitating the meeting today.

11 For any press-related or media questions, you
12 may contact FDA's Office of Media Affairs at
13 fdaoma@fda.hhs.gov. The transcriptionist for today's
14 meeting is Ms. Alison Bean. We will begin today's
15 meeting by taking a formal roll call for the Committee
16 members and temporary voting members.

17 When it is your turn, please turn on your
18 video camera and unmute your phone, then state your
19 first and last name, your expertise, and your
20 organization. And when finished, please turn your

1 camera off, and we will proceed to the next person.
2 Please see the member's roster slide in which we will
3 begin with the chair, Dr. Lisa Butterfield. Dr.
4 Butterfield, could you please introduce yourself.

5 **DR. LISA BUTTERFIELD:** Good morning. Again,
6 Lisa Butterfield, Parker Institute for Cancer
7 Immunotherapy, and UC San Francisco acting as chair
8 today.

9 **MR. JARROD COLLIER:** Okay. Thank you. Dr.
10 Berns.

11 **DR. KENNETH BERNS:** I'm Kenneth Berns. I'm a
12 Professor Emeritus of molecular genetics and
13 microbiology and the University of Florida,
14 Gainesville.

15 **MR. JARROD COLLIER:** Okay. Thank you, Dr.
16 Berns. Next, Dr. Christopher Breuer.

17 **DR. CHRISTOPHER BREUER:** Hi. My name's Chris
18 Breuer. I'm a pediatric surgeon at Nationwide
19 Children's Hospital, and my area of expertise is
20 regenerative medicine.

1 **MR. JARROD COLLIER:** Okay. Thank you, Dr.
2 Breuer. Next, we have Dr. Bernard Fox.

3 **DR. BERNARD FOX:** Yes. Sorry. My name's
4 Bernard Fox. I'm the Harder Family Chair for Cancer
5 Research at the Earle A. Chiles Research Institute in
6 Portland and adjunct faculty at Oregon Health Science
7 University.

8 **MR. JARROD COLLIER:** Okay. Thank you. Next,
9 we have Dr. Randy Hawkins.

10 **DR. RANDY HAWKINS:** Dr. Randy Hawkins,
11 pulmonary and critical care medicine, private practice
12 in Inglewood, California, consumer representative, and
13 Charles University of Medicine and Science.

14 **MR. JARROD COLLIER:** Okay. Thank you, Dr.
15 Hawkins. Next, we have Dr. Jeannette Lee.

16 **DR. JEANNETTE LEE:** Good morning, my name is
17 Jeannette Lee. I'm a professor of biostatistics at the
18 University of Arkansas for Medical Sciences, and I have
19 done a lot of work in cancer statistics. Thank you.

20 **MR. JARROD COLLIER:** Okay. Next, we have Dr.

1 Sean Morrison.

2 **DR. SEAN MORRISON:** Morning. I'm Sean
3 Morrison. I'm director of Children's Research
4 Institute at UT Southwestern Medical Center in Dallas.
5 My expertise is in stem cells in cancer.

6 **MR. JARROD COLLIER:** Thank you, Dr. Morrison.
7 Next, we have Dr. Geoffrey Nichol.

8 **DR. GEOFFREY NICHOL:** Good morning. I'm Geoff
9 Nichol. I'm Chief Medical Officer at BioMarin
10 Pharmaceutical and have been involved in therapeutic
11 development in cell and gene therapies for the past ten
12 years. I am the industry representative on the
13 advisory committee.

14 **MR. JARROD COLLIER:** Thank you, Dr. Nichol.
15 Next, we have Dr. Mark Walters.

16 **DR. MARK WALTERS:** Morning, Mark Walters. I'm
17 professor of pediatrics and chief of the division at
18 (audio skip) at California San Francisco. My
19 background is (audio skip) cell therapies.

20 **MR. JARROD COLLIER:** Okay. Thank you, Dr.

1 Walters. Next, we have Dr. Joseph Wu. Dr. Wu, I think
2 you might be muted.

3 **DR. JOSEPH WU:** Good morning. My name's
4 Joseph Wu. I'm a professor of medicine and radiology
5 at Stanford University. I direct the cardiovascular
6 institute. My research is on cardiac regenerative
7 medicine, tissue engineering, and gene therapy.

8 **MR. JARROD COLLIER:** Okay. Thank you, Dr. Wu.
9 And next, we have Dr. John Zaia. Okay. I'm not seeing
10 Dr. Zaia. Are you there, Dr. Zaia? Can you turn on
11 your camera and unmute your phone? Okay. We will move
12 on to the temporary voting members, and we'll start
13 with Dr. Sandy Feng.

14 **DR. SANDY FENG:** Hello. I'm Sandy Feng. I'm
15 a transplant surgeon at UCSF. I'm a professor of
16 surgery, the vice-chair of research for the department
17 of surgery, and my research interest is in tolerance
18 induction using regulatory T-cell therapies. Thank
19 you.

20 **MR. JARROD COLLIER:** Thank you, Dr. Feng.

1 Next, we have Dr. Lawrence Goldstein.

2 **DR. LAWRENCE GOLDSTEIN:** Good morning. I'm a
3 distinguished professor in the Department of Cellular
4 and Molecular Medicine and the Department of
5 Neurosciences at UC San Diego. I'm also scientific
6 director of the Sanford Consortium of Regenerative
7 Medicine. I'm a stem cell biologist and
8 neuroscientist.

9 **MR. JARROD COLLIER:** Okay. And next, we have
10 Dr. David Harlan.

11 **DR. DAVID HARLAN:** Good morning. I am the co-
12 director of the Diabetes Center of Excellence at the
13 University of Massachusetts. I've had a 35-year career
14 in treating patients with diabetes and understanding
15 the immuno-pathophysiology underlying the disease.
16 Thank you.

17 **MR. JARROD COLLIER:** All right. Next, we have
18 Dr. Ellen Leschek.

19 **DR. ELLEN LESCHEK:** Good morning. I'm Ellen
20 Leschek. I'm a pediatric endocrinologist and program

1 director at the NIH and the Diabetes Institute, and I
2 am involved in a variety of large clinical consortia
3 having to do with type 1 diabetes.

4 **MR. JARROD COLLIER:** Okay. Thank you, Dr.
5 Leschek. Next, we have Dr. Bashoo Naziruddin.

6 **DR. BASHOO NAZIRUDDIN:** Good morning,
7 everybody. I'm Bashoo Naziruddin. I am the director
8 of the Islet Cell Laboratory at Baylor University
9 Medical Center. I've been directly involved in
10 performing more than 200 clinical islet transplants.

11 **MR. JARROD COLLIER:** Okay. Thank you, Bashoo.
12 Next, we have Dr. Raymond Roos.

13 **DR. RAYMOND ROOS:** Hi. I'm Dr. Raymond Roos,
14 a professor in the Department of Neurology at the
15 University of Chicago and a member of the committees of
16 virology, immunology, and neurobiology.

17 **MR. JARROD COLLIER:** Thank you, Dr. Roos. And
18 we have Dr. Emmanuel Opara.

19 **DR. EMMANUEL OPARA:** Hi. My name is Emmanuel
20 Opara, professor of regenerative medicine and

1 biomedical engineering at Wake Forest School of
2 Medicine; expertise: diabetes, islet biology, and
3 transplantation.

4 **MR. JARROD COLLIER:** Okay. Thank you all for
5 your introductions. I would also like to acknowledge
6 our leadership team of the Center for Biologics
7 Evaluation and Research: Dr. Peter Marks, who is the
8 director; Dr. Celia Witten, deputy center director; Dr.
9 Wilson Bryan, director of Office of Tissues and
10 Advanced Therapies who will be providing FDA opening
11 remarks; and Dr. Rachael Anatol, deputy director for
12 Office of Tissues and Advanced Therapies. Dr. Peter
13 Marks will join the meeting later to provide his
14 closing remarks.

15 So before we begin with reading the Conflict
16 of Interest statement, I would just like to briefly
17 mention a few housekeeping items related to today's
18 virtual meeting format. For speakers, members, FDA
19 staff, and anyone else joining us in the Adobe room,
20 please keep yourself on mute unless you are speaking to

1 minimize feedback. If you have raised your hand and
2 are called upon to speak by our chair, Dr. Lisa
3 Butterfield, please speak slowly and clearly so that
4 your comments are accurately recorded for
5 transcriptioning and captioning. Lastly, for all
6 presenters, please try and stay within your allotted
7 presentation times so that we stay on schedule for
8 today.

9 I will now proceed with the Conflict of
10 Interest statement, thank you. The Food and Drug
11 Administration is convening virtually today, April
12 15th, 2021, for the 69th meeting of the Cellular,
13 Tissue, and Gene Therapies Advisory Committee under the
14 authority of the Federal Advisory Committee Act of
15 1972. Dr. Lisa Butterfield is serving as the chair for
16 today's meeting.

17 Today, on April 15th, 2021, the Committee will
18 meet in open discussion to discuss and make
19 recommendations on the following product from
20 CellTrans, Incorporated, biologics license application

1 125734 for donislecel, purified allogeneic deceased
2 donor pancreas derived Islets of Langerhans for the
3 indication for the treatment of brittle type 1 diabetes
4 mellitus. This topic is determined to be a particular
5 matter involving specific parties.

6 With the exception of the industry
7 representative member, all standing and temporary
8 voting or temporary, non-voting members of the CTGTAC
9 are appointed special government employees or regular
10 government employees from other agencies and are
11 subject to federal conflict of interest laws and
12 regulations. The following information on the status
13 of this Committee's compliance with federal ethics and
14 conflict of interest laws include, but are not limited
15 to, 18 U.S. Code Section 208, is being provided to
16 participants in today's meeting and to the public.

17 Related to the discussions at this meeting,
18 all members, RGE and SGE consultants of this Committee
19 have been screened for potential financial conflict of
20 interest of their own as well as those imputed to them,

1 including those of their spouse or minor children, and
2 for the purpose of 18 U.S. Code Section 208, their
3 employers. These interests may include investments,
4 consulting, expert witness testimony, contracts and
5 grants, cooperative research and development
6 agreements, teaching, speaking, writing, patents and
7 royalties, and primary employment. These may include
8 interests that are current or under negotiation.

9 FDA has determined that all members of this
10 Advisory Committee, both regular and temporary members,
11 are in compliance with federal ethics and Conflict of
12 Interest laws. Under 18 U.S. Code Section 208,
13 Congress had authorized FDA to grant waivers to special
14 government employees who have financial conflict of
15 interest when it is determined that the Agency's need
16 for the special government employee's services
17 outweighs the potential for conflict of interest
18 created by the financial interest involved; or to
19 regular government employees when the interest of the
20 regular government employee is not so substantial as to

1 be deemed likely to affect the integrity of the
2 services which the government may expect from the
3 employee.

4 Based on today's agenda and all financial
5 interests reported by committee members and
6 consultants, no conflict of interest waivers have been
7 issued under 18 U.S. Code Section 208 in connection
8 with this meeting.

9 We have the following consultants serving as
10 temporary voting members: Dr. Sandy Feng, Dr. Lawrence
11 Goldstein, Dr. David Harlan, Dr. Ellen Leschek, Dr.
12 Bashoo Naziruddin, Dr. Emmanuel Opara, and Dr. Raymond
13 Roos. Dr. Geoffrey Nichol of BioMarin Pharmaceutical
14 will serve as the industry representative to this
15 Committee.

16 Industry representatives are not appointed as
17 special government employees and serve as non-voting
18 members of the Committee. Industry representatives act
19 on behalf of all related industry and bring general
20 industry perspective to the Committee. Industry

1 representatives on this Committee are not screened, do
2 not participate in any closed session if held, and do
3 not have voting privileges.

4 Dr. Randy Hawkins is serving as the consumer
5 representative for this meeting and Committee.

6 Consumer representatives are appointed special
7 government employees and are screened and cleared prior
8 to their participation in the meeting. They are voting
9 members of the Committee.

10 The guest speaker for this meeting is Dr.
11 Klearchos Papas, who is the director of the Institute
12 for Cellular Transplantation at the University of
13 Arizona and has been cleared to participate as a guest
14 speaker for today's meeting. Disclosure of conflict of
15 interest for guest speakers follows applicable federal
16 laws, regulations, and FDA guidance. At this meeting,
17 there may also be regulated industry speakers and other
18 outside organization speakers making presentations.

19 These participants may have financial
20 interests associated with their employer and support

1 from other regulated firms. The FDA asks, in the
2 interest of fairness, that they address any current or
3 previous financial involvement with any firm whose
4 product they may wish to comment upon. These
5 individuals were not screened by the FDA for conflict
6 of interest.

7 FDA encourages all meeting participants,
8 including open public hearing speakers, to advise the
9 Committee of any financial relationships that they may
10 have with any affected firms, its products, and if
11 known, its direct competitors. We would like the
12 remind members, consultants, and participants that if
13 the discussions involve any other products or firms not
14 already on the agenda for which the FDA participant has
15 a personal or imputed financial interest, the
16 participants need to inform the DFO and exclude
17 themselves from such involvement, and their exclusion
18 will be noted for the record.

19 This concludes my reading of the Conflict of
20 Interest statement for the public record. At this

1 time, I would like to hand it over to Dr. Lisa
2 Butterfield. Thank you.

3 **DR. LISA BUTTERFIELD:** Thanks again, Jarrod.
4 So now that we have some of these important things out
5 of the way, I'd like to welcome our first speaker, the
6 introductory remarks from the FDA, Dr. Wilson Bryan,
7 Director of the Office of Tissue and Advanced Therapies
8 for CBER. Dr. Bryan, please.

9

10 **FDA OPENING REMARKS**

11

12 **DR. WILSON BRYAN:** Good morning, and welcome
13 on behalf of the FDA, the Center for Biologics
14 Evaluation and Research, and the Office of Tissues and
15 Advanced Therapies. One hundred years ago, Banting and
16 his colleagues first isolated insulin, thus beginning
17 the development of lifesaving treatment for patients
18 with type 1 diabetes. However, for some patients,
19 insulin administration has not provided good control of
20 their diabetes.

1 To address this unmet need, over ten years,
2 the National Institutes of Health sponsored an
3 important consortium to assess the safety and
4 effectiveness of allogeneic cadaveric islets in the
5 treatment of patients with type 1 diabetes that was
6 difficult to control with insulin. That consortium was
7 unique in that each study's center manufactured its own
8 distinct islet cell product, but all the centers used a
9 standardized manufacturing process and followed the
10 same study protocol.

11 Investigations of that NIH consortium are not
12 the focus of today's discussion. However, we very much
13 recognize and appreciate their work, which in many ways
14 provided the impetus for the development program that
15 this Advisory Committee will discuss today.

16 Today's meeting of the Cellular, Tissue, and
17 Gene Therapies Advisory Committee will focus on a
18 biologics license application, or BLA, from CellTrans
19 for the use of donislecel allogeneic islets for the
20 treatment of type 1 diabetes. Today's meeting has two

1 glucagon content for alpha cells in the preparation.

2 So my expectation is that it would be variable.

3 **DR. LAWRENCE GOLDSTEIN:** Okay. Good. Thank
4 you. My second question is, is there enough expression
5 of HLA in these islet preparations to determine HLA
6 type relatively straightforwardly?

7 **DR. KLEARCHOS PAPAS:** Yeah. This is not a
8 question that I could answer. This is not my area of
9 expertise. I would defer to somebody else on the Panel
10 who can answer that question.

11 **DR. LAWRENCE GOLDSTEIN:** Okay. And then
12 third, is there any mouse model that mimics brittle
13 type 1 diabetes?

14 **DR. KLEARCHOS PAPAS:** There may be other mouse
15 models being developed. The best we have is the STZ
16 induced mouse model, and that is what have been used.
17 There are mouse models being developed, and perhaps
18 some other members of the Panel could comment on new
19 mouse models that are available that are more closely
20 resembling brittle type 1 diabetes. But I don't think

1 the nude mouse model is identical or even close to
2 that.

3 **DR. LISA BUTTERFIELD:** Okay. I'm going to be
4 calling on the other questioners in the order in which
5 their questions so please leave your cameras off until
6 I call on you. The next person in line is Dr. Harlan.
7 Your question, please?

8 **DR. DAVID HARLAN:** I also want to thank Dr.
9 Papas for really an outstanding overview. I first can
10 comment on Dr. Goldstein's questions. And, Dr. Papas,
11 cited our paper looking at the huge variability in
12 islets, human islets, so thank you for that, Klearchos.

13 With regard to other hormone responses in
14 isolated islets, there are assays now looking at
15 hypoglycemia-induced glucagon release, but I'm unaware
16 of any studies that look at that in clinical islet
17 transplant outcomes.

18 With regard to the brittle type 1 diabetes,
19 that's operationally defined and usually develops after
20 several years of the disease. So I'm unaware of any

1 mouse model that could predict brittle Type 1 diabetes.

2 And I did have a question, but I was so
3 intrigued by Dr. Goldstein's, now I'm blanking on my
4 question. I'll raise my hand again, Dr. Butterfield,
5 if that occurs to me.

6 **DR. LISA BUTTERFIELD:** All right. Thank you,
7 Dr. Harlan. Then let's move to Dr. Morrison who is
8 next in line with a question.

9 **DR. SEAN MORRISON:** Yeah. Are there good
10 markers for alpha cells and delta cells and other cells
11 that would be in the islet preparations that could be
12 used to quantitate the numbers of those cells?

13 **DR. KLEARCHOS PAPAS:** Yes, there are. And, as
14 Dr. Harlan pointed out, some are used in the assays in
15 the papers that have been published. So there is quite
16 a bit published on that, so the answer is yes.

17 **DR. LISA BUTTERFIELD:** Thank you. Next, Dr.
18 Opara, your question.

19 **DR. EMMANUEL OPARA:** Okay. Right. Yeah. So
20 again, I want to thank, you know, Dr. Papas for, you

1 know, a wonderful presentation. You know, I think you
2 kind of covered a lot of the issues that, you know, we
3 face when islets are used to treat type 1 diabetic
4 patients.

5 Now, my question to you is, have you or do you
6 know of papers that have looked at the potency as
7 demonstrated by in vitro assay at a time of the
8 transplant or prior to transplantation with how that's
9 correlated with a clinical outcome? Because, you know,
10 there may be some intrinsic factors or some other
11 factors that we've, you know, kind of overlooked. And
12 I think we can talk more about that during the
13 discussion of this CMC method. So it would be really
14 nice to see if there is any correlation between the in
15 vitro potency that is, you know, obtained prior to
16 transplantation compared to what you get as a clinical
17 outcome.

18 **DR. KLEARCHOS PAPAS:** Yes. So thank you for
19 that question and the comment. The answer is yes, and
20 I very briefly touched on two papers who we published,

1 number one, with clinical islet autotransplant outcomes
2 where oxygen consumption rate was measured just prior
3 to transplantation and, in fact, reported to the
4 surgeon so that they could better manage the patient
5 based on that data. And that predicted, or was very
6 predictive, of insulin independence in these clinical
7 transplants with auto islets. That's in the absence of
8 immunosuppression and any autoimmunities, so it's a
9 simpler scenario than the clinical islet
10 allotransplant.

11 In a very small study with the group at
12 Edmonton, which I also quickly shared here due to time
13 limitations, again, the OCR dose, which essentially the
14 oxygen consumption rate to DNA ratios, the viability
15 measure by the assay multiplied by the dose, which is
16 measured in islet equivalents per kilogram body weight,
17 defined the viable islet dose that went into the
18 patient. That was also highly predictive for a very
19 small cohort of patients of insulin independence.

20 I wish we could do more, and I believe it's

1 important to create some more of this because I believe
2 it can be very useful going forward. I would not say
3 this at the level of our issue peer release criterium.
4 We should not -- data should be collected so that we
5 can learn more and improve our process and be more
6 predictive as we go forward.

7 **DR. LISA BUTTERFIELD:** Great. Thank you very
8 much. Next question is from Dr. Nichol. We can't hear
9 you, Dr. Nichol, or I can't.

10 **DR. GEOFFREY NICHOL:** Apologies. Thanks, Dr.
11 Papas for a remarkable presentation. One question I'd
12 like to ask you, a non-technical question is just the
13 nature of the usefulness of the discussions you had
14 with FDA regarding the chemistry, manufacturing, and
15 controls topics that we're discussing today.

16 **DR. KLEARCHOS PAPAS:** So your question is
17 whether the -- on the usefulness of my discussions with
18 FDA?

19 **DR. GEOFFREY NICHOL:** Of the sponsor
20 discussions with FDA.

1 **DR. KLEARCHOS PAPAS:** Yeah.

2 **DR. GEOFFREY NICHOL:** Perhaps I'm asking the
3 wrong person.

4 **DR. KLEARCHOS PAPAS:** Yeah. I may not be the
5 right person. Apologies. Or I may not be
6 understanding your questions.

7 **DR. GEOFFREY NICHOL:** Yeah. I'll address that
8 question to a member of the sponsor team later. My
9 apologies.

10 **DR. KLEARCHOS PAPAS:** No problem. Thank you.

11 **DR. LISA BUTTERFIELD:** Thank you. Dr. Wu,
12 your question.

13 **DR. JOSEPH WU:** Yes. So thank you, Dr. Papas,
14 for the great talk. So I have a quick question on
15 whether the pharmacokinetics or pharmacodynamics of
16 your product, in this case, the cell product. Once you
17 inject in vivo, how long did the cell survive, where
18 did they go, and if you did a repeated injection of
19 these cells, do you get a cell-related rejection
20 because of the buildup of the immune system?

1 **DR. KLEARCHOS PAPAS:** This is perhaps also
2 another question that may be better addressed by some
3 of the clinical people who are actually doing the islet
4 allotransplants. I could try and answer it if you
5 like, but I believe this may be more appropriate for
6 somebody else.

7 **DR. JOSEPH WU:** Okay. Thank you.

8 **DR. LISA BUTTERFIELD:** Thank you. Next
9 question is from Dr. Naziruddin.

10 **DR. BASHOO NAZIRUDDIN:** I'd like to respond to
11 Dr. Goldstein's question whether the HLA is (inaudible)
12 human islets. The answer is yes, Class 1 is inherently
13 expressed, but when the islets are subjected to pro-
14 inflammatic conditions, HLA Class 2 is also expressed.

15 **DR. LISA BUTTERFIELD:** All right. Our next
16 question is from Dr. Roos.

17 **DR. RAYMOND ROOS:** Yes, hi. I have a
18 question. I may be a little bit naïve, but how does
19 this islet transplantation compare to transplanting
20 some of the pancreas?

1 **DR. KLEARCHOS PAPAS:** I can try and answer
2 that as well. You know, the focus of my presentation
3 was on pre-transplant potency test, but I'm happy to at
4 least share some of what's published. And obviously,
5 the islet transplant is a much smaller volume of
6 tissue, and that is an important difference. And the
7 immunosuppression is required, and the islet product
8 undergoes certainly a lot of steps additional to the
9 whole pancreas transplant.

10 Now it is a simpler procedure, much simpler
11 surgical procedure. The five-year outcomes based on
12 what I have seen published, and others should be able
13 to comment better on that. Five-year outcomes of islet
14 transplantation are approaching those of the whole
15 pancreas transplant with improving immunosuppressive
16 protocols and improvements in the standardization of
17 islet manufacturing. And I will stop here, but that
18 would be my response.

19 **DR. LISA BUTTERFIELD:** Thank you. A couple
20 more minutes. Our next question is from Dr. Berns. We

1 can't hear you, Dr. Berns.

2 **DR. KENNETH BERNS:** Can you hear me now?

3 Okay. That was extremely informative since I'm a
4 complete outsider to this field. But one thing I
5 haven't seen in any of the literature in any great
6 detail or heard in your presentation is the extent to
7 which these preparations are screened for latent
8 viruses and whether it makes any difference in your
9 opinion.

10 **DR. KLEARCHOS PAPAS:** There are safety screens
11 that are being performed, you know, and this also at
12 the organ level, and I should let some other members
13 comment further on more specific because that is not my
14 area of expertise. But there are screens that have
15 been conducted.

16 **DR. KENNETH BERNS:** Yeah. It's just that
17 almost every DNA virus and a lot of others that we know
18 can persist and so the extent to which they can have an
19 effect upon a transplant I think would be interesting
20 to know. But thank you.

1 **DR. LISA BUTTERFIELD:** This might be our last
2 question, Dr. Harlan.

3 **DR. DAVID HARLAN:** I'll try to do better this
4 time. The question I had is, it follows up a little
5 bit of what Dr. Roos I think asked. And as Klearchos,
6 Dr. Papas, knows, a single pancreas reliably restores
7 glucose independence when transplanted, and with
8 islets, it requires, often times more than one dose.
9 So, Dr. Papas, I'm very intrigued that the oxygen
10 consumption rate assay looks to be predictive in the
11 small number, the small study you presented from
12 Edmonton. But it seems to me that that may be the
13 appropriate release criteria to do that assay. And I
14 just wonder if you'd comment.

15 Clearly, the nude mouse, you can't do because
16 it takes too long to get the result. Would you
17 advocate an oxygen consumption release assay for
18 product validation?

19 **DR. KLEARCHOS PAPAS:** I would advocate -- so
20 thanks for that question, Dr. Harlan. And indeed as

1 you pointed out, several islet preparations may not be
2 able to restore insulin independence. And sometimes
3 you may need more than one islet preparation, whereas
4 in one pancreas you can restore insulin independence.
5 And that of course is related to all the stresses and
6 all the additional steps that we have for processing
7 and purifying the islets among other things, but also
8 post-transplant factors.

9 I believe, based on all the data that I have
10 seen and also more than 20 years of work in this, I
11 believe that oxygen consumption rate assays can be
12 predictive and are important and should be pursued. I
13 would advocate for conducting them in parallel and with
14 more data as we acquire a potentially transitioning.
15 That would be my recommendation based on my experience
16 and the data that is collected and also data from the
17 field that suggests that mitochondrial-related assays
18 can be predictive.

19 And it also mechanistically makes sense
20 because the islet is pO sensor (phonetic), and oxygen

1 consumption and metabolism is related to its
2 functionality as well. I will stop here. I hope I
3 answered your question.

4 **DR. LISA BUTTERFIELD:** Thank you so much, Dr.
5 Papas. So that was our last question for this time
6 period, but please hold your questions because we have
7 other times for further discussion of the CMC. So
8 thanks again, Dr. Papas, and now we move to our sponsor
9 speakers: Drs. McGarrigle and Oberholzer. So let's
10 start with Dr. McGarrigle. Thank you very much.

11

12 **APPLICANT PRESENTATIONS - INTRODUCTION AND**
13 **MANUFACTURING PROCESS**

14

15 **DR. JAMES MCGARRIGLE:** Thank you, Dr.
16 Butterfield, and good morning everybody. My name is
17 Dr. James McGarrigle. I'm the chief operating officer
18 of CellTrans, based at UI Health in Chicago.

19 I would like to thank the Advisory Committee
20 for sharing their time today as well as the FDA for

1 organizing this meeting.

2 The agenda for today's presentation is as
3 follows. I will firstly introduce donislecel,
4 including an overview of the indication for type 1
5 diabetes and the manufacturing process. Then, Dr. Jose
6 Oberholzer, the president and chief medical officer at
7 CellTrans, will present the purity and potency assays
8 for donislecel, and the relationship to clinical
9 outcomes.

10 Type 1 diabetes is a disorder characterized by
11 the autoimmune-mediated loss of insulin-producing beta
12 cells within the islets of Langerhans of the pancreas.
13 Approximately 1.4 million American adults have type 1
14 diabetes. Brittle type 1 diabetes is a rare subtype
15 with current estimates of fewer than 80,000 individuals
16 affected by this condition in the U.S.

17 Brittle type 1 diabetes results in complete
18 insulin deficiency and may lead to severe and
19 potentially life-threatening hypoglycemia. It is
20 particularly difficult to control with patients

1 experiencing frequent, dramatic swings in glucose
2 levels.

3 Blood glucose levels are regulated by insulin
4 naturally produced in the pancreas. The pancreas is an
5 abdominal organ. It has two main functions: an
6 exocrine function that helps in digestion and an
7 endocrine function that regulates blood sugar.

8 The exocrine portion comprises approximately
9 95 percent of the pancreas mass, consisting of acinar
10 and duct cells. Acinar cells secrete digestive enzymes
11 into the duodenum of the small intestine while duct
12 cells form the epithelial lining of the branch tubes
13 that deliver enzymes produced by pancreatic acinar
14 cells into the duodenum.

15 The endocrine portion of the pancreas consists
16 of islets of Langerhans, commonly known as islets,
17 which regulate blood glucose levels through highly
18 regulated secretion of multiple hormones, such as
19 insulin, in response to fluctuations in blood glucose.

20 Here we have a representative image of an

1 islet. The average islet consists of around 1,500
2 cells, it's spherical in shape, 150 micrometers in
3 diameter, with a volume of approximately 1.8 million
4 cubic micrometers.

5 An islet is composed of five principle
6 endocrine cell types. Beta cells constitute
7 approximately 55 percent of the cells in the islets and
8 produce insulin that enables glucose uptake by
9 peripheral tissues. It is insulin that lowers blood
10 glucose in response to a meal.

11 Alpha cells make up approximately 35 percent
12 of the cells in the islets producing glucagon that acts
13 as a counterweight to insulin by mobilizing glucose
14 from the liver into circulation, thus raising blood
15 glucose levels when they get too low. The remaining
16 islet cell types, which together make up around 10
17 percent of the islet helps regulate these opposing
18 endocrine activities.

19 Donislecel, which consists of purified
20 allogeneic islets of Langerhans is produced at

1 CellTrans. CellTrans has a cGMP islet manufacturing
2 facility measuring approximately 2,250 square feet
3 located at UI Health, Chicago. The facility has
4 supported the donislecel IND since the program's
5 inception in 2004. All 56 donislecel lots transplanted
6 under IND for UIH-001 and 002, Phase 1, 2, and 3
7 clinical trials were manufactured at this site. An
8 additional 19 transplanted lots have been manufactured
9 at this site as part of the clinical islet
10 transplantation consortium. All manipulations are
11 performed aseptically in five dedicated biological
12 safety cabinets within the processing suite.

13 This is an overview of both the clinical and
14 manufacturing site procedures. The isolation of
15 purified pancreatic islets has multiple manufacturing
16 steps. Manufacturing of donislecel is well established
17 and controlled and consistently produces islets that
18 are safe, pure, and potent. Each donislecel lot
19 consists of islets isolated from a single donor
20 pancreas intended for a single designated recipient.

1 I will now describe in detail the donor
2 pancreas acceptance procedure prior to organ
3 processing. The donor pancreas is considered incoming
4 raw material for the manufacture of donislecel and is
5 thoroughly screened prior to acceptance. Medical
6 centers identify potential organ donors and report this
7 to their local organ procurement organization, the OPO,
8 which screens, tests, and manages the donor.

9 The OPO then informs the United Network for
10 Organ Sharing, UNOS, which organs are potentially
11 eligible for transplantation. UNOS allocates the
12 organs based on a national wait list of transplant
13 recipients. UI Health, which is the sole transplant
14 center for donislecel then screens the donor and
15 provisionally accepts or declines the organ as being
16 medically appropriate for their waitlisted patients.

17 Upon organ procurement, a visual inspection of
18 the organ is performed, and the organ is accepted. The
19 organ is then transported to CellTrans at UI Health
20 where donor screening verification and organ acceptance

1 for processing occurs prior to islet manufacture.
2 CellTrans has a rigorous chain of identity procedure
3 from donor organ to manufacturing to release of the
4 final product.

5 Following the acceptance of the pancreas, the
6 manufacturing process is continuous from the time the
7 organ arrives at CellTrans until the final drug product
8 is released through processing. The manufacturing
9 process is broken down into manufacturing steps for
10 drug substance, pre-islet culture, and drug product
11 post-islet culture. The incoming pancreas is trimmed
12 of excess fat tissue, spleen, and duodenum and then
13 decontaminated by at triple antimicrobial fungal agent
14 treatment. The pancreas is cannulated and perfused
15 with a collagenase solution and cut into pieces for
16 digestion.

17 The pancreas pieces are then placed into the
18 Ricordi digestion chambers. Here, enzymatic and
19 mechanical digestion of the pancreatic tissue occurs.
20 Islets are separated from the exocrine tissue, and the

1 digested pancreatic tissue is collected. The digested
2 tissue is then placed into COBE cell purification unit
3 to separate the islets from the majority of the
4 exocrine tissue.

5 The islets are collected into different islet
6 purity fractions based on cell density. After
7 purification, drug substance, quality control samples
8 are taken, and the islet purity fractions are cultured
9 at 37 degrees for up to 48 hours. Importantly, this
10 step maintains the islets prior to transplantation but
11 does not expand them.

12 Post-culture islet fractions are combined and
13 formulated. Quality control samples for safety,
14 identity, potency, and purity are performed on the
15 final formulations. Donislecel is transplanted within
16 six hours at the UI Health radiology department.

17 The quality control assessment sampling point
18 where the drug substance and drug products will now be
19 described. Post-purification quality control sampling
20 is performed for the different islet purity fractions

1 from morphology, tissue volumes, purity, islet yield,
2 sterility, and glucose stimulation index. The islet
3 fractions are then cultured for up to 48 hours. Post-
4 islet culture quality controlled sampling is performed
5 for the different islet fractions for morphology and
6 tissue volume.

7 After final formulation, samples are taken and
8 assessed for tissue volume, morphology, purity, islet
9 yield, viability, endotoxin, and sterility. Following
10 release, donislecel is infused into the portal vein of
11 the recipient.

12 Dr. Jose Oberholzer will now present
13 donislecel's critical quality attributes and the
14 relationship to clinical outcomes.

15

16 **APPLICANT PRESENTATIONS - POTENCY AND PURITY ASSAYS AND**

17 **RELATIONSHIPS TO CLINICAL OUTCOMES**

18

19 **DR. JOSE OBERHOLZER:** Thank you very much,
20 James, and good morning to the Agency and Advisory

1 Committee.

2 In the following, I would like to highlight
3 key aspects of the donislecel manufacturing, including
4 specifics about the purity and potency assay and the
5 relationship to clinical outcomes. One of the key
6 differences between donislecel and other drug products
7 is that each batch of islets is based on a single
8 donated human pancreas.

9 There can be significant variability in human
10 donors, including biological differences like age, body
11 weight, genetic and metabolic background, and cause of
12 death, as well as other characteristics like
13 differences in cold ischemia time. This variability is
14 illustrated on the graph for cold ischemia time, the
15 weight of the pancreas, as well as the donor BMI.

16 There are several critical quality attributes
17 for drug product release. These include
18 characteristics for container closure integrity, islet
19 appearance, safety, and identity. We will focus on the
20 purity and potency testing.

1 Islet purity is determined by estimating the
2 ratio of islet to exocrine tissue by staining with
3 dithizone. The zinc-chelating molecules dithizone
4 selectively stain beta cells within the islets due to
5 their elevated zinc content.

6 On the images on the right, you see an impure
7 and a pure islet preparation. The islet preparation is
8 considered for transplantation if a minimum of 30
9 percent stains bright red as you can see on the image
10 in the right upper corner, which is a rather pure islet
11 preparation.

12 On the graph on the right side, you see the
13 islet purity of the islet prep transplanted patients in
14 UIH-001 and UIH-002. In the following slides, I would
15 like to explain the trade-off between the islet purity,
16 islet quantity, and, if (inaudible), islet graph
17 volume.

18 While a greater number of islets may have the
19 potential to increase the rate of success, there are
20 limits to the volume of islets that can be safely

1 transplanted. Therefore, the islet purification
2 process involves a trade-off between islet purity and
3 islet quantity. The purification process of islets is
4 based on the density difference between islets and
5 exocrine tissue, as you can see on those Gauss curves.
6 And there is some overlapping. It's biology.

7 During purification, the maturity of islets
8 are present in the purest top islet fraction, which
9 ranges from 100 to 70 percent purity. However, less
10 pure fractions will still contain some islets that we
11 ideally would like to transplant. For transplantation,
12 no more than 10 milliliters of pelleted tissue should
13 be transplanted. Therefore, in order to maximize the
14 number of islets while maintaining a safe volume, a
15 portion of the less pure islet fractions may have to be
16 excluded.

17 The potency of islet preparation involves an
18 assessment of insulin production, viability, and islet
19 yields. The glucose stimulation index matches the
20 ratio of insulin secretion on the high glucose

1 stimulation to that under a basal low glucose
2 concentration. A glucose stimulation index above one
3 indicates glucose-responsive insulin secretion, which
4 represents the main function of donislecel. The graph
5 to the right summarizes the glucose stimulation indices
6 of the donislecel lots transplanted in each patient.

7 Before releasing an islet cell preparation for
8 transplant, we want to make sure that the viability is
9 above 70 percent. Evaluated viability islets are
10 subjected to SYTO Green ethidium bromide staining.
11 Live cells stain green, while dead cells stain red, on
12 the image, a preparation with a high viability. The
13 ratio of live to dead cells is then evaluated through
14 microscopic inspection.

15 The graph on the right shows measured
16 viability of the various donislecel lots transplanted.
17 The last assessment for potency is islet yield, or the
18 quantity of islets. Due to the variability in islet
19 size, islet quantity's expressed as the number of islet
20 equivalents. Islet equivalents are calculated based on

1 the number and diameter of islets present in the
2 preparation, mathematically corrected for islet volume,
3 as Dr. Papas has illustrated in his excellent
4 presentation. To the right, the graph summarizes the
5 islet equivalents of the various donislecel lots
6 transplanted in each patient.

7 In our clinical trials, an islet dose response
8 was observed for achieving the composite endpoints of
9 the hemoglobin A1C equal or less than 6.5 percent and
10 absence of severe hypoglycemia. As can be seen in the
11 graph on the right, more patients reach the composite
12 endpoints as the cumulative donislecel dose increased.
13 The dose response started to plateau at about a little
14 bit over a million islets equivalents given to the
15 patient.

16 Similar trends were also observed for
17 achieving insulin independence. Insulin independence
18 at one year after last transplant was observed with
19 greater frequency with increased cumulative donislecel
20 dose. (audio skip)

1 **MR. MIKE KACZYNSKI:** Hold on. Yep. Hold on a
2 second. Jose, we don't hear you right now. You
3 dropped your audio, sir. Give you a second to
4 reconnect it.

5 **DR. LISA BUTTERFIELD:** We heard all but
6 perhaps half of what you said on the previous slide,
7 and we haven't heard anything for the summary slide
8 yet.

9 **MR. MIKE KACZYNSKI:** Let him reconnect his
10 audio. Okay. Take your time, Dr. Oberholzer. Here he
11 comes. There you're back. How are you doing, Jose?

12 **DR. JOSE OBERHOLZER:** My apologies. Am I back
13 in?

14 **MR. MIKE KACZYNSKI:** That's okay. Yeah.

15 **DR. JOSE OBERHOLZER:** Okay.

16 **MR. MIKE KACZYNSKI:** We just missed about a
17 little bit of the tail end of this slide and then going
18 forward. Okay, sir?

19 **DR. JOSE OBERHOLZER:** Okay. So my apologies
20 again. So the product release testing includes --

1 we'll go back up to islet dose response. So, as I
2 said, similar trends were also observed for achieving
3 insulin independence. So insulin independence at one
4 year after last transplant was observed with greater
5 frequency with increased cumulative donislecel dose.

6 In summary, the product release testing
7 includes assessments of several critical product
8 characteristics, including identity, purity, and
9 potency. Despite variability of the incoming donor
10 pancreas, the standardized manufacturing process leads
11 to the production of donislecel lots that are
12 consistent with respect to critical quality parameters.
13 Using the defined lot release specifications for
14 donislecel, insulin independence lasting for at least
15 one year was achieved in 20 of 30 donislecel
16 recipients.

17 I would like to thank you for your attention
18 and apologize for my phone deciding to disconnect.

19 **DR. LISA BUTTERFIELD:** Thank you so much to
20 both of our sponsor speakers. So now we move to our

1 FDA speaker, and then, at the end, we'll have
2 clarifying questions for both speakers. So I'd like to
3 introduce from the FDA, Dr. Jayachandra from the Cell
4 Therapy Branch.

5

6 **FDA PRESENTATION**

7

8 **DR. SUKHANYA JAYACHANDRA:** Good morning. My
9 name is Sukhanya Jayachandra. I am the product
10 reviewer in the Cell Therapy Branch, Division of
11 Cellular and Gene Therapies within the Office of Tissue
12 and Advanced Therapies in the Center for Biologics
13 Research and Evaluation, also known as CBER.

14 I will be giving the FDA presentation on
15 product characterization for donislecel, an allogeneic
16 pancreatic islet cell therapy for the treatment of type
17 1 diabetes mellites. My talk today will focus on
18 product characterization, which is an important part of
19 the chemistry, manufacturing, and controls, or CMC for
20 short. The purpose -- could we advance this slide,

1 please? I'm unable to do it on my end. Yeah. Thank
2 you. The purpose of my talk today is -- a little bit
3 of a technical issue.

4 **MR. MIKE KACZYNSKI:** We made you a presenter.
5 You should be able to move your slides now. Go ahead.

6 **DR. SUKHANYA JAYACHANDRA:** Okay. Can -- am I
7 a presenter now?

8 **MR. MIKE KACZYNSKI:** Yes. Yes, you are,
9 ma'am.

10 **DR. SUKHANYA JAYACHANDRA:** Okay. Thank you.
11 So if you can just give me a minute. Yeah. Okay. So
12 the purpose of this morning's session and my talk today
13 is to discuss the quality attributes of donislecel,
14 specifically product purity and potency; and the
15 relationship to product quality and effectiveness, and
16 to discuss whether these quality attributes are
17 sufficient to evaluate lot-to-lot consistency in
18 manufacturing, product quality, and strength.

19 The next two slides I will -- before we delve
20 into the specifics of donislecel, I would like to

1 introduce the key regulatory and scientific terminology
2 to aid in our further discussion. We rely on three
3 types of controls as part of our strategy to ensure
4 product quality and consistency. For each type of
5 control, we determined characteristics to assess or
6 measure and set specifications for those measurements.

7 Listed in this slide are a limited list of
8 parameters that are controlled under the key control
9 types. The three product controls are considered
10 together by the FDA to establish that the product
11 quality is consistently maintained from lot to lot.
12 The first is source control meaning that we control the
13 quality of the starting material used in manufacturing,
14 in this case, the pancreatic organ from cadaver donors.
15 This is important as mentioned by the talks earlier
16 regarding (inaudible) times in the control of the
17 donated organs.

18 The second key control is the manufacturing
19 process controls that are listed here. Included in
20 this list is the control of reagents and enzymes that

1 are used in manufacturing of the products and various
2 in-process tests.

3 The third key control is product testing. At
4 the end of manufacturing, we want to test the product
5 to ensure that the product meets pre-specified quality
6 requirements and to ensure the product has the same
7 characteristics from batch to batch. Product testing
8 focuses on properties of the product that we call
9 attributes.

10 In this next slide, we will talk about these
11 attributes. The quality and critical quality
12 attributes - a quality attributes is defined as
13 molecular or product characteristics that is selected
14 for its ability to help indicate the quality of the
15 product.

16 We also identify critical quality attributes,
17 which consist of physical, chemical, biologic, and
18 microbiological property or characteristic that should
19 be within an appropriate limit, range, or distribution
20 to ensure the desired product quality. Collectively,

1 these quality attributes define the safety, purity,
2 potency, and identity, and stability of the product.
3 The applicant describes their product, donislecel, as
4 an allogeneic pancreatic islet and has defined the
5 properties as shown in this slide.

6 Based on Dr. Papas' presentation and adapted
7 from Table 3 obtained from the applicant's briefing
8 documents, the shape is roughly spherical with a
9 diameter that varies from 50 to 500 microns with an
10 islet volume listed here. These three-dimensional
11 islets are composed of at least five major cell types
12 whose approximate relative abundance and endocrine
13 secretion are listed in this table.

14 So how did we determine what are the useful
15 quality attributes and the critical quality attributes
16 of such a cellular product? Quality attributes can be
17 developed and established to understanding the
18 characteristics and biological properties of the
19 product.

20 The applicant has identified the following key

1 critical attributes, CQAs, for their product. Shown
2 here are quality attributes and the methods used to
3 evaluate those attributes. These include product
4 testing for safety, identity, potency, viability, and
5 purity. I've highlighted these CQAs for identity,
6 potency, and purity because they are the primary focus
7 of our discussion this morning.

8 Identity tests define what is in the product.
9 The dithizone, or DTZ, staining of islets is an
10 important analytical tool, and the results of this
11 assay are used to determine not only identity, but also
12 morphology, yield, and purity. Briefly, as mentioned
13 in the previous talk, DTZ is (inaudible) agent known to
14 selectively stain beta cells dark red or purple due to
15 their high zinc content.

16 The potency test measures the biologic
17 function of the product, in this case, the function of
18 the beta cells present in the islets. When beta cells
19 are stimulated with glucose, they release insulin,
20 which is measured by an ELISA. The glucose stimulation

1 index is defined as the ratio of insulin secretion
2 between a high glucose to a low glucose stimulation.

3 Viability of the cells is measured by staining
4 the SYTO 13 ethidium bromide dye that discriminates
5 between live and dead cells as visualized under
6 microscopic evaluation.

7 I will focus on the purity and potency today.
8 But, before we go further, I would like to introduce
9 three regulatory definitions of purity and potency and
10 how they relate to critical quality attributes for
11 donislecel.

12 In this slide, I will talk about the
13 regulatory definition for purity. It is codified in
14 the U.S. code of regulations that a BLA may be approved
15 on the basis of demonstration that the biological
16 product, that is the subject of the application, is
17 safe, pure, and potent. The federal regulations
18 provide the following definitions of purity that apply
19 to cell therapy products, "Purity means relative
20 freedom from extraneous materials in the finished

1 product whether or not harmful to the recipient or
2 deleterious to the product. Products should be free of
3 extraneous materials except that which is unavoidable
4 in the manufacturing process described in the approved
5 biological license."

6 These definitions allow for the presence of
7 multiple cell types in the final product, even those
8 that do not contribute to the product's mechanism of
9 action. However, in general, lot release criteria are
10 established for the cellular composition of the final
11 formulated cellular product, including cell types that
12 are not anticipated to have a therapeutic effect.
13 In the case of donislecel, the minimum criterion for
14 purity is set such that it allows for about 70 percent
15 other cell types.

16 While DTZ staining is one of the commonly used
17 methods for identifying beta cells in islets, other
18 methods can be used to identify other cell types that
19 are present in the islets. These other cells in the
20 islets play a role to regulate glucose, and it may also

1 aid in engraftment. So additional characterization
2 data on other cell types present in the final product
3 means some decision on specifications that limit the
4 quality, quantity of a particular cell type to ensure
5 product engraftment consistency.

6 The other critical attribute is potency as
7 defined by the U.S. code of federal regulations for
8 biologic products. Potency refers to "the specific
9 ability or capacity of the product, as indicated by
10 appropriate laboratory tests or by adequately
11 controlled clinical data obtained through the
12 administration of the product in a manner intended to
13 effect a given result." Ideally, the potency assay
14 will represent the product's mechanism of action. In
15 some cases, the mechanism of action can be very
16 complex.

17 Tests for potency, we rely on bioassays
18 including in vivo analytical assays; in vitro organ,
19 tissue, or cell culture systems; or a combination of
20 these. We can also rely on non-biological analytical

1 assays which are methods that measure immunochemical,
2 molecular, or biochemical properties of the product
3 outside of living systems. We refer to these as
4 surrogate measurements. These surrogate measurements
5 can be substantiated by correlation to relevant
6 product-specific biological activities.

7 If one assay is not sufficient, a matrix
8 approach including multiple complementary assays that
9 measure different product attributes associated with
10 quality, consistency, and stability may be used. The
11 collection of assays, or matrix, generally consist of
12 biological assays, biological analytical assays, or
13 analytical assays alone. However, analytical potency
14 assays may be used if surrogate measurements of
15 immunochemical, biochemical, and/or molecular
16 attributes of the product can be substantiated by
17 correlation to a relevant product, specific biological
18 activities.

19 Potency assays used under these conditions
20 should be sufficiently robust, in terms of

1 reproducibility and as indicators of product quality
2 and product stability. For allogeneic cadavers islet
3 products, we recognize that biological assays measuring
4 islet function may not be rapid enough to use in
5 routine lot released testing. However, we continue to
6 encourage developers of islet products to explore the
7 development of rapid analytical methods that correlate
8 to well-established biologic assays.

9 Based on the above definitions of potency and
10 to apply those to donislecel, all lots of donislecel
11 were tested for sterility using well-established tests.
12 Further, donislecel lots are subjected to
13 specifications designed to assure at least 30 percent
14 islet purity. In addition to measuring the product
15 purity attributes, a DTZ staining was used for identity
16 testing and to enumerate islets also referred to as
17 yield. The DZT stained islets are counted using a
18 calibrated grid in the eyepiece of a microscope.

19 The results of this assay are used to
20 calculate the dose based on the equivalent islet number

1 that was eluded to in the previous talk. An islet
2 equivalent is equal to the volume of the islet with
3 about a 150-micron diameter, which is determined using
4 well-established conversion factors.

5 Viability is measured using SYTO 13. Potency,
6 as mentioned before, is measured by glucose stimulation
7 index.

8 In this BLA, the potency matrix includes
9 islet's yield, viability, and insulin-producing ability
10 of beta cells by evaluation of insulin secretion under
11 a high glucose stimulation as compared to no glucose
12 stimulation. However, the assessment of purity can
13 also be included in the potency assay matrix given that
14 the purity and potency are sometimes interrelated. For
15 example, achieving a certain level of purity of the
16 desired cell population may be necessary to achieve the
17 specified potency assay threshold.

18 So how does this actually play into the
19 mechanism of action in the context of purity and
20 potency? As we know, the applicant has implemented the

1 DTZ stain as discussed previously for identity, yield,
2 and purity. Shown here in Panel A, the DTZ stain of
3 human islets, this stain is specific for beta cells.
4 However, islets are composed of multiple cell types,
5 including other endocrine cells. And to reiterate, the
6 endocrine cells, or islets, make up only five percent
7 of the pancreatic tissue.

8 In Panel B, the schematic shows a high-level
9 view of how all islets and their respective secreted
10 hormones regulate each other and help maintain glucose
11 levels within the normal range, through a highly
12 regulated manner in response to increases and decreases
13 in blood glucose. The open arrows in this schematic
14 show the flow of blood through the islets. Given the
15 mechanism of action as shown on the right, controlling
16 the composition of the product is crucial to
17 maintaining consistent product quality.

18 Although use of DTZ staining of beta cells is
19 consistent with the hypothesized mechanism of action of
20 hormone-secreting activity, this approach does not

1 evaluate the contribution of other cells present in the
2 islet. It's not clear whether the same ratio of
3 exocrine to endocrine tissue that is present in a
4 healthy pancreas is maintained in donislecel because
5 the applicant has not evaluated the other cell types.

6 So how does this relate to the applicant's
7 product manufacturing experience? This slide shows the
8 product lots manufactured to support the applicant's
9 clinical trials. There were two main trials that the
10 applicant conducted to support this BLA. The details
11 of the clinical trials will be presented this afternoon
12 in the afternoon session by Dr. Patricia Beaston.

13 The first clinical study was a Phase 1-2 proof
14 of concept study called UIH-001, and the second
15 clinical trial was UIH-002, the applicant's Phase 3
16 pivotal study. Shown here are the subjects in each
17 trial and the number of transplants or doses a subject
18 received and the total doses of product lots
19 manufactured for each trial. In each trial, subjects
20 received one, two, or three doses of donislecel. Each

1 dose or transplant is from a different cadaveric donor
2 pancreas.

3 There is lot-to-lot variability due to
4 starting material differences. Additionally,
5 variability in product quality attributes measured make
6 it difficult to predict or correlate product attributes
7 to the proposed clinical outcome. The issue of
8 reliable prediction of biological activity is
9 particularly challenging for allogeneic cadaveric islet
10 products.

11 The challenge is the evaluation of data. The
12 applicant's manufacturing experience reveals
13 substantial variability among the 56 donislecel lots
14 manufactured to support Study 1 and Study 2. In this
15 graph, the islet yield, shown in blue bars, for each
16 donislecel lot is shown along with the corresponding
17 purity percentage, shown in the red line. The black
18 line shows the minimum specification for purity which
19 is 30 percent.

20 From the perspective of assuring islet purity,

1 the applicant's specification of greater than 30
2 percent islet purity using a stain specific for beta
3 cells permits 70 percent non-beta cells. Owing to the
4 technical limitation of DTZ staining, purity may be
5 overestimated by 20 to 30 percent. The applicant has
6 acknowledged that they cannot rule out overestimating
7 the precise purity of the final product using the
8 current method, which probably has implications to dose
9 that is delivered to the subject.

10 The applicant further states that, if the
11 purity percentage is overestimated, then the doses they
12 require would also be higher than the actual islet
13 number. Thus, the higher islet number required for
14 transplant would offset the potential overestimation.
15 Irrespective, the accuracy of the DTZ staining method
16 remains a question because it is not clear whether the
17 overestimation is by a constant factor. And the
18 applicant does not assure that the cells present in the
19 final product are present in similar ratios as a
20 healthy human islet.

1 This slide shows the potency of the 56
2 clinical donislecel lots manufactured to support both
3 clinical trials. In this graph, the islet yield is
4 shown in blue bars. Each donislecel lot is shown, and
5 along with it is the corresponding purity. Potency
6 measure is shown in the red line. The range for GSI is
7 from 0.4 to 11.3.

8 The black line shows the minimum specification
9 for GSI, which is one. Although the quality
10 measurement used by the applicant is consistent with
11 the hormone-producing properties of beta cells, these
12 attributes may not fully capture the crucial biological
13 heterogeneity in islets. The potency assay evaluating
14 glucose-stimulated insulin secretion has not been shown
15 to correlate to clinical outcomes.

16 Further, based on the lots given to the
17 subject, there does not seem to be apparent differences
18 in the mean value of the product given to responders or
19 non-responders. And further, there is even variability
20 between lots given to subjects who received multiple

1 doses.

2 In conclusion, considering the available data,
3 FDA's position is, while the CQAs identified by the
4 applicant and controlled in the product by in vitro lot
5 release assays may have some value in assuring
6 consistent manufacturing process, these CQAs may not be
7 adequate to ensure the quality of the product that will
8 be provided to patients and may not represent the
9 specific ability or capacity of the product to deliver
10 a given effect.

11 Finally, I would like to acknowledge my fellow
12 CMC experts and our clinician, Dr. Beaston, our office
13 leadership and regulatory project manager, CBER AC
14 staff for their assistance with this presentation. I'd
15 also want to thank our special government employees and
16 Advisory Committee Panel for their participation today.
17 We look forward to a meaningful discussion and to your
18 valuable comments. Thank you.

19

1 **CMC CLARIFYING QUESTIONS TO PRESENTERS**

2

3 **DR. LISA BUTTERFIELD:** Thank you very much.
4 So we're now moving to a period of time for clarifying
5 questions from both our FDA and sponsored presenters.
6 So I'm watching for your raised hands, and let's move
7 first to Dr. Morrison for your question.

8 **DR. SEAN MORRISON:** Thanks, Dr. Butterfield.
9 I have a few focus questions for the sponsors. The
10 first is, is there a compelling reason not to
11 quantitate alpha, delta, and epsilon cells in the
12 release product?

13 **DR. JOSE OBERHOLZER:** This is Jose
14 Oberholzer. Our main limitation is the time available
15 from, you know, finishing the islet preparation and
16 transplantation. So, while in the research context, we
17 do, of course, analyze the cell composition with
18 immunohistochemistry. We haven't found a good
19 methodology that would be real-time and be
20 accomplished. In addition, the question would be, what

1 would be the consequence from that?

2 And the reality is that we really do not know
3 what an ideal islet cell composition would look like.
4 And when we take, for example, histology of human
5 pancreases, there is significant variability, and
6 still, those pancreases regulated the patients to
7 achieve normal glycemia. So I think that that will be
8 certainly very important to understand for the future
9 when, for example, stem cell-derived islets will enter
10 the field and where the composition really would be
11 important.

12 For us, taking the pancreas from a donor that
13 was screened for the absence of T1D, to the normal
14 hemoglobin, A1C eight and under, normal glycemia eight
15 and under, so having all those clinical attributes
16 indicates that the pancreas has a normal physiology in
17 that donor. And so we have to make the assumption that
18 those islets are going to work the same way as we do
19 pancreas transplants where we accept an organ donor
20 based on the clinical attributes and then transplant

1 without any further tests.

2 **DR. SEAN MORRISON:** And I assume we're --

3 **DR. JOSE OBERHOLZER:** Mm-hmm.

4 **DR. SEAN MORRISON:** I assume it's the same
5 rationale for why you don't assay the cellular
6 composition of the cell clusters that don't contain
7 beta cells, the contaminating clusters.

8 **DR. JOSE OBERHOLZER:** That's correct.

9 Actually, I hope I'm not going too far to the
10 sidelines, but this is actually a very interesting
11 question: what happens to the exocrine tissue? So
12 there is a much larger (inaudible) on autologous islet
13 cell transplant. So that's a situation where patients
14 have pancreatitis, and the clinicians decide to do a
15 total pancreatectomy and reinject their own islets.

16 And those preparations mostly are not purified
17 at all. And interestingly, if you do a liver biopsy in
18 those patients a few months later, or a year let's say,
19 for a patient who needs another procedure and allows
20 you to take a biopsy, we do not see any of the exocrine

1 tissue survive in the liver biopsy. We do not
2 understand why that is, but we have reproduced that.

3 And we have also done liver biopsies in
4 patients who received allogeneic islets, and the same
5 (inaudible). They only find the endocrine part of the
6 preparation that was injected, but we cannot identify
7 any exocrine tissue of the -- in biopsies that were
8 done of the transplant.

9 **DR. SEAN MORRISON:** Have you ever looked at
10 whether your product contains infiltrating donor immune
11 cells -- myeloid, lymphoid -- if you had a donor with a
12 low level of pancreatitis, would you know?

13 **DR. JOSE OBERHOLZER:** So we would know that.
14 So we would know that for medical history base of
15 course. We have laboratory -- we always have amylase,
16 lipase in the donor before we would accept, and then
17 there's the visual inspection of the surgeon. So when
18 the procurement surgeon goes out, we will typically get
19 a call with a description of how the pancreas looks
20 like, and then, of course, we have the visual

1 inspection when the pancreas arrives.

2 And so in pancreatitis, you would typically
3 see little white spots, fat necrosis, and so on. And
4 in such a situation we would normally not proceed.

5 **DR. SEAN MORRISON:** Last question.

6 **DR. LISA BUTTERFIELD:** Very short question.

7 **DR. SEAN MORRISON:** A really short question,
8 my understanding is that there's no HLA matching and no
9 blood group antigen matching. Is that right?

10 **DR. JOSE OBERHOLZER:** So we do blood group
11 matching, the UNOS requirement. I think it makes sense
12 because there are surely endothelial cells in an islet
13 preparation, but we do, unfortunately, not do HLA
14 matching. And that's just a probability issue because
15 the patient population is so small, the donor
16 population is so small. It will probably be meaningful
17 to do it, but just the probability that it really could
18 change the outcome with matching is very, very small.
19 Excellent question.

20 **DR. LISA BUTTERFIELD:** Thank you. Dr.

1 Hawkins, please, your question.

2 **DR. RANDY HAWKINS:** This is a question of
3 product availability and thanks again. Can you give us
4 some idea of the number of islet transmissions that
5 would be available (inaudible) and the impacts on the
6 entire organ transplants available?

7 **DR. JOSE OBERHOLZER:** Yes. So that's a very
8 good and practical question. We have studied the
9 registry data and asked the question, are we going to
10 take away organs from whole pancreas transplants, and
11 the answer is no. Because the criteria to accept
12 organs for an islet isolation are a little bit wider in
13 terms of the donor's biology in terms of age, body
14 weight, and so on.

15 A typical example would be a 50- or 55-year-
16 old organ donor who is overweight would not be accepted
17 for whole pancreas transplantation because there's a
18 high risk of complications with pancreatitis afterward.
19 But that will be a very acceptable organ donor for
20 islet isolation.

1 So just doing a very, very quick numbers game
2 here so that there are probably somewhere around 3,
3 4,000 organ donors that potentially could be suitable
4 for islets in the U.S. And of those, about 1,500 would
5 go to pancreas transplantation preferential, but there
6 is an allocation algorithm by UNOS that the organs that
7 are specifically good for whole pancreas will go to
8 whole pancreas, and then the ones that are either not
9 accepted or are outside those criteria, they will be
10 allocated for islet cell transplant.

11 **DR. LISA BUTTERFIELD:** Thank you. Dr. Opara.

12 **DR. EMMANUEL OPARA:** Okay. Yes. So again,
13 this question is for the sponsors. I have a couple of
14 questions. The first one is the 30 percent purity
15 that, you know, you've accepted for product release.
16 Is that based on dithizone of the other staining that
17 is more sensitive, you know, than the DTZ?

18 And I understand that on some reason that
19 you're setting, you know, the bar that low to 30
20 percent because of the presence of, you know, islets in

1 the other fractions when you collect them. But is
2 there any particular reason why you think that 30
3 percent is very good?

4 And then the other question is, have you tried
5 to explore the relationship between glucose stimulation
6 index in vitro pre-transplants with, you know, maybe
7 another functional assay like oxygen consumption, which
8 is pretty, you know, rapid to measure?

9 Since we do know that, while GSI does not
10 correlate very well with clinical outcomes, again, as
11 we heard from Dr. Papas, it appears that oxygen
12 consumption may be a, you know, better index, you know?
13 So those are my questions.

14 **DR. JOSE OBERHOLZER:** And thank you, Dr.
15 Opara, and good seeing you again. So that purity is
16 estimated by dithizone staining. And, of course, a
17 more precise way would be to do histology, you know, to
18 take a palliative volume and then to cross-section.
19 The time is too short to do that.

20 Now, in terms of having other insulin assays

1 or potency assays, that the difficulty is the
2 correlation to a clinical outcome would require a
3 significantly larger number of patients than we were
4 able to enroll on the trial condition for a number of
5 reasons: cost, and other aspects. And you know that
6 our group has been working out for many years on
7 microfluidic assays. We have established microfluidic
8 assays with oxygen controls, we published on our gas
9 permeable microperfusion assays, and that's certainly
10 something we will continue to do.

11 We have been funded by NIH to do that, and
12 it's something that we surely must do in a hopefully
13 post-marketing period where we hope to have a
14 significantly large number of patients to study exactly
15 those questions.

16 I think I agree with Dr. Papas and with the
17 Agency, there is really a big need for the future to
18 have tests like this. Also as stem cells enter the
19 field, they will also need an adequate assay before a
20 lot can be present. But what we have been showing is,

1 I think, the best that can be done with the current
2 available technology.

3 **DR. LISA BUTTERFIELD:** Thank you. So short
4 answer, short questions please to finish up, Dr. Zaia.

5 **DR. JOHN ZAIA:** Just a question for Dr.
6 Oberholzer. Tell us about how you determine the high-,
7 medium-, and the low-dose islets and how they differ
8 physiologically in terms of glucose stimulation index
9 or even oxygen consumption.

10 **DR. JOSE OBERHOLZER:** So the differentiation
11 is done visually by dithizone stain, and then we
12 estimate the number of islets compared to the number of
13 non-islet tissue. And the assay of, you know, looking
14 at islet cells from high fraction or low fraction has
15 to be done by hand-picking the islets out of the
16 preparations, and then we actually don't see a
17 difference in the count. If you want to do an assay
18 out of a sample that contains exocrine tissue, it
19 disturbs the assays very dramatically because the
20 exocrine tissue releases enzymes that will break down

1 the insulin rapidly.

2 That's the main reason we do not do the
3 insulin secretion assays in the less pure fraction.
4 It's just a very unreliable test. And then, of course,
5 if you handpick, then you will have the selection bias
6 of the person doing the test, and that's why we are not
7 doing -- we only analyze the function of the purest
8 fraction.

9 **DR. JOHN ZAIA:** I think about the question is
10 the --

11 **DR. LISA BUTTERFIELD:** We've only got three
12 more minutes, so thank you, Dr. Zaia, we're going to
13 have to move to Dr. Harlan.

14 **DR. DAVID HARLAN:** Good morning, Dr.
15 Oberholzer. Nice to see you.

16 **DR. JOSE OBERHOLZER:** Good seeing you.

17 **DR. DAVID HARLAN:** You shared that 66 percent
18 of your 30 patients were insulin independent at one
19 year. Would you share how many of those recipients
20 received islets from one donor versus more than one

1 donor?

2 **DR. JOSE OBERHOLZER:** Yeah. To make the
3 answer short, I will show that this afternoon. We will
4 show you the individual patients.

5 **DR. DAVID HARLAN:** Okay.

6 **DR. LISA BUTTERFIELD:** Thank you. Dr. Nichol.

7 **DR. GEOFFREY NICHOL:** Yes, I'll ask my earlier
8 question to the right person. Dr. Oberholzer, could
9 you comment on the conversations you've had with OTAT
10 as you've moved forward in development concerning these
11 CMC questions, and comment perhaps on the nature and
12 value of those discussions?

13 **DR. JOSE OBERHOLZER:** Well, it has been a long
14 journey, and I think it's fair to say that we both, the
15 Agency and ours, have been learning along this. And
16 it's always the question between what we have ideally
17 and what is practically possible with the limited
18 organs available. So many questions we have is
19 difficult to answer because it's a human that donates
20 an organ and, you know, it's always an ethical

1 question, how much can you use for pure research
2 purposes? So that's a limitation. But our hope is
3 that as this hopefully becomes approved that the number
4 of patients would be higher and that many of those
5 questions could be addressed in a more meaningful way.

6 **DR. LISA BUTTERFIELD:** Thank you. Let's see
7 if we can get two more questions in. Dr. Breuer.

8 **DR. CHRISTOPHER BREUER:** I have a question for
9 the Agency and a question for the sponsor and they're
10 related. My question to the Agency is, given the
11 nature of the product and the critical role of time
12 which limits the release testing, what is the role of
13 post-process monitoring?

14 **DR. LISA BUTTERFIELD:** I think we've got
15 someone who should be on mute who's not presenting
16 right now.

17 **MR. MIKE KACZYNSKI:** Yep. I just took care of
18 it.

19 **DR. LISA BUTTERFIELD:** Sorry. Dr. Breuer
20 again.

1 **DR. CHRISTOPHER BREUER:** Yeah. Sorry. Just
2 to reiterate quickly, to the Agency, what is the role
3 of post-process monitoring given that there's a limited
4 time to allow for release testing? And the follow-up
5 question to the sponsor is, are you doing any post-
6 process monitoring? Thank you.

7 **DR. SUKHANYA JAYACHANDRA:** Thank you for that
8 question. We understand that there is, you know,
9 limitations because of the time from when the product
10 is released to transplant. However, there is a period
11 of 24 to 48 hours where cells are in culture where some
12 of the, you know, more easier or more rapid analytical
13 methods could be used for further product
14 characterization that could aid from, you know, lot-to-
15 lot consistency.

16 We do understand the challenges faced by cell
17 therapy products that it's not specifically to this
18 kind of product or to this kind of -- the islet
19 products specifically, but across the board. You know,
20 we do understand the challenges, and we are just

1 looking for lot-to-lot consistency. And are there
2 other assays that could be used which we are trying to
3 get from, you know, the experts on the Panel today?

4 **DR. JOSE OBERHOLZER:** So, to answer the
5 question addressed to me, so we do testing and follow-
6 up even after transplantation, most importantly for
7 safety. So there are bacteria and fungal cultures done
8 that in case this would ever come back positive, of
9 course, we're looking for the clinician and discuss the
10 treatment of the patient. Does that answer your
11 question then?

12 **DR. LISA BUTTERFIELD:** Thank you.

13 **DR. CHRISTOPHER BREUER:** Do you do any potency
14 or purity measurable, non-release, but post-process
15 monitoring testing? For example, like a nude mouse
16 test?

17 **DR. JOSE OBERHOLZER:** So, in the initial
18 trials, we did this actually probably in about 20 lots
19 we did data. But, because it really didn't have
20 consequences for afterward, we dropped that. It's

1 quite involved. You know, you use animals, and it
2 really didn't have a consequence for patient care. It
3 would be something that we surely would be open to use
4 in validating a new assay for potency.

5 **DR. LISA BUTTERFIELD:** Thank you for that
6 clarification. So let's have one final question before
7 we move to the Committee discussion from Dr. Wu.

8 **DR. JOSEPH WU:** Yes. So I was wondering if
9 your potency assays are negatively affected by the age
10 of the donor when the donors die, and also whether the
11 potency assay's negatively affected by the harvest time
12 between the patient death to organ harvest and then the
13 cell isolation.

14 **DR. JOSE OBERHOLZER:** Yes. So your last point
15 is an important one. So, if you go beyond a certain
16 amount of ischemia, it negatively affects everything.
17 It affects the purity because of cell swelling, it
18 affects the viability, and it affects the function. So
19 that's why we have to set a time limit and, you know,
20 that probably starts going down around 10 hours after

1 ischemia, but can still be acceptable up to, you know,
2 14, 15, 16 hours.

3 **DR. JOSEPH WU:** Thank you.

4 **DR. JOSE OBERHOLZER:** And then the age
5 variable, again, it's a problem to do correlation on so
6 small numbers. We have tried to do many correlations
7 to donor characteristics and describe, you know, of
8 course, that would allow you to better select the
9 donor. So those things are available, being used.

10 **DR. LISA BUTTERFIELD:** All right. That
11 concludes the clarifying questions. So now let's move
12 to the Advisory Committee CMC questions for discussion.

13

14 **CMC QUESTIONS TO THE COMMITTEE/COMMITTEE DISCUSSION**

15

16 **DR. LISA BUTTERFIELD:** We have two questions.
17 I'll read those questions aloud, and then we have
18 primary and secondary discussants to initiate the
19 discussions. So you see discussion question one on the
20 CMC with three parts.

1 What is the contribution of the endocrine,
2 exocrine, or other cell types expected to be in the
3 final product? How might the relative proportions of
4 those other cell types play a role in the clinical
5 outcomes and potency? And what are the specific types
6 of non-beta cells that the applicant should
7 characterize or possibly control for in the product?
8 And so our primary discussant on this is Dr. Opara,
9 please.

10 **DR. EMMANUEL OPARA:** Okay. Right. So it is
11 certainly interesting that, you know, during the
12 discussions, I mean, during the presentations, you
13 know, most of the issues raised, especially as it
14 related to purity, you know, it's focused on exocrine,
15 you know, acinar cells and the endocrine cells. You
16 know, at least when I read these questions that were
17 posed by the FDA, it really got me thinking a lot, as
18 I'm sure it also got the Committee members thinking.

19 So we do know that there are other cell types
20 that possibly present in the product, the pancreatic

1 ductal cells for instance. And I mention these because
2 they have significant potential to affect the outcome
3 of, you know, the transplantation. You know, ductal
4 cells have been shown in vitro, although somewhat
5 controversial yet, to differentiate into beta cells.

6 And we also know that ductal cells can induce
7 early damage to cells when they contaminate the product
8 through the involvement in tissue (inaudible)
9 inflammatory events. So I think it would be really
10 nice if there is some mechanism or some way to have the
11 presence of ductal cells, you know, documented. What
12 proportion, you know, of those cells are present in the
13 -- in a given lot, and then see how that varies.

14 The other cell type that I would mention would
15 be stromal cells, mesenchymal stromal cells. We do
16 know that (inaudible) fiberglass can, you know,
17 differentiate into mesenchymal stromal cells, which in
18 turn themselves can differentiate to insulin-producing
19 cells. Although again, that appears to be something
20 that has been shown more in in vivo situation than in

1 vitro.

2 So in vivo, if you do a transplant that has
3 significant contamination with these cells, again they
4 could affect the outcome. Although they could
5 contribute in a positive way to the clinical outcome
6 but again, it will -- that would mean that there would
7 be a lot of variation in the clinical outcome.

8 So these are my thoughts as I initiate the
9 discussion in this area, and then I would welcome the
10 comments of the other Committee members.

11 **DR. LISA BUTTERFIELD:** Thank you, Dr. Opara.
12 Dr. Goldstein.

13 **DR. LAWRENCE GOLDSTEIN:** Okay. Thank you, Dr.
14 Butterfield. I think that my own thinking on this set
15 of issues parallels the issues raised by FDA staff, by
16 Dr. Morrison, and others. So I think in answer to
17 question 1A here, the assumption is that it's the
18 endocrine cells that are the final arbiters of potency.
19 I have to say, looking at the data from the various
20 transplant lots, I am troubled by the degree of

1 variability. That doesn't seem to be well controlled,
2 and I think that translates directly to the amount of
3 endocrine cells transplanted.

4 For 1B, I -- and for 1C, these are sort of the
5 same issues. There is, in my mind, a substantial
6 reason to think that the contributions of non-beta
7 cells to the outcome may be particularly critical in
8 brittle type 1 diabetics where, you know, a reasonable
9 possibility is that it's the absence of some of those
10 other cell types that may be important to the brittle
11 behavior of those folks.

12 So I have to say that if I were allowed to
13 say, or ask for retrospective data, I would love to
14 know if analyzed retrospectively following transplant,
15 if one had a sample of messenger RNA from the isolated
16 fractions and one could look to see whether expression
17 of non-beta cell hormones was determinative of the
18 outcome in the patients. And it would be interesting
19 to know that.

20 Similarly, UNOS must have very good tissue

1 typing that is potentially available to the sponsor.
2 And similarly, it would be good to know, what is the
3 degree of HLA and other antigen matching to the
4 recipients and is that somehow determinative of the
5 final outcome. Thank you.

6 **DR. LISA BUTTERFIELD:** All right. Thank you
7 very much for that. So for these first series of CMC
8 discussions for the overall Question 1, this is now
9 open to the rest of the Committee, and I will look for
10 you to raise your hands. Dr. Harlan, please.

11 **DR. DAVID HARLAN:** Yeah. I just have several
12 comments. One is, we heard from Dr. Papas, I thought,
13 that using the nude mouse model that the beta-cell
14 constituents of the prep did influence or did predict
15 outcome. And there are assays now, flow-based assays
16 that can be done within six hours on a small aliquot of
17 the islets to determine the cellular proportion of the
18 islet prep. And we've published on that, and we've
19 correlated it with the immunohistology. So a fairly
20 quick flow-based assay can tell you what proportion of

1 an islet prep is alpha cells, beta cells, delta cells,
2 et cetera.

3 The other general comment I have is that when
4 the subject came up about autotransplants and isolating
5 or digesting the pancreas of a patient with chronic
6 pancreatitis and infusing the whole cellular mix, it
7 must be stated that patients with chronic pancreatitis
8 don't have pancreases that weigh with a volume of 100
9 mills but more like 20 or 30 mills because, with
10 chronic pancreatitis, the acinar tissue degenerates.
11 So there's not nearly as much tissue that's implanted.
12 So those are my comments.

13 **DR. LISA BUTTERFIELD:** Thank you. Dr.
14 Morrison.

15 **DR. SEAN MORRISON:** Yeah. I'd like to
16 strongly agree with the comments from Dr. Harlan and
17 Dr. Goldstein that it should be a straightforward
18 matter to set up flow-cytometric assays to assess the
19 cellular composition of the product while the product
20 is in culture. And even if it's not possible to do

1 that prior to release of the product, collecting that
2 data retrospectively to determine whether differences
3 in cellular composition correlate with differences in
4 outcome will be important to do because it's limited
5 data now.

6 And I think, not only the alpha cells and beta
7 cells and epsilon cells, but also the non-islet cell
8 clusters, and what is their cellular composition, and
9 is there infiltration by immune cells? It should be
10 possible to run relatively quick flow-cytometric assays
11 to determine those things.

12 The last point that I want to make is that in
13 Dr. Jayachandra's comments and the way the FDA comments
14 were written, I think there's a little bit of
15 confusion. The 30 percent number is sometimes
16 described as 30 percent of cells being beta cells. But
17 my impression is that what it really means is that 30
18 percent of cell clusters contain beta cells. And I
19 think it would be helpful, for me at least, if we can
20 have clarity on that point, and what the 30 percent

1 means, and what the denominator is. Thank you.

2 **DR. LISA BUTTERFIELD:** Thank you. Do we have
3 someone from the Agency who would like to respond at
4 this time? Okay. I'm not seeing. So let me give some
5 time up. Thank you, Dr. Jayachandra. We can't hear
6 you.

7 **DR. SUKHANYA JAYACHANDRA:** Sorry. I was on
8 double mute. So the 30 percent is the cells that are
9 from the top fraction that were taken. So it is all of
10 the cells that are given to the patient. So that is
11 the minimum cutoff but, you know, that's the purity
12 specification. It's based on the DTZ staining. I
13 would also ask CellTrans to clarify a little bit more.

14 **DR. LISA BUTTERFIELD:** Yes. Dr. Oberholzer.

15 **DR. JOSE OBERHOLZER:** The 30 percent refers to
16 the number of islets. So let's say if you would have
17 one milliliter of tissue volume, then 0.3 would
18 correspond to the islets, and that's from the final
19 preparation that goes into it. That's achieved by
20 mixing the top layers with -- that has the highest

1 purity with less pure fractions to maximize the number
2 of islets to keep the volume below ten milliliters
3 total. Does that answer the question?

4 **DR. LISA BUTTERFIELD:** Thanks for that
5 clarification.

6 **DR. SEAN MORRISON:** So therefore it's 30
7 percent then of islet equivalents that contain beta
8 cells, not 30 percent of cells that are beta cells?

9 **DR. JOSE OBERHOLZER:** Correct.

10 **DR. SEAN MORRISON:** Thank you.

11 **DR. LISA BUTTERFIELD:** All right. Thank you
12 both. Let's move to Dr. Harlan next, and then Dr.
13 Nichol.

14 **DR. DAVID HARLAN:** I just want to comment on
15 what Dr. Goldstein asked earlier, and I'm sure Dr.
16 Oberholzer would agree with this. Even in whole
17 pancreas transplant, the numbers are so small that HLA
18 matching between donor and recipient is just not done.
19 And it's even more complicated with islet transplant
20 because recipients need islets very often from more

1 than one donor. So you couldn't do the statistics to
2 know whether the degree of matching had any effect on
3 survival. It's just statistically not practical.

4 **DR. LISA BUTTERFIELD:** Thank you for that
5 clarification, Dr. Harlan. Dr. Nichol, a statement on
6 behalf of industry regarding the CMC questions?

7 **DR. GEOFFREY NICHOL:** Yes. Thank you very
8 much, Dr. Butterfield. I've taken soundings from
9 industry groups who are involved in cell and gene
10 therapy, and I just clearly cannot comment on the
11 specific technical issues here, but they do reflect
12 some broader issues that affect the whole field and the
13 industry. We certainly commend the FDA for recognizing
14 -- well, first of all for holding this Advisory
15 Committee on these maybe not seemingly narrowed
16 technical issues, but still important issues broadly
17 for the field, and for recognizing that while much is
18 known, not everything is yet knowable about what
19 product attributes are clinically important nor how the
20 can be or should be measured.

1 In addition, patients can show marked
2 variability in their responses to the same lot of cell
3 or gene therapy product.

4 I'd just like to say that industry stands
5 ready to invest to close this gap, this knowledge gap
6 that wants to engage with CBER, OTAT, patients, and
7 academia in what we see as a virtuous cycle where it
8 involves firstly being open, detailed, and proactive
9 communication with FDA on CMC issues during development
10 with a view of avoiding new and unexpected issues
11 arising during a review. Challenging therapy sponsors
12 are reporting difficulty receiving timely and
13 consistent responses to CMC questions during
14 development.

15 Second, we recommend a focus on patient
16 benefit/risk as the primary driver for approval and
17 avoidance, if possible, of CMC issues becoming the
18 rate-limiting step in development and approval. In
19 this regard, we encourage the use of post-approval CMC
20 commitments as a pragmatic approach to achieve this.

1 And third and finally, a commitment to joint
2 work to agree and codify best practices, best CMC
3 practices as was done a generation ago for monoclonal
4 antibodies and other biologics.

5 I just wanted to make this statement as the
6 voting members of the Committee consider their
7 positions on some of the questions that are being
8 posed. Thank you very much.

9 **DR. LISA BUTTERFIELD:** Much appreciated, Dr.
10 Nichol. So then let's move to Dr. Breuer still about
11 CMC discussion Question 1 and its parts.

12 **DR. CHRISTOPHER BREUER:** Two general comments.
13 One is regarding variability, given the small n, the
14 variability doesn't surprise me at all, especially
15 given the complexity of the product. Not only is there
16 variability within the product between the donor and
17 the recipient, but one thing we haven't touched on is
18 engraftment, which adds a whole other confounding
19 factor. What strikes me is what was said by the Agency
20 at the beginning of this presentation, is that I think

1 we've got an incredible biologic readout that we've got
2 a product where two-thirds of the patients are insulin
3 free after one year. And sometimes the enemy of good
4 is better.

5 **DR. LISA BUTTERFIELD:** All right. So those
6 are the hands that were raised for CMC Question 1. So
7 let's move to CMC Question 2, please, and here you see
8 it.

9 Are the product quality attributes of purity
10 and potency sufficient to evaluate lot-to-lot
11 consistency? And, if not, what additional product
12 characteristics not previously identified would provide
13 more meaningful measures? So here we start for the
14 discussion, Dr. Opara, please.

15 **DR. EMMANUEL OPARA:** Okay. So, in my opinion,
16 I would think that, and especially with the
17 availability of the rapid, you know, (inaudible)
18 assays, that it may be necessary to have some
19 additional, you know, assays that really defines the
20 endocrine cells, the proportion of endocrine cells, and

1 then a proportion of these are the non-endocrine cells
2 that we've mentioned at the start of this discussion.
3 Because I think that would probably in some way
4 contribute to, you know, narrowing the variability that
5 we see, you know, after transplantation.

6 **DR. LISA BUTTERFIELD:** Okay. Thank you very
7 much. Dr. Goldstein.

8 **DR. LAWRENCE GOLDSTEIN:** Yes. Thank you, Dr.
9 Butterfield. Question 1A in some way harkens -- sorry,
10 Question 2a in some ways harkens back to the discussion
11 we had about Questions 1A through C, which is, does
12 apparent purity and beta-cell contribution in the final
13 product adequately evaluate the potency of that
14 product? And I have to say, I think we just don't
15 know, ultimately.

16 You know, Dr. Morrison pointed out that there
17 may be useful flow assays. I think that there are a
18 variety of retrospective assays that could be done to
19 find out whether the different cell types present in
20 the final product adequately predicted potency and

1 long-term behavior of the patients.

2 Similarly, I do understand that HLA typing
3 prior to transplant may not be feasible. I don't see
4 any particular reason why HLA typing retrospectively of
5 donor and recipient might not be useful information to
6 obtain, but we can discuss that in one of the afternoon
7 sessions. Thank you.

8 **DR. LISA BUTTERFIELD:** Thank you. And now,
9 Dr. Naziruddin, please.

10 **DR. BASHOO NAZIRUDDIN:** Thank you for letting
11 me comment on this. Based on the data provided by the
12 sponsor and also provided by the Committee that there
13 is a lot of heterogeneity when it comes to product
14 (inaudible), so it's extremely hard to have kind of a
15 uniform large release particularly maintaining the
16 consistency between lot and lot. For example, the
17 glucose stimulating insulin release assay submitted by
18 the applicant shows the glucose stimulating insulin
19 release of an index of below 1 in one preparation, 11
20 in the other.

1 Then they have some in terms of viability and
2 even purity that is so much variation. And that could
3 be attributed to operator-dependent manners that these
4 are estimated, particularly the purity could be
5 overestimated by 20 percent, that's also very
6 important.

7 And in terms of what else can be done,
8 particularly when you understand the nature of the
9 organs in terms of the donor, the cold ischemia, the
10 enzyme lot that is used, and the enzyme that is used to
11 report those use isolated, it's all different.

12 So to have it consistent lot-to-lot
13 similarities is extremely difficult. So, with that in
14 mind, the applicant can introduce other assays like,
15 for example, in 19' - -- 2015 the (inaudible) paper
16 published in American Journal of Transplantation by
17 E.G. et. al (phonetic), they used an excellent estimate
18 of not only the function of the islet in terms of
19 glucose stimulant (inaudible) but also in terms of the
20 composition of the islet. It can be done within 24

1 hours, and the sponsor can (inaudible) that. And also
2 the oxygen consumption rate very nicely aggregated by
3 Dr. Papas can also be introduced. That's my comment.

4 **DR. LISA BUTTERFIELD:** Terrific. Thank you
5 very much. So those are the three primary discussants,
6 and now this is open to the Committee to discuss the
7 CMC Question Number 2. So looking at the hands that
8 are raised, Dr. Feng, please.

9 **DR. SANDY FENG:** Thank you. Let me turn on my
10 camera as I speak. So just in looking at the data that
11 was presented, I'm struck by the slides that were shown
12 related to islet dose response and the achievement of
13 the primary endpoint for the clinical trials, and the
14 islet independence frequency. I think that this islet
15 dose response appears to be a conglomerate or a
16 composite of several of the assays.

17 And I wonder if this parameter could be
18 discussed further as something to gauge the purity and
19 the potency of the product. I think it's very
20 important to minimize the number of transplants that

1 are required to achieve islet independence because the
2 multiple donors, as has been mentioned in the past,
3 introduced different HLA.

4 Currently, just to dispel some of the
5 discussion about HLA, the donor is typed at a high
6 level of resolution in 2021, and the recipients can of
7 course readily be typed. However, current
8 immunosuppression, certainly for organs like kidney
9 transplants, current immunosuppression has overcome a
10 large amount of the benefit associated with better
11 matching such that the only really bang for your buck
12 with matching is if you have a perfectly matched, or
13 very highly matched donor/recipient pair, which is, of
14 course, not realistic.

15 I think the importance to minimize the number
16 of donors is also related to the fact that once the
17 islet product stops working, and we're only talking
18 about one year of islet independence, you know, what
19 happens at three years and five years?

20 As people are weaned off of the

1 immunosuppression that they may no longer benefit from,
2 if the product is working poorly, there is clear data
3 that you become sensitized to the HLA of the donor.
4 And remember, these are type 1 diabetics who are at
5 high risk of renal insufficiency, chronic kidney
6 disease, and need for kidney transplant down the line,
7 and sensitizing people to donor HLA antigens through
8 multiple islet donors to achieve a product is a
9 concern, obviously, for their future transplantability
10 if they were to need a kidney transplant down the road.
11 So again, I wanted to ask a question about this islet
12 dose response as a parameter. Thank you.

13 **DR. LISA BUTTERFIELD:** All right. Thank you.
14 So, for the moment, let's hold that question and first
15 hear from Drs. Harlan and then Dr. Wu, and then let's
16 see if we can have a response then about your question
17 about the assays, please. Dr. Harlan.

18 **DR. DAVID HARLAN:** Can you hear me? I can't -
19 - for some reason, my camera's not working.

20 **DR. LISA BUTTERFIELD:** Yes, we can hear you.

1 **DR. DAVID HARLAN:** Yeah. So I just strongly
2 endorse what Dr. Feng just said. And I had my hand
3 raised. I should have lowered it because I also
4 completely agree with what Dr. Naziruddin said earlier.
5 There's three assays that predict outcomes in -- well,
6 there's two assays that predict outcomes in nude mice,
7 and that is beta-cell mass transplanted and the oxygen
8 consumption rate of the islets that are transplanted.
9 And the third assay that predicts results in humans is
10 the nude mouse, which is impractical because of the
11 time. So my response to Question 2B would be a product
12 release criteria should be the beta-cell mass and the
13 oxygen consumption rate, but Dr. Naziruddin already
14 said that.

15 **DR. LISA BUTTERFIELD:** Thank you very much.
16 Dr. Wu, please.

17 **DR. JOSEPH WU:** Yeah. So I think I too have
18 some concerns about the immune reaction of the product,
19 especially when you're pooling different products. And
20 so my question to the company is that have you guys

1 sent detailed panel reactive antibodies, you know,
2 before allotransplant and then also after serious
3 implantation because these are important information to
4 gather. And this is the comment.

5 **DR. LISA BUTTERFIELD:** Sorry, the two areas
6 you need further clarification? Sorry, I didn't catch
7 those.

8 **DR. JOSEPH WU:** Yeah. So, were the panel
9 reactive antibodies done before, after
10 transplantations?

11 **DR. LISA BUTTERFIELD:** Thank you. So can we
12 have a response from the sponsor about a couple of
13 these questions that have come up, please? Dr.
14 Oberholzer.

15 **DR. JOSE OBERHOLZER:** So, for Dr. Wu, we do
16 measure the panel reactive antibodies. That's actually
17 a UNOS requirement. You do not want to match an organ
18 donor to a recipient that would have a donor-specific
19 antibody. And we do the panel just to see are they
20 sensitized or not.

1 And then, if they are sensitized, we do
2 actually analyze the donor specific antibodies, and the
3 patients then will have on their UNOS listing, what we
4 call a voice (phonetic), that these are HLAs that need
5 to be avoided then.

6 On top of that, we do follow after
7 transplantation for donor-specific antibodies and
8 panel-reactive antibodies in general. And we have, if
9 I remember correctly, this information is in our
10 briefing package, and this afternoon I could answer and
11 more specifically I can pull out the specific data to
12 give you exact number.

13 It's understandable that allogeneic transplant
14 patients do get sensitized. Not all of them, but most
15 patients will develop some kind of reactive
16 (inaudible). Also, the autoimmunity of this disease,
17 we also measure autoantibodies before and after
18 (inaudible) see whether there is a reactivation,
19 something that would be standard of care for most
20 pancreas transplants. That would answer your

1 questions?

2 **DR. LISA BUTTERFIELD:** Dr. Wu, is your
3 question answered?

4 **DR. JOSEPH WU:** Yes. I think we would like to
5 see those numbers to see after the transplantation how
6 high did it go up, and did it go up higher if you have
7 pool islets versus a single donor. Because, you know,
8 I think as the other panelists were concerned about,
9 because some of the patients may, later on, require
10 real transplantation, and then if you sensitize the
11 patients repeatedly to a whole bunch of allotransplants
12 from various donors, then we set up problems in the
13 future.

14 **DR. JOSE OBERHOLZER:** So actually, we have in
15 our back up slides that I could show after the clinical
16 presentation, we have data from Rina Greisner
17 (phonetic) who has a small series of pancreas
18 transplants in patients who have previously lost an
19 islet cell transplant, and that gives a bit of an
20 impression, you know, how consequential the presence of

1 antibodies are. So it will make matching more
2 difficult, but as you will see from that series, the
3 outcome after pancreas transplantation, patients who
4 lost an islet cell transplant are actually, you know,
5 equivalent to patients who didn't have an islet.

6 **DR. JOSEPH WU:** Thank you.

7 **DR. LISA BUTTERFIELD:** Now that we have Dr.
8 Oberholzer, Dr. Feng, did you want to restate your
9 questions?

10 **DR. SANDY FENG:** Yes. Thank you. Jose, just
11 if you could talk a little bit about this islet dose
12 response and how that parameter figures in the release
13 of your islet product.

14 **DR. JOSE OBERHOLZER:** Yes. That's actually an
15 excellent question, and I think Dr. Shapiro will
16 briefly address this this afternoon. So, in Canada
17 where the health authorities have approved islet cell
18 transplantation 20 years ago, the main criteria that
19 they use is actually the number of islets because
20 that's really the most predictive for islet function.

1 But that's why we have a cutoff that's based on the
2 Edmonton series of wanting to transplant at least 5,000
3 islets per preparation.

4 Now, of course, if you select your recipients
5 with low body weight and low insulin requirements, you
6 can go higher, and you will have a higher success rate
7 with single islet cell transplants. And so among all
8 the parameters that we have looked at, the strongest
9 correlation is islet equivalent, which, you know, is
10 what we would hope for, that there is a dose response
11 that we are getting. Does this answer your question?

12 **DR. LISA BUTTERFIELD:** Great. Thank you both.
13 And then we have one more hand raised. Dr. Naziruddin,
14 please.

15 **DR. BASHOO NAZIRUDDIN:** I have a question for
16 Dr. Oberholzer. Whether we are talking about immune
17 response and islet quality or not, a huge factor is the
18 instant (inaudible) reaction. As soon as the islets
19 are infused intraportally, there are several studies in
20 Europe as well as in U.S.A, including your own team,

1 has established that up to 50 percent of the islets are
2 lost within days due to innate immune response. So
3 whether the islet is pure or less pure, it doesn't
4 matter. It just happens both in allogeneic as well as
5 in autologous islet transplant. So what are your
6 comments on that?

7 **DR. JOSE OBERHOLZER:** So I know the published
8 papers very well, and I would just like to put a caveat
9 on this. So, if you look at the original paper
10 published in *Lancet* by the Uppsala Group, they
11 published about this. And when you read the fine
12 print, you realize that their outcomes were not very
13 good then, and so they had very few patients achieving
14 insulin independence.

15 So when I look at our own data, and I'm going
16 to show one slide this afternoon with a mixed meal
17 test, and if you pay attention to the C-peptide levels
18 on that slide which represent endogenous insulin
19 surrogate marker, you will see that the C-peptide
20 levels achieved are not far away from what you would

1 see in a pancreas transplant.

2 So I am not that confident with the data that
3 says that 50 percent of islets are lost, because in a
4 basic correlation between the difference between basal
5 and stimulated C-peptide in metabolic tests and the
6 number of islet cell transplants, and if you did really
7 lose 50 percent, I think it would be impossible to
8 achieve (inaudible). So yes, I do believe there is an
9 instant (inaudible) reaction.

10 For now, the only approved method is to give
11 heparin. I can imagine that in the future other
12 pharmacological interventions could further reduce that
13 reaction and surely improve the results. But
14 personally, based on the data published, I do not
15 believe that this is (inaudible).

16 **DR. LISA BUTTERFIELD:** Great. Thanks for
17 addressing that. All right. So as I look for raised
18 hands on these two CMC questions, everything has been
19 addressed. So last call for additional questions. Dr.
20 Roos.

1 **DR. RAYMOND ROOS:** Yes. I guess this relates
2 more in a broad sense to purity. The transplant field
3 has suffered quite a bit with respect to prion
4 transmissions, and I wondered whether donors -- what
5 eliminates a donor? Dementia, family history of
6 dementia, are there screenings for unconventional
7 agents like prions?

8 **DR. JOSE OBERHOLZER:** So that's an excellent
9 question. So, in the donor screening, the organ
10 procurement organizations, they follow 12 CFR 1271 and
11 the 21 CFR 127185, so these are the rules on what
12 testing needs to be done. The prion is ruled out by
13 accepted medical history questions. So all the donors
14 are screened.

15 And, if they have a risk factor for prion
16 exposure, let's say living a certain amount of time in
17 the United Kingdom and so on, so there are defined by
18 criteria, then that donor is being ruled out. That
19 screening does happen, and Dr. McGarrigle could go into
20 more detail than I am able to.

1 In terms of serological and molecular testing,
2 all the testing is done: HIV, Hepatitis B, (inaudible),
3 West Nile Virus. I just have a list in front of me of
4 things that are done, so Hepatitis B/C, HIV, of course.
5 All that is done both by molecular assay and serology.

6 And Dr. McGarrigle, do you have maybe
7 additional information in regard to the risk screening?
8 It's a whole long list of policy guidelines. Does this
9 answer your question or would like us to go into more
10 specifics?

11 **DR. RAYMOND ROOS:** There is a PCR-like test
12 for prion presence?

13 **DR. JOSE OBERHOLZER:** I do not think prion PCR
14 is part of the routine testing in organ procurement
15 organizations in the United States. And I would have
16 to verify information, but I don't think that's being
17 done. It's history based, and the history is very
18 strict. So we rule out a number of organ donors just
19 based on the history, if possible, even very unlikely
20 exposure.

1 **DR. RAYMOND ROOS:** Do you have family
2 histories on these donors too?

3 **DR. JOSE OBERHOLZER:** Yes. We would not
4 accept an organ donor that does not have a reliable
5 history. So absence of reliable history is an
6 exclusion, is a rule-out criteria for us.

7 **DR. LISA BUTTERFIELD:** All right. Thank you.
8 And Dr. Wu.

9 **DR. JOSEPH WU:** So maybe I'm confused. Can
10 you clarify who most of these donors are? I mean,
11 we're not talking about kidney transplant donors in
12 which any transplant donors can, you know, write down
13 what their family medical history are. I would assume
14 some of these donors are, for example, motor vehicle
15 accidents, people who die all of a sudden, right? So
16 who are these donors?

17 **DR. JOSE OBERHOLZER:** No. So we only accept
18 brain-dead donors at this point, and so there is quite
19 some time for the organ procurement organization to
20 ensure family history. So they do phenomenal work

1 because sometimes it takes calling neighbors and
2 investigating. They will go very far to find all the
3 information, and it's very reliable.

4 So, if the organ procurement organization
5 cannot answer all the questions that they have on an
6 entire book of questions they need to fill out, then
7 they let us know and then maybe becomes a high-risk
8 donor, which is an automatic rule out. They would not
9 even call us.

10 **DR. JOSEPH WU:** Thank you.

11 **DR. JOSE OBERHOLZER:** So all the donors are
12 brain dead, they are in an intensive care unit, and all
13 the serologies and molecular assays can be done. So it
14 can take up to two days to complete all the testing for
15 an organ.

16 **DR. LISA BUTTERFIELD:** Thank you for that
17 clarification. Dr. Berns. We can't hear you, Dr.
18 Berns.

19 **DR. KENNETH BERNS:** Is it better now?

20 **DR. LISA BUTTERFIELD:** Now we can hear you.

1 **DR. KENNETH BERNIS:** Okay. Sorry. Thank you.
2 And to extend it to some sneaky viruses that may also
3 be around, have you given any thought now at use of
4 CRISPR-Cas 16, for instance. It gives the opportunity
5 for very rapid tissue diagnosis. Have you given any
6 consideration to extending your monitoring of the
7 preparations?

8 **DR. JOSE OBERHOLZER:** So currently such assays
9 are not being done. Are you alluding to the presence
10 of, for example, endogenous retroviruses or...

11 **DR. KENNETH BERNIS:** Yeah. It could be, you
12 know, the beauty of some of the most recent CRISPR-Cas
13 assays is that they really extended the range of what
14 can be detected, RNA as well as DNA sequences, et
15 cetera, and they're fast. And so the -- my real
16 question is not -- I know they're not being done now.
17 The question is, have you thought about starting to
18 implement that kind of screening for your samples?

19 **DR. JOSE OBERHOLZER:** This is a very
20 interesting question, and you may know that in the late

1 '90s there was a hypothesis that endogenous retrovirus
2 could be at the root of type 1 diabetes. And there was
3 a group where I was at the University of Geneva that
4 looked into that and the complexity of it, and
5 correlations were very weak at the end. So this
6 hypothesis was struck a little bit. But, within a
7 research project, I would be surely interested in
8 looking at.

9 **DR. KENNETH BERNS:** Thank you.

10 **DR. LISA BUTTERFIELD:** All right. Thank you
11 both. So with that, let me do my best to summarize
12 some of the points that were raised by the members of
13 the Committee in discussing these two multi-part CMC
14 questions.

15 So for CMC Question Number 1 regarding the
16 variability of the different cell types in the
17 products, the relative proportions, specific cell
18 types, and the characterization, the Committee
19 acknowledged the great variability seen in the product
20 among the cell types.

1 And that a couple of cell types were raised as
2 being particularly critical, ductal cells that could
3 possibly differentiate into beta cells and have a
4 functional impact, mesenchymal stromal cells that could
5 also be tracked, and that, right now, the product as
6 shown is a highly variable product without much control
7 over that. So there was a suggestion that there are
8 other assays that could be -- you can turn off your
9 cameras if you're not presenting right now.

10 So there was a suggestion that there are
11 assays that are currently available that could be used
12 to better characterize these, including flow-cytometry
13 assays that could characterize different subtypes that
14 could be done. So candidate assays exist, and there
15 are also ways to retrospectively collect RNA and do
16 analyses of other potential functional attributes that
17 could be correlated with clinical outcomes in patients
18 to better understand what the critical parameters are
19 in this highly variable product.

20 There was also the suggestion that this

1 especially important in the brittle diabetics who might
2 be more sensitive to these variabilities.

3 There was also the point that the numbers of
4 patients are small, the numbers of donors are small,
5 the immunosuppression does address the HLA variability
6 and other variabilities, and that, perhaps that the
7 most important focus at this point is about patient
8 outcomes and that the post-approval setting is the best
9 setting in which to further dissect the specifics of
10 the product, and to track those variables and look at
11 their functional impact.

12 So let me pause there and -- well, let me go
13 ahead because the CMC questions are interrelated. So
14 let me summarize some of the discussion of the second
15 CMC question, and then I will ask members of the
16 Committee to point out if I've missed anything. So, in
17 the second question, actually additional variables were
18 mentioned, including operator variability in processing
19 the cells during manufacture, and that the patients may
20 receive multiple donor products in order to achieve the

1 desired level of islets, which further complicates the
2 analysis and characterization.

3 There's no way right now with the
4 manufacturing process to have any type of consistency
5 lot-to-lot because each product from each donor is its
6 own product. Then there was some clarification about
7 the dose response and that it's the number of islets
8 that is most important. And this is from the Canadian
9 data collected in the years since the approval of
10 related processes and products in that country.

11 However, the goal of greater consistency would
12 be important to potentially reduce the number of donors
13 and the number of procedures that these patients are
14 exposed to. So greater understanding of the product
15 variables and their clinical impact could have the
16 important functional effect of reducing the procedures
17 and the number of donors and the downstream impact of
18 the HLA sensitization, and what could happen with
19 downstream need for other organ transplants in this
20 patient subset.

1 There was also some additional clarification
2 from both the regulators and several clarifications
3 from the sponsor about the testing before the
4 procedure, the antibody reactivities, HLA reactivities,
5 prions, and the donor population, and the ability to
6 collect the necessary medical record information.

7 And lastly, we were reminded that thinking
8 about assays to include, in addition to the flow assay,
9 which might be quick and able to be added, the oxygen
10 consumption rate, which was shown to have some
11 tantalizing data that might correlate with functional
12 impact as opposed to nude mice, which really aren't
13 practical for inclusion right now.

14 So I'll ask if anyone on the Committee would
15 like to add anything to that summary at the points of
16 discussion we had. Looking for hands and not seeing
17 any. All right. I will consider that then the summary
18 of the discussion points for these first two CMC
19 questions. And with that, I believe we get to take a
20 break.

1 So unless someone put something in the chat to
2 me, I'm going to announce that we now have our lunch
3 break or late morning additional caffeine break for
4 those of us on the west coast. And we will be meeting
5 again at 1:00 p.m. Eastern or 10:00 a.m. on -- it's
6 almost 10. So anyway, 1:00 p.m. lunch break and we
7 will come back after 45 minutes (inaudible) at 1:45
8 p.m. Eastern to resume the meeting and go on to the
9 next section.

10 **[BREAK]**

11 **OPEN PUBLIC HEARING**

12
13 **MR. MIKE KAWCZYNSKI:** All right. And welcome
14 back to the 69th Cellular, Tissue and Gene Therapies
15 Advisory Committee meeting, and I now hand it back to
16 Dr. Lisa Butterfield. Dr. Butterfield, take it away.

17 **DR. LISA BUTTERFIELD:** Thank you so much. All
18 right. Welcome back, everyone, to the second half of
19 our meeting today.

20 Welcome to the open public hearing session.

1 Please note that both the Food and Drug Administration,
2 FDA, and the public believe in a transparent process
3 for information gathering and decision making. To
4 ensure such transparency at the open public hearing
5 session of the Advisory Committee meeting, FDA believe
6 it's important to understand the context of an
7 individual's presentation.

8 For this reason FDA encourages you, the open
9 public hearing speaker, at the beginning of your
10 written or oral statement to advise the Committee of
11 any financial relationship that you may have with the
12 sponsor, its products, and, if known, direct
13 competitors. For example, this financial information
14 may include the sponsor's payment of expenses in
15 connection with your participation in this meeting.
16 Likewise, FDA encourages you at the beginning of your
17 statement to advise the Committee if you do not have
18 any such financial relationship. If you choose not to
19 address this issue of financial relationship at the
20 beginning of your statement, it will not preclude you

1 from speaking. So with that, let me turn it over to
2 Jarrod.

3 **MR. JARROD COLLIER:** Thank you so much, Dr.
4 Butterfield. We will begin with Dr. Piotr Witkowski
5 from the University of Chicago. Dr. Witkowski, you
6 have 15 minutes.

7 **DR. PIOTR WITKOWSKI:** Thank you very much. Is
8 my first slide on already?

9 **MR. JARROD COLLIER:** Yes, it is.

10 **DR. PIOTR WITKOWSKI:** First of all, thank you
11 very much for the opportunity to speak today. I have
12 nothing to disclose. Dear Advisory Committee members,
13 on behalf of the Islets of U.S. Collaborative we ask
14 that the Advisory Committee to recommend against
15 approval of BLA 125734 for allogeneic human islets as
16 it raises significant legal, policy, and public health
17 consideration that should be first properly addressed
18 by the Secretary of Health and Human Services. Next
19 slide, please.

20 Islets for U.S. Collaborative consists of more

1 than 40 experts and leaders in the fields of
2 transplantation, diabetes, and cellular therapy from
3 leading U.S. academic institutions who have long-
4 standing concerns about the regulatory status of islets
5 transplantation in the U.S. Slide number 3, please.
6 Human pancreatic islets are isolated from diseased
7 donor pancreas and transplanted into the recipient
8 liver. Islet transplant recipients require the same
9 complex medical therapy, including immunosuppression,
10 medication as any other patient receiving organ
11 transplantation.

12 Islets are human micro-organs, and they should
13 be regulated as pancreas and other human organs which
14 are not regulated by FDA and for which BLA is not
15 required. Islets are not drugs, and they are not
16 cellular therapy. Islets, as any other organ for
17 transplantation, exist naturally in the human body.
18 They are not artificially manufactured.

19 They consist of many different type of cells
20 with unique, very well integrated function. Islets, as

1 any other organ, have their own internal blood vessels
2 and neural network. They maintain their own morphology
3 structure and, most importantly, biological
4 characteristics during the processing and preparation
5 for and after transplantation. Islets connect their
6 own vasculature to the recipient blood vessels network
7 after the transplantation. Islets, as any other organ,
8 cannot be frozen and can be preserved only for a short
9 period of time.

10 Most importantly, in contrast to drugs, the
11 potency of islet, as any other organ for
12 transplantation, cannot be reassured by a single test
13 prior to transplant but can be reassured only by the
14 transplant team's continued assessment of complex
15 parameters and supervision from the moment of donor
16 selection through pancreas recovery, processing,
17 preservation, transplantation, and finally post-
18 transplantation care in order to provide safety,
19 effectiveness, and appropriate clinical outcome of the
20 transplant procedure. This is why islets, as any other

1 organ, cannot be kept on the shelf, and there are no
2 human organ banks providing organs or islets for
3 transplantation. Organ and islets potency can be only
4 verified based on successful clinical outcome, and
5 that's why transplant programs are held accountable for
6 that.

7 As we see and hear today, human islets, as
8 well as human organs, are naturally highly variable,
9 and most importantly, islets, as well as organs for
10 transplant, have not and will not fit into the frame of
11 drug regulation, including drug assessment for purity,
12 potency, consistency. But despite that, organs and
13 islets do benefit patients when they're transplanted in
14 the proper setting with proper clinical oversight.
15 Slide number 4, please.

16 FDA's position that allogeneic islets are
17 drugs and require a BLA has prevented islet
18 transplantation from becoming a standard of care
19 procedure in the U.S. in contrast to many other
20 countries. Many academic transplant centers in the

1 U.S. have successfully processed human islets for
2 transplantation in clinical trials, benefiting diabetic
3 patients without BLA over the last 20 years. However,
4 transplant centers are not drug manufacturers and are
5 not in the position to sponsor a BLA and comply with
6 FDA other drug manufacturing requirements.

7 BLA submissions are not aligned with the
8 mission of academic transplant centers. They lack
9 appropriate organizational structure and resources,
10 making it extremely difficult and practically
11 impossible to meet necessary BLA demands, nor are such
12 requirements in fact necessary for safe and effective
13 islet transplantation. Consequently, after 20 years of
14 research and clinical trials, islets transplantation is
15 still not broadly available to Americans with Type I
16 diabetes.

17 Over the last five years, the number of
18 patients treated with islets transplantation dropped to
19 only a few per year in the entire country, as depicted
20 in the picture. In contrast, many other countries in

1 Europe, Canada, Australia, and Japan regulate islets
2 not as drugs but as organ for transplantation, and they
3 have already implemented clinical islet transplantation
4 as a standard of care procedure. In fact, these
5 programs have directly benefited from U.S. islet
6 isolation and transplantation technology developed
7 through millions of dollars of federally funded
8 research. Slide number 5, please.

9 Granting a BLA to a private, for-profit
10 company will not solve the problem of islet
11 transplantation in the U.S., but it will lead to its
12 further demise. Once the BLA is approved, a for-profit
13 entity will have a right to commercialize human islets
14 as biological drug for use in transplantation. This is
15 inconsistent with federal prohibition on
16 commercialization of human organs.

17 For-profit entity will have seven years of
18 marketing exclusivity for human islets under the Orphan
19 Drug Act. For-profit entity will have a significant
20 leverage in terms of the contract with any transplant

1 center to provide islets for transplantation, including
2 the price for islets. For-profit entity will have
3 significant influence over which transplant centers are
4 able to offer their patients islet transplantation.

5 As a consequence, transplant centers will have
6 no alternative source of islets for clinical use.
7 Transplant centers will have less control over quality
8 of islets for their patients. Access to islet
9 transplantation may be reduced because of the cost and
10 limited availability of the islets. Slide number 6,
11 please.

12 Granting this BLA will also compromise patient
13 safety. The Health Resources and Services
14 Administration, HRSA, developed regulations to ensure
15 safe and ethical allocation and transplantation of
16 human organs in the United States. Under HRSA, Organ
17 Procurement and Transplantation Network and UNOS
18 oversee transplant programs that provide complex
19 medical therapy through a multidisciplinary team of
20 transplant physicians. OPTN/UNOS oversight framework

1 is critical to reassure patient safety and
2 effectiveness of this very complex transplant therapy.

3 As a result of BLA requirement, islets will
4 not be included into the complete OPTN/UNOS oversight.
5 The commercial BLA order and patients after islet
6 transplantation will not be subject to OPTN post-
7 transplant monitoring of patient outcomes. As the
8 result, islets will be less regulated than any other
9 human organs. Slide number 7.

10 As a solution, we propose that human islets
11 should be regulated as organs by HRSA through OPTN and
12 UNOS, not as drugs by FDA. The National Organ
13 Transplantation Act defines a human organ to include
14 both all organs and subparts of organs based on the
15 amendment in 1988. Islets are subparts of the
16 pancreas, and, therefore, they should be regulated as
17 human organs. And they should not be subject to BLA.

18 However, the problem is that the definition of
19 human organ under OPTN final rule has not been amended
20 to match the statutory definition and to include human

1 islets. Consequently for the past 20 years, FDA has
2 taken the position that islets are a biological drug
3 requiring BLA. Slide number 8.

4 We propose that the secretary of HHS under his
5 authority should designate allogeneic islets for
6 transplantation as human organs under the OPTN final
7 rule. Legally, it would conform with the statutory
8 definition of human organ under the National Organ
9 Transplantation Act. Providing OPTN and UNOS with
10 legal authority for holistic, systematic clinical
11 oversight over islets transplantation would protect
12 patients by ensuring safety and effectiveness of islet
13 transplantation therapy.

14 It would prevent eminent commercialization of
15 human islets, which is prohibited under NOTA by
16 preventing the FDA from granting a biological license
17 application for human islets to commercial entity. HHS
18 Secretary decision in 2013 to include vascularized
19 composite allograft under OPTN and UNOS rather than
20 under the FDA jurisdiction was stimulated by the same

1 organ-like nature and safety rationale that provides
2 strong precedence for including human islets under the
3 OPTN final rule. A solution that regulates islets as
4 organ rather than a drug would not compromise islet
5 regulatory oversight, which could remain subject to FDA
6 good tissue practice requirements as currently is the
7 case for islets for autologous use processed in the
8 same manner as islets for allogeneic use. Next slide,
9 please, slide number 9.

10 FDA's position that BLA is required for
11 unrelated allogeneic islets is inconsistent with the
12 Agency approach for autologous islets. If the islets
13 are for use in the same person, autologous use, no BLA
14 is needed, and no drug manufacturing conditions are
15 required for processing. If the islets are for use in
16 the first and second degree relative in allogeneic
17 setting, again, no BLA is needed. But if islets are
18 for use between unrelated people in allogeneic use,
19 then BLA and drug related regulations are indeed
20 required.

1 Although the same islet isolation technique is
2 used for allogeneic and autologous islet, only
3 unrelated allogeneic islet requires a BLA. Despite FDA
4 applying different regulatory requirements, depending
5 only on clinical use, FDA in fact does not provide any
6 regulatory oversight over clinical transplantation
7 because it's not FDA but OPTN and UNOS regulations
8 which provide appropriate regulatory framework for the
9 clinical use of allogeneic organs and islets and assure
10 safety and effectiveness. Therefore, islets should be
11 rather regulated as organs, not as drugs. Slide number
12 10.

13 Regulating islets under OPTN/UNOS will allow
14 academic centers to continue processing and
15 transplanting human islets, which leads to health
16 competition stimulating progress in the field and
17 access to the procedure for our patients. And here is
18 another illustration. On the left, application of drug
19 manufacturing regulation does not provide appropriate
20 regulatory oversight of patient care and clinical

1 outcomes. In contrast on the right, OPTN/UNOS
2 constantly monitor transplant programs for appropriate
3 clinical outcomes as a condition for maintaining their
4 accreditation. Outcomes are also under public scrutiny
5 and available on the UNOS public website.

6 Slide 11, in conclusion, BLA 125734 raises
7 significant legal, policy, and public health
8 considerations that should be properly addressed by the
9 Secretary of HHS. We are concerned that the Advisory
10 Committee may not have been aware of the adverse,
11 potentially irreversible consequences to the patient
12 safety and access of recommendation to approve the BLA.
13 Therefore, we ask the Advisory Committee to recommend
14 against approval of BLA for allogeneic human islets.

15 Slide number 12, this is a list of
16 supplementary materials, which include our request
17 letter to the Secretary of HHS as well as our articles
18 with more information relating to this presentation.
19 Thank you very much for the opportunity to speak today.

20 **MR. JARROD COLLIER:** Thank you very much, Dr.

1 Witkowski. Next, we have Dr. Camillo Ricordi from the
2 Diabetes Research Institute Federation. Dr. Ricordi,
3 you have five minutes.

4 **DR. CAMILLO RICORDI:** Thank you and thank you
5 for the opportunity to briefly present my position. So
6 my point is "Why Pancreatic Islets Should be Regulated
7 Like Organs and Patients Should Be Able to Benefit from
8 Them at Academic, Non-Profit Centers of Excellence."
9 I've been -- slide number 2, I've been involved in
10 islet isolation and transplantation for my entire
11 career, for over four decades, and since we developed
12 the method which is still largely used in islet
13 isolation and processing with Paul Lacy at Washington
14 University and then the first successful transplant
15 with Professor Statz (phonetic) in Pittsburgh all the
16 way to the completion of the Phase 3 trial of islet
17 transplantation.

18 I've been also involved with co-PI with James
19 Shapiro of the multi-center trial of the Edmonton
20 protocol before the Phase 3 trial. And we've been

1 involved in this -- I wish I could have been a part of
2 the discussion this morning because I was very
3 interested, and I have so many comments about potency
4 and composition and others. But I will leave it until
5 another opportunity.

6 Anyway, the Phase 3 trial, the Clinical Islet
7 Transplantation Consortium has been carrying forward
8 successfully for over ten years took a massive effort
9 from each center in North America. It produced
10 remarkable results, both at one year and two years.
11 And recently we also published this sort of valuable
12 data on slide number 3, "Survival After Islet
13 Transplantation in Subjects with Type I Diabetes:
14 Twenty-Year Follow-up," which indicated despite
15 immunosuppression islet transplantation was not
16 associated with an increased risk of mortality, may
17 actually reduce the mortality risk associated with Type
18 I diabetes which are (Inaudible) with adult median age
19 43 years plus or minus eight years. To compare to
20 publish a statistic on (Inaudible) viable in subjects

1 with diabetes treated with insulin and without
2 immunosuppression, the results of islet transplantation
3 look very favorably, and it may then be considered a
4 life-saving procedure in for prevention of severe
5 hypoglycemic episodes.

6 So unfortunately, as Dr. Witkowski mentioned,
7 we started addressing this issue in 2019 when I
8 published the paper "Transplanting Islets can Fix
9 Brittle Diabetes" in slide number 4 why it isn't
10 available in the United states. And we got a series of
11 commentaries in (inaudible) the official journal of the
12 Cure alliance congratulating use for the progress but
13 also being sorry for United States being the only
14 country where islet transplantation couldn't move
15 forward. Also interesting was the fact that the UK
16 approved an islet transplantation based on the clinical
17 data obtained in the United States when money paid by
18 our taxpayers and our clinical trials. So they did the
19 assessment and approved it. And it's so in many other
20 countries from Canada, Australia where I contributed

1 with establishing the definition of the national
2 program for islet transplantation, in Switzerland --
3 networking friends that did the first successful
4 randomized prospective trial of islet transplantation
5 compared to intensive insulin treatment. And it has
6 been really, as Dr. Witkowski said -- has been
7 something dramatic and tragic for us to see this
8 evolution and being blocked in the United States after
9 developing the field worldwide. Slide number 5,
10 please.

11 This is an email that I received from France -
12 - from the head of the French program in Lille, and I'm
13 not showing it for the thank you note -- the thank you
14 from France to me personally but because even France in
15 July 2020 approved islet transplantation as standard
16 practice fully endorsed by social security, the same to
17 Japan and China and many other countries.

18 So the issue of why islets should be regulated
19 as an organ has been addressed brilliantly also by
20 tourism, commentary and opinion papers in (Inaudible)

1 this month or last month. One is from Gordon Weir and
2 Susan Bonner-Weir from Harvard, "Why Pancreatic Islets
3 Should be Regarded and Regulated Like Organs," and the
4 other is from PO Berggren from the (Inaudible)
5 Institute in Stockholm on the "Pancreatic Islet: A
6 Micro-Organ in Control."

7 And has been said already before, islets have
8 so much composing -- like, thousands of cells of
9 differing kinds of which endocrine cells are just one
10 component. You have vascular (Inaudible) cell
11 parasites, endothelia cells and many other cell types
12 that comprise the islets. And the variability donor to
13 donor is such that we can't -- that the beta cell can't
14 -- to referred to in a question this morning, beta cell
15 content in human islets can vary between 11 percent and
16 80 percent. So when you talk about the 30 percent
17 purity, the purity in beta cells can actually be
18 incredibly even more variable than the purity of islets
19 versus endocrine in tissue.

20 And for those interested you can see *American*

1 *Journal of Transplantation* in 2005, first author Ichii
2 "A Novel Method for the Assessment of Cellular
3 Composition and Beta Cell Variability in Human Islets,"
4 which we eventually decide not to follow because it was
5 too complicated and doesn't address the fact that if
6 you have islets from a donor --

7 **MR. MICHAEL KAWCZYNSKI:** Dr. Camillo.

8 **DR. CAMILLO RICORDI:** Okay. I will go to the
9 conclusion.

10 **MR. MICHAEL KAWCZYNSKI:** Okay. Go ahead.

11 **DR. CAMILLO RICORDI:** So in conclusion islets
12 are micro-organs and should be regulated like organs.
13 A 20-year patient survivor indicate that could be life-
14 saving. Non-profit, academic centers should be able to
15 offer islet transplant locally like they offer organ
16 transplant. Commercial, for-profit entity could
17 propose and commercialize processing and distribution
18 services for islet transplant in addition to academic
19 centers of excellence, but in this case, commercial
20 entity decided they will file a BLA and proper

1 regulatory path since the islet will be shipped to
2 remote sites, introducing additional regulatory
3 challenges.

4 In our Phase 3 trial, we didn't include
5 shipment to remote sites. We have trained and
6 contributed to approval of islets under organ
7 transplant regulation in the rest of the world, and it
8 would be a disservice to selectively damage U.S.
9 academic centers and patients with Type I diabetes only
10 in the U.S. Thank you and sorry if I'm one minute
11 late.

12 **MR. JARROD COLLIER:** Thank you, Dr. Ricordi.
13 The next two speakers will provide oral presentations
14 without PowerPoint slides. They will be only audio, so
15 we will move on next to Dr. Meg Seymour from the
16 National Center for Health Research. Dr. Seymour, you
17 have five minutes.

18 **DR. MEG SEYMOUR:** Thank you for the
19 opportunity to speak today on behalf of the National
20 Center for Health Research. I am Dr. Meg Seymour, a

1 senior fellow at the center. We analyze scientific
2 data to provide objective health information to
3 patients, health professionals, and policy makers. We
4 do not accept funding from drug or medical device
5 companies, so I have no conflicts of interest.

6 Today, you are asked to discuss sinosylisal
7 (phonetic) transplant treatments for brittle, Type I
8 diabetes in adults whose symptoms are not well-
9 controlled despite intensive insulin therapy. We agree
10 that safe and effective treatments are need for the
11 treatment of brittle diabetes, but we agree with the
12 concerns of the FDA reviewers regarding the benefit-
13 risk profile of the transplant treatments.

14 First, let's talk about efficacy. As FDA
15 notes, the applicant did not provide baseline data on
16 the number of severe hypoglycemic events for 50 percent
17 of the patients, which we agree makes it impossible to
18 determine that transplant could have benefited patients
19 by reducing these events. Additionally, for the 50
20 percent of the sample where there actually are data on

1 severe hypoglycemic events, 83.3 percent did not have
2 any in the year prior to their first transplant, which
3 FDA scientists point out means that any finding that
4 patients did not have severe hypoglycemic events
5 following their transplant would not represent a
6 clinically meaningful improvement.

7 Another problem with the evidence is that 25
8 of the 30 patients had mild to severe anemia during the
9 study. Anemia can falsely lower hemoglobin A1C, which
10 affects the interpretation of hemoglobin A1C levels as
11 an endpoint. FDA scientists note that this means the
12 data can't demonstrate a clinically meaningful
13 improvement in the hemoglobin A1C.

14 It's important to keep in mind that both
15 studies were single arm and were quite small, with a
16 total of 30 patients between them. With only six men
17 and zero people of color in the studies, it is not
18 possible to generalize any of the findings to all
19 adults with brittle diabetes. Even if the efficacy
20 data were more persuasive, for example if in the future

1 the company could provide more baseline data and
2 longer-term outcome data, they only relate to white
3 women. We would be very concerned if this treatment
4 were at any point approved for patients who are not
5 adequately included in the clinical trials.

6 Next, I would like to talk about safety. FDA
7 notes in their clinical summary that during the
8 clinical studies different patients received the
9 transplants at different time points, so comparison of
10 rates of adverse events is not always possible,
11 especially since there was no control group. We agree.
12 And due to the small size of the sample, it is
13 difficult to compare the adverse events between those
14 receiving the treatment to those receiving a
15 traditional pancreas transplant.

16 Nevertheless, it is notable that only 30
17 patients experienced a total of 452 adverse events in
18 years two through five after the first transplant. 20
19 percent of patients experienced life threatening
20 events. For most patients, the assessment of safety

1 was limited to two years. We agree with the FDA that
2 given the potential risks of the transplants and the
3 immunosuppression required to maintain viability, two
4 years is not a sufficient duration for assessing
5 adverse events.

6 New treatments are needed and could be of
7 great benefit for brittle diabetes patients. However,
8 FDA approval should be based on evidence that a
9 treatment is proven to be safe, to be effective, and to
10 have a positive risk-benefit profile for patients. As
11 a public health agency, it is FDA's responsibility to
12 only approve treatments shown to have a favorable risk-
13 benefit profile, rather than approving a treatment for
14 the sake of having more treatment options. We urge you
15 to consider FDA's strong concerns about efficacy and
16 safety during your discussion later today. Thank you.

17 **MR. JARROD COLLIER:** Thank you very much, Dr.
18 Seymour. Our last oral presenter is Dr. Sanjoy Dutta
19 from the Juvenile Diabetes Research Foundation. Dr.
20 Dutta, you have five minutes.

1 **DR. SANJOY DUTTA:** -- funding Type I diabetes
2 or T1D research with a mission to accelerate life
3 changing breakthroughs to offer better treatments along
4 the way to curing and, eventually, preventing T1D. JDRF
5 does not have any financial disclosures.

6 The key points I'm focused on today are, one,
7 the unmet need that still exists in T1D, particularly
8 for those with severe hypoglycemia unawareness and,
9 two, how islet transplantation has been shown to
10 improve glycemic control, protect patients from severe
11 hypoglycemia, restore hypoglycemia awareness, and, for
12 many, provide insulin independence. The mainstay of
13 T1D disease management, insulin, has been around for
14 almost 100 years, but it is not a cure. The burden and
15 risks of T1D disease management falls almost entirely
16 on people with T1D and their caregivers, requiring 24
17 hour a day diligence to survive.

18 Significant unmet needs still exist,
19 particularly considering the lower age of onset and
20 longer duration of diabetes. While technologies to

1 administer insulin and monitor glucose levels have
2 improved, subcutaneous exogenous insulin replacement is
3 not technology and insufficient to restore the body's
4 natural ability to maintain glucose homeostasis,
5 leading to short- and long-term complications, as well
6 as increased morbidity and mortality.

7 Recent reports also suggest the prevalence of
8 severe hypoglycemia has increased to as high as 35
9 percent in people with Type I diabetes. It is well-
10 known that hypoglycemia begets hypoglycemia, thus
11 worsening the outcomes. And continued exposure of
12 severe hypoglycemia has been associated with an
13 increased risk of cardiovascular events, injury, and
14 all cause mortality in people with Type I and Type II
15 diabetes.

16 Simply put, there is an urgent need for a
17 treatment to address severe hypoglycemic unawareness.
18 In many countries outside of the United States islet
19 isolation and transplantation, like the product being
20 discussed today, is a currently available treatment

1 option for this group of people. The Clinical Islet
2 Transplantation Consortium, which was led and funded by
3 the NIH, completed a successful Phase 3 safety and
4 efficacy study for islet transplantation, a study that
5 was designed in collaboration with the FDA and followed
6 their 2009 guidance on considerations for allogeneic
7 pancreatic islet products.

8 While not the focus of this meeting, the data
9 and results from this study provides important and
10 relevant context. The primary endpoint, a composite
11 level of an A1C of less than 7 percent and freedom from
12 severe hypoglycemic events, was achieved by 87.5
13 percent of the subjects at year one and 71 percent at
14 year two. Median A1C results went from 7.2 percent at
15 baseline to 5.6 percent, and insulin independence was
16 also achieved by 52 percent of patients, both at year
17 one post-transplant. The trial also demonstrated
18 benefits and other measures of glyceimic control,
19 including glyceimic liability index, mean amplitude
20 glyceimic excursions, and time and target glucose

1 ranges.

2 Restoration of hypoglycemia awareness was also
3 shown by markedly reduced (Inaudible). These results
4 demonstrate that islet cell transplantation can
5 significantly improve glucose control and, most
6 importantly, protect patients with unawareness from
7 severe hypoglycemic events and restore control
8 regulatory measures.

9 JDRF is disappointed that physicians who care
10 for people with T1D and would be prescribing a product
11 like this are not more represented on this Committee
12 and that a T1D patient representative is also not a
13 member of this Committee to share their perspective.
14 The patient perspective on clinical meaningfulness,
15 especially around insulin independence, as well as
16 other outcomes, is critical because of the clinical
17 decisions and risk management patients with T1D and
18 their caregivers have to manage every day. JDRF
19 encourages the sponsor and FDA to reconsider use of the
20 terminology "brittle" in the description of the T1D

1 patient population that this therapy would be indicated
2 for. Brittle is a subjective term that lacks
3 appropriate context.

4 We recommend including "severe hypoglycemia
5 unawareness" in the indication to accurately
6 characterize the appropriate population and clinical
7 condition, consistent with the ADA 2021 standards of
8 care recommendations for pancreas and islet
9 transplantation. We are pleased that this product, if
10 approved, could fill an unmet need, and provide an
11 important therapy option for T1D patients who are at
12 increased risk of severe morbidity and mortality. This
13 therapy would not be possible without the generosity of
14 organ donors, and we share our sincere gratitude and
15 thanks to the donors and their families.

16 We thank the Committee, FDA, and the sponsor
17 for the careful consideration of the benefits and risks
18 of this therapy for those T1D patients with severe
19 hypoglycemia unawareness who have significant unmet
20 needs for safe and effective therapy options. Thank

1 you.

2 **MR. JARROD COLLIER:** Thank you so much, Dr.
3 Dutta. At this time, this concludes the open public
4 hearing session. At this time, I will turn the meeting
5 back to Dr. Butterfield.

6 **DR. LISA BUTTERFIELD:** Terrific. Thank you,
7 Jarrod, and thank you to all those presenters. Now, we
8 will move to the FDA clinical introductory remarks, so
9 I'd like to introduce Dr. Hart from the Division of
10 Clinical Evaluation and Pharmacology/Toxicology. Dr.
11 Hart, please.

12

13 **FDA CLINICAL INTRODUCTORY REMARKS**

14

15 **DR. ELIZABETH HART:** Good afternoon. My name
16 is Elizabeth Hart. I'm a pediatric endocrinologist,
17 and I serve as the general medicine 1 clinical branch
18 chief in the Division of Clinical Evaluation and
19 Pharmacology/Toxicology in the Office of Tissues and
20 Advanced Therapy in the Centers for Biologics

1 Evaluation Research, otherwise known as CBER. On
2 behalf of the FDA, I would again like to welcome and
3 thank the members of the Advisory Committee for
4 participating in this afternoon's session, which will
5 focus on clinical aspects of the BLA for Donislecel
6 Allogeneic Islets for treatment of a subset of adults
7 with Type I diabetes.

8 As you heard, Type I diabetes is a serious
9 chronic medical condition caused by autoimmune
10 destruction of pancreatic islet cells. This ultimately
11 leads to an absolute deficiency in production and
12 secretion of endogenous insulin. Type I diabetes is
13 fatal without endogenous insulin treatment.

14 The mainstay treatment in current standard of
15 care for most patients with Type I diabetes is
16 intensive insulin therapy. This involves the frequent
17 monitoring of glucose levels and administration of
18 insulin by injection or insulin pump based on dietary
19 intake, but the goal of (Inaudible) is closely
20 impossible to prevent hypoglycemia, low blood sugar, or

1 hyperglycemia, high blood sugar.

2 Hypoglycemic control is important to mitigate
3 acute symptoms and reduce long term risks of
4 microvascular and macrovascular complications. Over
5 the past 25 years there have been advances in insulin
6 formulation with improvements in pharmacokinetic and
7 pharmacodynamic profile. Especially over the past
8 decade, new devices have become available to support
9 patients in managing their blood glucose.

10 While these advancements continue to improve
11 the ability of many patients to manage their diabetes
12 and achieve treatment goals, there are still some
13 patients experiencing recurrent severe metabolic
14 instability, including life threatening severe
15 hypoglycemic episodes and diabetic ketoacidosis. We
16 believe that the patient perspective is very important,
17 and we understand from patients and their families the
18 impact that Type I diabetes, particularly difficult to
19 control Type I diabetes, can have due to these life-
20 threatening complications.

1 FDA appreciates this unmet medical need and
2 published the guidance "Considerations for Allogeneic
3 Pancreatic Islet Cell Products," which was finalized in
4 2009. The guidance offered the Agency's perspective
5 and advice on product development, including clinical
6 study design for allogeneic pancreatic islet cell
7 products. It was published after the clinical study
8 performed by the applicant were initiated.

9 The applicant is providing primary safety and
10 effectiveness data for Donislecel from two open-label
11 single arm studies in 30 subjects. As will be
12 presented by Dr. Patricia Beaston, the applicant
13 provided data demonstrating that 21 of 30, or 70
14 percent, of subjects were able to achieve more than one
15 year of independence from exogenous insulin while
16 maintaining or improving glycemic control. And 10, or
17 33 percent of subjects, maintained insulin independence
18 while maintaining glycemic control for at least five
19 years. The maximum duration of insulin independence
20 was 13 years at the time the data were censored.

1 From a safety perspective, there were many
2 serious safety events, including death. The etiology
3 of most of these serious adverse events were generally
4 expected as they related to procedural complications or
5 the immunosuppressive regimens. For the FDA to approve
6 a BLA, the application must provide substantial
7 evidence of effectiveness, sufficient evidence of
8 safety to support the overall favorable balance of
9 benefits and risks within the target population.

10 As the Committee discusses the subset of Type
11 I diabetics for whom Donislecel may have a favorable
12 benefit-risk profile, we ask them to consider the
13 supply of Donislecel being inherently limited, as it is
14 manufactured from donated cadaveric pancreata. For the
15 patients and their families who are listening, we
16 remind you that, if approved, the ability to receive an
17 islet transplantation is not only determined by
18 clinical need but also by the availability of a donor
19 match. We look forward to hearing the deliberations of
20 the Committee on the benefits and risks of Donislecel.

1 Thank you. I will now turn it back to the chair.

2 **DR. LISA BUTTERFIELD:** Thank you, Dr. Hart.

3 Now, we move to our sponsor speakers who will present

4 on their clinical perspectives. We'll have in order

5 Drs. Oberholzer, Hatipoglu, and Shapiro. Dr.

6 Oberholzer?

7

8 **APPLICANT PRESENTATION: INTRODUCTION, AGENDA, EXECUTIVE**

9 **SUMMARY**

10

11 **MR. MICHAEL KAWCZYNSKI:** You're muted, Dr.

12 Oberholzer. No, not in Adobe. You're unmuted in

13 Adobe. Your own phone is muted. I'll unmute you in

14 Adobe. Just make sure your own phone isn't muted.

15 You're connected. You're just not -- make sure you

16 don't have your own phone muted. No, we don't hear

17 you, sir. I see your phone's connected. No, I think

18 it's your headset, sir. Make sure it's on. We'll give

19 you a minute. No, sir. We do not hear you. He's

20 reconnecting. I think his wireless headset went a

1 little wonky on him. That happens. No problem. He's
2 coming right back in.

3 **DR. JOSE OBERHOLZER:** Can you hear me now?

4 **MR. MICHAEL KAWCZYNSKI:** There you go, sir.

5 **DR. JOSE OBERHOLZER:** Again, my apologies.

6 **MR. MICHAEL KAWCZYNSKI:** That's okay. No
7 problem.

8 **DR. JOSE OBERHOLZER:** My phone doesn't play
9 well today. So hi, I'm Jose Oberholzer. I'm the
10 founder of CellTrans, and I am the principal
11 investigator of the clinical trials that led to the
12 submission of this biologics license application.

13 I would like to thank the Advisory Committee
14 members and the FDA team for organizing this meeting
15 and providing the opportunity to speak. After a short
16 overview, I'm honored to have Dr. Betul Hatipoglu from
17 Case Western University in Cleveland give us a short
18 introduction to brittle Type I diabetes and the unmet
19 clinical need. He will be followed by Dr. James
20 Shapiro from the University of Alberta in Edmonton in

1 Canada, who will introduce islet cell transplantation.
2 Dr. Shapiro will also share his pioneering experience
3 with islet cell transplantation in Alberta. And
4 finally, I'll present the key efficacy and safety data
5 from our own program and will wrap up the discussion of
6 the benefit-risk assessment for Donislecel.

7 I would like to take a moment to quickly
8 introduce our product and its intended use. Donislecel
9 consists of purified allogeneic pancreatic islets that
10 are suspended in a transplant medium. Donislecel is
11 delivered to patients via infusion into the portal
12 vein. The target indication for Donislecel is the
13 treatment of brittle Type I diabetes in adults whose
14 symptoms are not well-controlled despite intensive
15 insulin therapy. And as mentioned before, this
16 requires a further narrowing.

17 Qualifying patients will be those who meet
18 American Diabetes Association and Medicare criteria for
19 pancreas transplantation. Finally, Donislecel BLA is
20 being submitted specifically for the use at University

1 of Illinois Hospital in Chicago, but we are not
2 submitting for shipping islets around.

3 Next, I'd like to highlight that our BLA
4 filing in July 2020 was the product of a clinical
5 program that my team began in 2004 at the University of
6 Illinois at Chicago, known as UI Health. Based upon a
7 successful outcome in our initial Phase I/II clinical
8 trials, we continued into a Phase 3 trial in 2007 to
9 study our product in additional patients. In 2016, UI
10 Health transferred the Donislecel IND to CellTrans with
11 the purpose to submit a BLA and manufacture islets for
12 UI Health. In February 2017, the FDA awarded Orphan
13 Drug designation for Donislecel for the treatment of
14 brittle Type I diabetes, a rare disease with serious
15 and potentially life-threatening complications.

16 Of note, we've also closely collaborated with
17 the National Institute of Health in best practices for
18 islet manufacturing and administration and participated
19 in three of the CIT consortium trials, and this data
20 was submitted with the biologic license application but

1 will not be further discussed today as the results are
2 very similar to what you are going to see (Inaudible).

3 Importantly, the driver of our entire islet
4 cell transplant development program has been to help a
5 small group of patients with brittle Type I diabetes.
6 Because of this, our patients wanted to be heard today
7 and offered to share with you what all of this has
8 meant to them. If my colleague can maybe show the
9 first video, please.

10 **MR. MICHAEL KAWCZYNSKI:** Yes, all right. Just
11 as a reminder, I have all of you muted. You will need
12 to unmute yourself in the -- or unclick the speaker
13 symbol in the top corner to make sure you can hear it.
14 So here we go.

15 (BEGIN VIDEO)

16 **UNIDENTIFIED FEMALE:** I was having
17 hypoglycemic episodes where I would pass out with no
18 symptoms prior to my 2005 transplant.

19 **UNIDENTIFIED FEMALE:** My blood sugar would go
20 low when I was asleep, and I wouldn't know. I wouldn't

1 wake up, and also I would never know my blood sugar was
2 low.

3 (END OF VIDEO)

4 **DR. JOSE OBERHOLZER:** Thank you, Michael.
5 Glad this worked out. And now it's my great pleasure
6 to introduce Dr. Betul Hatipoglu to provide some
7 additional insight in brittle Type I diabetes and the
8 unmet clinical need that Donislecel is intended to
9 fill. Dr. Hatipoglu was actually the endocrinologist
10 for the patient you just hear from, and she has
11 extensive experience working with brittle Type I
12 diabetic patients. Dr. Hatipoglu, please.

13

14 **INTRODUCTION TO DIABETES AND UNMET CLINICAL NEED**

15

16 **DR. BETUL HATIPOGLU:** Thank you. Thank you
17 for this great opportunity and my invitation to be part
18 of this important meeting. My presentation really will
19 only confirm what has been already very well said. I
20 have no financial conflicts to disclose at this time.

21 As you already heard many times and you

1 already know, Type I diabetes is a very unique form of
2 diabetes. It's extremely different than Type II
3 diabetes. It is an autoimmune disease involving
4 destruction of insulin producing beta cells within the
5 pancreas and insulin being a very important hormone to
6 control our blood sugar. It affects millions of
7 individuals in the United States, and opposite to Type
8 II diabetes, currently there is no prevention or known
9 cure.

10 However, decades of research taught us that
11 intensive blood glucose control delays long term
12 complications, such as kidney disease, eye damage,
13 nerve damage, and here in this graph you can see,
14 though, the challenge of this condition we face. When
15 we try to improve the glucose control for our patients,
16 we at the same time increase the risk of hypoglycemia.
17 Hypoglycemia is an acute complication of insulin
18 therapy in diabetes, and severe hypoglycemia can be
19 life threatening and usually requires assistance from
20 another person.

1 Unfortunately, it is a big barrier between us
2 and our intention to prevent complication. A subset of
3 our patients suffers a very serious condition we call
4 brittle Type I diabetes in which, as you have already
5 heard, their blood sugar level frequently and
6 unpredictably moves from low to high, high to low. It
7 is rare, but it is complicated by hypoglycemic
8 unawareness and severe hypoglycemic episode. This
9 makes treatment for us very challenging, leaving us to
10 choose within a dilemma of exposing our patients to
11 complications such as hyperglycemia versus leaving them
12 vulnerable with consequences, including potentially
13 death from hypoglycemia.

14 However, here in the United States there is an
15 alternative option available currently, the pancreas
16 transplantation, which is the only option we have that
17 is non-experimental. Because it is a major surgery and
18 with its own risks and exposure to immunosuppressive
19 drugs, pancreas transplantation alone could only be
20 offered to few selected patients who can safely receive

1 this treatment. However, there is an alternative
2 option available in the world for these patients.

3 Islet transplantation may be an appropriate
4 treatment option as it is minimally invasive and
5 represents a safer alternative to whole pancreas
6 transplantation, especially for those of our patients
7 who otherwise will suffer hyperglycemia and its
8 complications or severe consequences of hypoglycemia.

9 I thank you for allowing me to be a part of this
10 important meeting and be a voice on behalf of my
11 colleagues and our patients. Next, I would like to
12 invite Dr. James Shapiro.

13

14 **INTRODUCTION TO ISLET CELL TRANSPLANTATION**

15

16 **DR. JAMES SHAPIRO:** Thank you. Can you hear
17 me? Thank you. Good afternoon. I hope you can hear
18 me okay.

19 **MR. MICHAEL KAWCZYNSKI:** Yes, we can.

20 **DR. JAMES SHAPIRO:** Yeah. It's a really great

1 honor to be part of this FDA discussion this afternoon,
2 and I would like to extend my congratulations to Dr.
3 Jose Oberholzer and his incredible team for putting
4 together the data they've done and conducting the
5 trials that they have to get to this stage. So I'm
6 from the University of Alberta in Canada, and I run the
7 clinical islet transplant program here at the
8 University of Alberta.

9 At the outset I would emphasize that I have no
10 financial conflicts to disclose in this matter. I am
11 not being paid by CellTrans for providing this
12 presentation or for any contribution to their work.
13 I've not been paid for the preparation for this
14 Advisory Committee meeting or for any work related to
15 CellTrans.

16 Islet cell transplantation is a fairly simple
17 concept. The idea is to store insulin producing cells
18 in patients that have destroyed the beta cells that
19 normally would make insulin by extracting those cells
20 from the pancreas of organ donors through a complex

1 process of digestion and purification and then infusing
2 those cells into the liver where they nest and form a
3 new blood supply in a procedure that can be conducted
4 without the need for surgery in the vast majority of
5 cases. This is a safe and fairly established technique
6 today.

7 Islets are infused into the liver once they
8 have fulfilled all of the release criteria. And in
9 Edmonton, we do not use the OCR or other techniques.
10 We use the islet cell count and be sure that we're
11 providing a minimal islet transplant engraftment mass,
12 and we ensure that the cells are viable with complete
13 viability scores. And we ensure that the product is
14 sterile. And in all of our infusions we've found
15 variants to be the most effective and practical means
16 to assess the safety of the product before infusion.

17 We have to occasionally carry out a cross-
18 match between a donor and a recipient to make sure they
19 have no preformed antibodies to destroy the islet cells
20 and that their cells are compatible with the recipient.

1 The patient is then admitted to hospital. Usually a
2 pre-operative induction or antibody -- induction of
3 treatments are given, together with anti-rejection
4 drugs and anti-infectious prophylactic agents. The
5 patient is then, in our case, taken down to the X-ray
6 department -- the radiology suite where an expert
7 intervention radiologist will assess the liver by
8 ultrasound, access one of these peripheral twig
9 branches of the portal vein, and then thread a fine
10 catheter through into the main portal vein up into the
11 liver, and there the cells can be infused. Or we
12 intermittently monitor the portal pressure to be sure
13 that it does not rise.

14 This procedure in our hands typically takes
15 around 20 to 30 minutes. At the end of the procedure
16 the catheter is withdrawn under ultrasound and
17 thoracoscopic guidance, and the tract through the liver
18 where the cells have been infused is sealed with a
19 hemostatic agent to prevent risk of bleeding. A
20 patient is then followed for hours or sometimes up to a

1 day or so by a serial ultrasound and blood test
2 monitoring to make sure there's been no complications
3 such as bleeding or portal vein thrombosis, which in
4 our experience in a large group of patients now is very
5 rare.

6 We've carried out islet cell transplant under
7 Alberta government funding and the Health Canada
8 approval since the 1st of April 2001. We've had
9 continuous approval for islet cell transplantation over
10 the past 20 years at the University of Alberta. Our
11 longest patient now has remained off insulin with their
12 original transplant 21 years after their first
13 infusions. There's been no death as a direct result of
14 the islet infusion or as a direct result of the islet
15 product. We've carried out a total of 693 intraportal
16 islet cell infusions at our single center.

17 This graph shows the patient survival for both
18 our islet cell transplant patients and our whole
19 pancreas recipients across the 20 years after the
20 transplant, and you can see the islet transplants shown

1 in blue here. Including patients at the beginning,
2 often in the age range between 60 and 70, we'll have a
3 75 percent 20-year survival. We therefore regard this
4 therapy as being relatively safe and well accepted by
5 patients with life threatening risks in the vast
6 majority of cases.

7 This graph shows on the left the rates of
8 insulin independence, in other words when a patient is
9 separated from the need for injected insulin therapy.
10 In the red are the whole pancreas transplantation
11 where, of course, the vast, vast majority of patients
12 are able to discontinue insulin immediately after the
13 pancreas is reinfused. In the islet cell transplant
14 this accumulates over time as patients receive their
15 second or occasionally third islet cell infusion, such
16 that by the end of time, we can achieve insulin
17 independence for periods of time in up to 95 percent of
18 patients. Over the course of time, once patients have
19 established insulin independence, we can follow this in
20 both our pancreas transplanted patients over 20 years

1 and our islet cell transplant patients. But not
2 surprisingly, patients that receive a whole pancreas
3 have more durable metabolic control in terms of being
4 fully free of insulin, but nonetheless, these islet
5 transplant patients would go back on to small amounts
6 of insulin -- still continued to benefit from their
7 islet cell infusions irrespective of their achievement
8 or maintenance of insulin independence.

9 Our data from Edmonton studied prospectively
10 over time includes a number of scoring systems,
11 including the Clark score, the hypoglycemic score -- or
12 hypo score, and the (Inaudible) index. Here I'm
13 showing you are data for our hypo score measured before
14 transplant. Scores in the range of 1,500 to 2,000
15 indicate these patients have very brittle, difficult to
16 control Type I diabetes and represent a very small
17 subset of the large numbers of patients that have this
18 disease. These patients are very difficult, if not
19 impossible, to control by other means and have been
20 optimized by all medical therapies or attempts to

1 optimize by medical therapies before they are included
2 in the islet cell transplant.

3 The islet cell transplant procedure rapidly
4 and effectively corrects risk of hyperglycemia, and
5 this is a very durable response. In the vast majority
6 of patients you can see here that these scores remain
7 near zero for 20 years after islet cell transplants
8 irrespective of their ability to achieve insulin
9 independence. The hemoglobin A1C measure, a degree of
10 how well controlled a patient achieves insulin glucose
11 control -- you can see here before transplant our
12 patients have a very wide range of hemoglobin A1Cs, a
13 mean of 8.5 percent. But over the course of 20 years
14 in follow up, these are a subset of patients that are
15 completely insulin dependent.

16 The vast majority of patients maintain their
17 hemoglobin A1C in a 6.5 percent range for long periods
18 of time. And that's the rationale for why we believe
19 that over the course of time this will impact and
20 reduce the risk of secondary complications of diabetes

1 just like it has been proved to multiple times in whole
2 pancreas transplantation.

3 So to conclude our experience, we have
4 achieved near normal glycemic control after islet cell
5 transplantation in the vast majority of patients
6 treated. We've demonstrated long-term islet graph
7 function can be achieved and maintained in most
8 patients, irrespective of the need for small amounts of
9 insulin. And we've been able to establish this therapy
10 as an approved standard of care under Health Canada
11 jurisdiction for the patients with uncontrollable,
12 brittle Type I diabetes for the past 20 years in
13 Canada.

14 Across the world there's been regulation
15 approval for islet cell transplantation, and in this
16 regard the U.S. has lagged behind other countries for
17 various reasons. But we can clearly state that several
18 national and provincial governments have made islet
19 cell transplantation available and funded by government
20 means for the treatment of brittle Type I diabetes as

1 an approved and reimbursable therapy, including
2 Australia, several provinces across Canada, in France
3 now and in Italy, in Switzerland, and through the
4 United Kingdom's National Institutes for Clinical
5 Excellence. Donislecel would be the first approved
6 islet cell therapy to achieve this in the U.S.,
7 hopefully the first of many.

8 And again, finally, I would like to echo my
9 congratulations to Dr. Jose Oberholzer and his team for
10 putting together some remarkable data and very
11 impactful rationale for moving this forward in the U.S.
12 just like it has been successfully applied in many
13 other countries. Thank you.

14

15 **EFFICACY, SAFETY, AND RISK-BENEFIT ASSESSMENT**

16

17 **DR. JOSE OBERHOLZER:** Dr. Shapiro, thank you
18 very much and Dr. Hatipoglu, thank you very much for
19 the introductions and for agreeing to be part of this.

20 With this introduction, I would like now to

1 proceed to discuss our clinical trials. Before
2 presenting the data, I'd like to take a moment to
3 discuss some of the key study design elements from our
4 clinical program. We conducted two pivotal studies,
5 UIH-001 and UIH-002, in addition to participation in
6 the CIT and the small trial that we performed with the
7 University of Chicago where we shipped islet
8 preparation.

9 Both were designed as single armed studies.
10 Endpoints included a composite of the hemoglobin A1C of
11 equal to lesser than 6.5 percent and freedom of severe
12 hypoglycemic episodes and, separately, insulin
13 independence. To enroll, a patient needed to present
14 with Type I diabetes for more than five years,
15 complicated by either hypoglycemia unawareness,
16 exceeding a certain number of hypoglycemic episodes, or
17 suffering from rapidly progressing secondary diabetes
18 complications.

19 Islet doses are typically expressed in islet
20 equivalence per kilogram of recipient body weight as

1 Dr. Papas outlined earlier in the morning. Based on
2 pioneering work by Dr. Shapiro, the recommended dose
3 for our trials was at least 10,000 islet equivalence
4 per kilogram of the recipient's body weight. To
5 achieve this dose, some patients required more than one
6 islet cell transplant, but none received more than
7 three. Our patients received a median dose of 6,600
8 islets equivalent for kilogram per transplant and a
9 cumulative dose of around 700,000 islet equivalents.

10 Because of the allogeneic nature of our
11 product, patients need systemic immunosuppression to
12 prevent rejection of the islet graft and to reduce the
13 risk of recurrent Type I diabetes autoimmunity.
14 Induction immunosuppression was initiated before the
15 islet infusion with the non-depleting monoclonal IO2
16 receptor antagonist, daclizumab; the TNF inhibitor,
17 Etanercept; the calcium inhibitor, tacrolimus; and the
18 N4 inhibitor, sirolimus. Tacrolimus and sirolimus were
19 used for maintenance immunosuppression. Notably,
20 tacrolimus was given at significantly lower doses than

1 used in pancreas transplantation, and no steroids were
2 given. For UIH-002, we added the anti-metabolite, MMS,
3 as an alternative to sirolimus, and thymoglobulin was
4 offered to pre-sensitize the patients. Thymoglobulin
5 is a depleting polyclonal anti-T cell.

6 I'll now briefly discuss the patient
7 disposition, demographics, and the baseline
8 characteristics of our patients. All but two of the
9 patients completed the primary study follow up period,
10 which was defined as one year after a patient's last
11 islet transplant. 63 percent of the patients required
12 more than one islet transplant. Almost half of the
13 patients completed an additional five year follow up
14 period, and 40 percent of patients continued to be
15 followed under the long-term follow up study
16 (Inaudible).

17 The median age of our patients at initial
18 transplant was in the mid-40s, which a range from 21 to
19 67 years of age. Most patients were female,
20 white/Caucasian, with a normal body weight and body

1 mass index. And as in the public forum raised by a
2 public health person, I would be happy to discuss why
3 that is.

4 Prior to transplantation, all patients
5 required insulin with a median of 0.5 units per
6 kilogram per day. The median hemoglobin A1C of
7 enrolled patients was around 7.3 percent. Hemoglobin
8 A1C is measured primarily to determine the three-month
9 average blood sugar levels. All patients were
10 experiencing hyperglycemia unawareness, which was
11 evaluated by the medical history, the patient's
12 endocrinologist, and the multi-disciplinary evaluation.

13 We will now look at various efficacy
14 parameters through year one after the last islet cell
15 transplant, which was the primary follow up period.
16 The first assessment is an analysis of change in
17 hemoglobin A1C values from baseline through year one
18 after the last transplant. The lines in each plot
19 represent a single patient from either UIH-001 or UIH-
20 002. You can see that the majority of patients across

1 both these exhibited a reduction in hemoglobin A1C with
2 most patients achieving a hemoglobin A1C less to or
3 equal to 6.5 percent.

4 The composite efficacy endpoint was a
5 hemoglobin A1C equal to or less to 6.5 percent and
6 absence of severe hypoglycemic events at one year after
7 last transplant. Most patients were successful for
8 this composite efficacy endpoint. The primary reason
9 for failure was roughly equal within having a
10 hemoglobin A1C greater than 6.5 percent and occurrence
11 of severe hypoglycemia. The latter was slightly more
12 frequent, and in most cases the severe hypoglycemic
13 episodes had occurred early after transplantation and
14 not close to the one-year assessment day. Still,
15 because of our trial design, we had to call them a
16 failure.

17 Insulin independence is another important
18 outcome of islet cell transplantation. The restoration
19 of insulin independence removes the risk of
20 hypoglycemia from exogenous insulin. Of the entire

1 pooled population, 20 patients were insulin independent
2 at one year after the last transplant. Notably, four
3 patients who had failed to reach the composite endpoint
4 where insulin independent at one year after the last
5 transplant. These four patient failed the composite
6 endpoint because of severe hypoglycemia early after
7 transplantation but had excellent glycemic control by
8 the time of assessment one year after the last islet
9 cell treatment.

10 The mixed meal test was the secondary
11 assessment used to analyze islet cell function in
12 transplanted patients. For this test fasting blood
13 samples are taken. The patient is then given a liquid
14 meal beverage, and additional blood samples are taken
15 90 minutes later. The purpose of the mixed meal test
16 is to measure insulin production in response to
17 standardized meal with carbohydrates, proteins, and
18 lipids.

19 The left plot displays basal blood glucose
20 level while fasting and 90 minutes following a

1 standardized meal, both at baseline before and one year
2 after islet cell transplantation. Following
3 transplantation there was a significant reduction in
4 both basal and 90-minute medium blood glucose levels,
5 as well as decreased variability for each.

6 The right plot displays C-peptide levels,
7 which is a surrogate marker for endogenous insulin
8 production. At baseline, no patient had measurable C-
9 peptide levels. Following transplant, baseline C-
10 peptide level significantly increased, and there was a
11 very robust physiological increase in C-peptide
12 secretion in response to the mixed meal.

13 To look at blood glucose level data in a
14 little bit more detail, we have created a plot of
15 fasting blood glucose levels at baseline and at one to
16 four week increments through one year after the first
17 transplant. Compared to baseline, fasting blood
18 glucose levels declined within the first week after
19 transplant and remained well below baseline over the
20 entire assessment period. We also assessed blood

1 glucose levels at various times throughout the day
2 before and after meals.

3 The last plot displays blood glucose levels
4 before islet cell transplantation, while the right plot
5 displays blood glucose levels after one year after the
6 last islet cell transplant. You can see that prior to
7 transplant, blood glucose levels were, in general,
8 higher and with more variability compared to after
9 islet cell transplantation, supporting high glycemic
10 control with islet transplant.

11 In addition to the primary follow up, we also
12 assessed the longer-term stability of the islet cells
13 beyond ten years. In this (Inaudible) analyze graft
14 was defined as two consecutive measures of basal C-
15 peptide level below 0.3 nanogram per milliliter. The
16 graft survival probability of donislecel following
17 first transplant was approximately 80 percent or great
18 through five years and greater than 60 percent through
19 10 years post transplant. Following donislecel
20 transplantation, median hemoglobin A1C levels remained

1 below 6.5 percent throughout the entire follow up
2 period of over 10 years.

3 To visualize long term insulin dependence
4 after islet cell transplantation for the individual
5 patient, we have created this plot. Periods of insulin
6 independence are represented by the white boxes and
7 times of insulin use are in black. The X axis displays
8 months after initial transplant.

9 With the exception of five patients in UIH-
10 002, all patients displayed at least one period of
11 insulin independence with many patients being insulin
12 independent for several years. Looking at both the
13 composite endpoint as well as insulin independence, at
14 least 50 percent of patients remaining in the study
15 were successful for each endpoint. All of these data
16 support the long-term stability and the efficacy of
17 donislecel.

18 So how does donislecel compare to other
19 standard of care treatment? While this study did not
20 include active controls, the efficacy of donislecel

1 were compared to standard of care insulin therapy as
2 well as to other islet transplant center data through
3 historical data. On the left you can see the reduction
4 of hemoglobin A1C values following donislecel
5 transplantation is comparable to that of other islet
6 centers, supporting the efficacy of islet cell
7 transplantation overall. On the right, hemoglobin A1C
8 is displayed following insulin therapy at baseline and
9 during follow up. No reduction in hemoglobin A1C was
10 seen with conventional insulin therapy, not even
11 intensive insulin therapy was able to achieve the
12 target of less or equal to 6.5 percent.

13 While intensive insulin therapy's able to
14 reduce hemoglobin A1C levels compared to conventional
15 insulin therapy, intensive insulin therapy has been
16 correlated to an increase in severe hypoglycemic events
17 and thus poses severe risks for brittle Type I diabetic
18 patients. The prevalence of insulin independence was
19 also compared between donislecel and other islet
20 transplant centers. Donislecel displayed comparable or

1 better rates of insulin independence.

2 If I may conclude on the efficacy of
3 donislecel, 20 out of 30 islet cell transplant
4 recipients achieved insulin independence for at least
5 one year. 19 of 30 patients achieved the composite
6 endpoint of a hemoglobin A1C equal to or lesser than
7 6.5 percent and absence of severe hypoglycemia. The
8 most common reason for failing the composite endpoint
9 was a severe hypoglycemic episode early after
10 transplant. There was no primary non-function, and I
11 think this is important when we're going to discuss
12 product relief criteria. So every preparation we
13 transplanted was followed by patients exhibiting C-
14 peptide positivity. The probability of graft survival
15 was over 60 percent through 10 years post-transplant.

16 I'd now like to discuss the safety data of
17 donislecel as collected across our two main clinical
18 trials. All patients in this trial experienced at
19 least one treatment emergent adverse event during the
20 study. Approximately half the patients experienced a

1 serious adverse event. No adverse events lead to the
2 study discontinuation or death during primary follow
3 up. All patients reported an adverse event considered
4 to be related to the study treatment or procedure, and
5 around 80 percent of patients experienced a grade 3 or
6 higher adverse event.

7 The occurrence of adverse events over time is
8 illustrated in this next graph. You can see that the
9 highest incidence of adverse events occurs within one
10 week after transplantation, then declines steadily and
11 reaches consistently low levels from one year after
12 transplant through the remainder of follow up, which
13 here is beyond 10 years. Similar transfers are for
14 serious adverse events and adverse events at grade 3.
15 And just for the sake of precision, we chose to use the
16 denominator of patients who had adverse events for the
17 curve that you see for serious adverse events and
18 higher than grade 3 just to make it fit into that
19 graph, and we show the trend.

20 During primary follow up, gastrointestinal

1 disorders compromised some of the most frequently
2 reported events. Many events are typical of those
3 expected for immunosuppressant use. Diarrhea, anemia,
4 and nausea were the most common adverse events of grade
5 3 or higher.

6 As mentioned before, half of the patients
7 experienced at least one serious adverse event. All
8 serious adverse events listed occurred in three
9 patients or fewer. As shown on the left, anemia,
10 pneumonia, and nausea were the most frequent serious
11 adverse events during primary follow up. These events
12 were not as prevalent during long-term follow up as
13 indicated by the table on the right. We'll go into
14 more detail on those.

15 While no deaths occurred within the primary
16 follow up period, two deaths occurred during the long
17 term follow up. One patient died from fulminant sepsis
18 of unknown origin with multi-organ failure 20 months
19 after islet cell transplant, and the only finding was a
20 previous tick bite. And we could not identify any

1 other cause for the passing away of this patient.
2 Another patient died from the consequences of severe
3 dementia in a confusional state nine years after islet
4 cell transplant. On the right a Kaplan-Meier curve
5 shows the patient survival probability of approximately
6 80 percent of 12 years after the first transplant.

7 Few life-threatening events occurred during
8 the entire follow up period, the most common being
9 recurrent neutropenia in two patients. All of the
10 life-threatening adverse events were reported in only
11 one patient. Most of these events were likely linked
12 to immunosuppression.

13 Four bleeding events were observed after
14 percutaneous transhepatic infusion of islets. Three
15 were treated conservatively, and one patient required a
16 laparoscopy for hemostasis after liver puncture. Six
17 types of malignant tumors were reported throughout the
18 study, primarily occurring several years following the
19 first transplant. This includes one case of post-
20 transplant lymphoproliferative disease with a known

1 complication in organ transplant. All cases of
2 malignancy were diagnosed at an early stage and
3 successfully treated. No patient died from cancer or
4 presented with disease progression.

5 In this next video, we'll share a few of the
6 side effects reported by the patients in our trial.

7 Mike, I will try the second video.

8 (BEGIN VIDEO)

9 **UNIDENTIFIED MALE:** We all have different side
10 effects. Mine were mouth sores. I got them about once
11 every three months.

12 **UNIDENTIFIED FEMALE:** So coping with the side
13 effects, really I didn't find that difficult.
14 Basically it was the first three months after my
15 transplant I had a lot of nausea. I had a lot of mouth
16 sores. Once the initial adjustment happened, I felt
17 like I was a normal human being again, and I hadn't
18 been able to say that for a lot of years. I did end up
19 losing my transplant. I happened to be diagnosed with
20 PTLT, and in order to help get through that they did

1 have to lower my immunosuppression, which ultimately
2 caused me to lose my transplant. I would give anything
3 to have another transplant.

4 (END OF VIDEO)

5 **DR. JOSE OBERHOLZER:** Thank you, Michael.
6 Treatment with immunosuppression is known to increase
7 the risk of developing various infections. Therefore,
8 as expected, several viral and opportunistic infections
9 were reported. Cold sores were very common and likely
10 related to herpes infections. My apologies.

11 Several immunosuppressants are also associated
12 with a decrease in renal function. As a result, the
13 estimated glomerular filtration rate was assessed
14 across the full follow up period. This box plot shows
15 a slight decrease approximately 12 weeks following
16 transplantation. No large decreases in glomerular
17 filtration rates were observed through the long-term
18 follow up. No severe renal impairment and no
19 (Inaudible) renal diseases were observed. It's also
20 important to note that the renal function naturally

1 declines with age, starting in the 30s or 40s, and that
2 the median age at baseline was the mid-40s and that we
3 did not do any adjustment for age for this analysis.

4 So if I may conclude on the safety of
5 Donislecel, treatment emergent adverse events were more
6 frequent in the first year and most frequently in the
7 first week, declining to a low level by the end of the
8 first week. There remained a low occurrence of adverse
9 events through the long-term follow up. Most side
10 effects were considered related to immunosuppression,
11 and there were no procedure related deaths.

12 Given the efficacy and safety data for
13 Donislecel that you just saw, I'd like to take now a
14 moment to place these results in the overall benefit-
15 risk assessment for our product in patients with
16 brittle Type I diabetes. Donislecel fulfills an unmet
17 medical need for patients with brittle Type I diabetes,
18 which again is both a rare and serious disease. It
19 does so by durably improving glycemic control, reducing
20 the progression of secondary complications, and

1 improving patient quality of life.

2 We haven't touched on those last two bullets
3 in great detail, but we know that there is published
4 data that do support the ability of islet
5 transplantation to reduce the progression of secondary
6 complications and to improve patient quality of life.
7 On that last point, I also hope that the patient's
8 testimonials that we are presenting today and those
9 submitted by our patients at the public comment section
10 have provided some insight into the overall patient
11 experience with Donislecel.

12 In addition to the benefits, we also must
13 consider the risks to patients who are administered
14 donislecel and receive immunosuppressants. These
15 include sensitization to the donor antigens and the
16 potential for procedure related bleeding, as well as
17 certain risk that we did not observe in our studies
18 that nevertheless are possible, including donor derived
19 infections and portal vein thrombosis. In addition to
20 this, there are the known side effects of

1 immunosuppression, which are in most cases treatable
2 and reversable with dose adjustments and standard
3 medical care.

4 To reduce the risk associated with Donislecel,
5 we have submitted a risk management plan to the FDA as
6 part of our biologic license application. In
7 accordance with this plan, Donislecel will be
8 manufactured and administered only at the University of
9 Illinois Hospital. Doing so enables us to ensure tight
10 control of the entire process from donor organ
11 procurement all the way through administration of
12 Donislecel to the patients and the follow up.
13 Importantly, only those patients with an acceptable
14 benefit-risk profile will be eligible to receive
15 donislecel. As mentioned previously, this means that
16 eligible patients must meet the American Diabetes
17 Association and Medicare qualifications for pancreas
18 transplantation.

19 In addition, CellTrans will be implementing an
20 ongoing pharmacovigilance program to ensure the ongoing

1 safety of our patients. This will include a
2 continuously updated Donislecel safety database and
3 reporting safety data at least annually to the
4 Collaborative Islet Transplant Registry and surveyance
5 activities. In addition, the transplant centers report
6 the outcomes of the patients via UNOS. Together, these
7 measures should promote the safe and effective use of
8 Donislecel.

9 In conclusion, brittle Type I diabetes is a
10 rare and serious disease associated with severe and
11 potentially life-threatening episodes of hyperglycemia,
12 significant comorbidity, excess mortality, and
13 diminished quality of life. It is a disease for which
14 treatment options are limited to whole pancreas
15 transplantation in the event that insulin therapy
16 fails. Donislecel demonstrates substantial clinical
17 benefit in most patients via durable improvement in
18 glyceimic control and insulin independence that can last
19 for many years.

20 Improved glyceimic control in these patients

1 can reduce secondary diabetes complication and
2 dramatically improve quality of life. Risks are
3 primarily related to the transplant procedure and
4 concomitant medication. Procedure risks are limited
5 and manageable by trained health providers and of
6 significantly more benign nature than those observed
7 after pancreas transplantation. The long-term risks
8 are consistent with those observed with extended
9 immunosuppression, similar to those observed after
10 pancreas transplant. There is also a wealth of
11 clinical data from other islet transplant centers
12 across the U.S. and worldwide over the past 20 years.
13 Collectively, these experiences support islet cell
14 transplantation as an effective treatment option with
15 an acceptable risk profile in patients with brittle
16 Type I diabetes who fail insulin therapy.

17 In closing, I'd like to once again thank the
18 FDA review team and staff and Advisory Committee
19 members for the opportunity to present to you today.
20 I'd like to offer a special expression of gratitude to

1 our patients without whom none of this would have been
2 possible. They are the true heroes of our story, and
3 all the donor families and donors who made this
4 possible, you are our heroes. With that, I'd like to
5 conclude with a final patient testimonial and thank you
6 again. Michael, that will be the last video.

7 (VIDEO PLAYED)

8 **UNIDENTIFIED FEMALE:** I've been off insulin
9 for 16 years now. My first transplant was in 2005 --
10 my islet cell transplant.

11 **UNIDENTIFIED MALE:** I've been off insulin for
12 10 years, going on 11. My crews, my family is huge --
13 my co-workers, none of them have to watch over me. No
14 one's looking to see if I'm crashing.

15 **UNIDENTIFIED FEMALE:** I was off of insulin for
16 over a decade.

17 **UNIDENTIFIED FEMALE:** I would definitely do it
18 again. If for some reason I were to go back on insulin
19 and had the opportunity to get another islet cell
20 transplant, I would do it because I know that it works.

1 It basically functionally cured me of diabetes to help
2 me to live a better life.

3 (END OF VIDEO)

4 **DR. JOSE OBERHOLZER:** Thank you very much.

5 **MR. MICHAEL KAWCZYNSKI:** All right, Lisa. Let
6 me make sure you're unmuted here. Hold on one second.
7 Go ahead.

8 **DR. LISA BUTTERFIELD:** All right. Thanks
9 again to the sponsor team for all of that information,
10 and now I know we're ahead of schedule. But we're
11 going to go ahead and take that 10-minute break, so I
12 have 12:11 here in the West. So we'll come back at
13 12:21 or 3:21 in the East. Thanks very much.

14

15 [BREAK]

16

17 **MR. MICHAEL KAWCZYNSKI:** All right and welcome
18 back to the 69th Cellular Tissue and Gene Therapies
19 Advisory Committee Meeting from our last break of the
20 day. All right. I will hand it back to Dr. Lisa

1 Butterfield. Take it away.

2 **DR. LISA BUTTERFIELD:** Thank you so much. All
3 right, welcome back everyone. And now I'm pleased to
4 introduce our FDA clinical speaker Dr. Beaston who is
5 Medical Officer for the Division of Clinical Evaluation
6 and Pharmacology/Toxicology. Dr. Beaston, please.

7

8 **FDA PRESENTATION**

9

10 **CLINICAL CONSIDERATIONS**

11

12 **DR. PATRICIA BEASTON:** Thank you, Dr.
13 Butterfield. I'm Patricia Beaston. I'm the clinical
14 reviewer for the donislecel (inaudible 05:24:21 YouTube
15 video). I'm an adult endocrinologist currently still
16 practicing (inaudible 05:24:29 YouTube video).

17 So the applicant's proposed indication is
18 donislecel is an allogenic pancreatic islet cellular
19 therapy indicated for the treatment of brittle Type 1
20 diabetes and with labile diabetes in adults whose

1 symptoms are not well controlled despite insulin
2 therapy. We'll discuss elements of this indication for
3 a better understanding of (inaudible 05:25:33 YouTube
4 video) diabetes as you've heard earlier.

5 So from Type 1 diabetes, as you've heard
6 earlier, results from autoimmune destruction of
7 pancreatic islet cells. There are two main issues in
8 the treatment of diabetes with insulin.

9 They are hyperglycemia, complications
10 (inaudible 05:25:43 YouTube video) short-term
11 complications from an inadequate amount of insulin
12 includes hyperglycemia (inaudible 05:25:49 YouTube
13 video) under certain circumstances diabetic
14 ketoacidosis, otherwise called DKA, which is a serious
15 condition that can result in diabetic coma and/or
16 death. In the long-term, persistent hyperglycemia is
17 associated with microvascular disease and the
18 development of (inaudible 05:26:12 YouTube video)
19 neuropathy (inaudible 05:26:15 YouTube video).

20 Hypoglycemia can cause autonomic and

1 neurologic symptoms. Autonomic symptoms associated
2 with hypoglycemia include anxiety, heart palpitations,
3 tremor, sweating, hunger, and paresthesia. If left
4 untreated, hypoglycemia may become severe and cause
5 neurocognitive changes otherwise called neuroglycopenia
6 such as confusion, disorientation, loss of
7 consciousness, seizure, and potentially permanent brain
8 injury (phonetic 05:27:02 YouTube video). (Inaudible
9 05:27:03 YouTube video) cases in most of the cases.

10 Next, I will cover two terms that are
11 important (inaudible 05:27:09 YouTube video). Brittle
12 diabetes represents the most severe phenotype of
13 glucose variability. Historically, brittle diabetes
14 was defined as severe instability of blood glucose
15 levels with frequent and unpredictable episodes of
16 hypoglycemia and/or diabetic ketoacidosis that disrupts
17 life activities, often requiring frequent and/or
18 prolonged hospitalizations. Given the imprecision of
19 the term "brittle" diabetes, it is no longer commonly
20 used, and instead, clinicians focus on individual

1 problems, recurrent DKA or severe hypoglycemia.

2 Brittle diabetes predominately occurs in a
3 setting of absolute insulin (inaudible 05:27:57 YouTube
4 video) undetectable or very low levels of (inaudible
5 05:28:01 YouTube video) compares with Type 1 diabetes,
6 (inaudible 05:28:07 YouTube video). Such patients are
7 treated with multiple daily insulin injections
8 (inaudible 05:28:15 YouTube video) continuous
9 subcutaneous insulin therapy with an insulin pump.

10 It is important to understand that brittle
11 diabetes is a concept and not a defined (inaudible
12 05:28:24 YouTube video). One of the topics we would
13 like the Committee to discuss is the characteristics of
14 patients that might support a favorable benefit-risk
15 assessment for the intraportal administration
16 (inaudible 05:28:36 YouTube video).

17 Today I will present the two main studies
18 conducted with two (inaudible 05:28:43 YouTube video).
19 First, we will review Severe Hypoglycemic Event. As
20 defined by the applicant, it is an event with symptoms

1 compatible with hypoglycemia in which the patient
2 requires the assistance of another person that was
3 associated with either a blood glucose level less than
4 50 milligrams per deciliter or prompt recovery after
5 oral carbohydrate, intravenous glucose, or glucagon
6 administration. We will revisit this definition later
7 in the talk.

8 (Inaudible 05:29:32 YouTube video) previously
9 described, the applicant resubmitted the results of two
10 single-arm open-label studies to support their
11 application. For UIH-001, a Phase 1/2 study and UIH-
12 002, a Phase 3 study, (inaudible 05:29:57 YouTube
13 video) I will refer to them as Study One and Two. It
14 is the natural history for the requirement (inaudible
15 05:30:04 YouTube video) Type 1 diabetes (inaudible
16 05:30:09 YouTube video) and for whole pancreas
17 transplant for the safety of immune suppression in Type
18 1 diabetes received (inaudible 05:30:17 YouTube video).

19 The inclusion criteria look very different in
20 Study One and Study Two. Study One subjects could have

1 reduced unawareness of hypoglycemia and metabolic
2 lability or instability characterized by two or more
3 episodes of documented severe hypoglycemia, or two or
4 more hospital visits for DKA over the last year, and
5 despite efforts at optimal glucose control, progressive
6 to secondary complications of diabetes. These are
7 (inaudible 05:30:59 YouTube video), nephropathy, or
8 neuropathy.

9 Hypoglycemic unawareness is defined as the
10 absence of adequate autonomic symptoms that capillary
11 (phonetic 05:31:08 YouTube video) glucose levels of
12 less than 54 milligrams per deciliter as reported by
13 the (inaudible 05:31:14 YouTube video) contrast Study
14 Two are at least 1 episode of severe hypoglycemia in
15 the past 3 years and a reduced awareness of
16 hypoglycemia (inaudible 05:31:25 YouTube video).

17 Similarly, there were different initial
18 endpoints for those studies. Study One defined success
19 as insulin independence whereas Study Two, as we
20 previously discussed, primary composite endpoint of

1 hemoglobin A1c less than 6.5 percent at Day 365 and
2 free of severe hypoglycemic events from Day 23 to Day
3 365 following the first and last transplant.

4 Secondary was an absence of exogenous insulin
5 reported at Day 1. (Inaudible 05:32:08 YouTube video)
6 composite endpoint in Study Two was suggested in the
7 FDA 2009 guidance which was after the initiation of
8 those studies. And independence was considered to be a
9 key (inaudible 05:32:22 YouTube video) outcome in the
10 guidance.

11 We will discuss the results of these two
12 studies. In total, 30 subjects were enrolled. All had
13 Type 1 diabetes, predominantly female. All were
14 Caucasian with an additional -- there was one subject
15 also identifying as Native American and another one
16 identifying as Hispanic. There were 10 subjects in
17 Study One. We add that our tables may differ from the
18 applicant's. And we identified 20 subjects in Study
19 Two where they may identify 21 subjects.

20 One subject from Study One received an

1 additional transplant (inaudible 05:33:06 YouTube
2 video) performed all analyses considering this subject
3 to represent the outcomes of one subject receiving
4 three transplants rather than one subject receiving two
5 transplants in Study One and another subject receiving
6 one transplant. (Inaudible 05:33:22 YouTube video).

7 Baseline characteristics of the subjects
8 (inaudible 05:33:31 YouTube video) the wide variability
9 in age, diagnosis from 1 to 53 years of age, duration
10 of diabetes from 9 to 53 years of age, and age of
11 treatment 21 to 67 years of age. No patient had high
12 insulin requirements with (inaudible 05:33:52 YouTube
13 video) BMIs (phonetic 05:33:52 YouTube video) that were
14 generally within the normal range. All but 3 subjects
15 had a BMI less than 60 -- 30 -- less than 25 milligrams
16 per meter squared, and the remainder had BMIs less than
17 27.

18 All subjects in Study One and Study Two had
19 hypoglycemic unawareness. Six (phonetic 05:34:14
20 YouTube video) subjects used a personal CGM (inaudible

1 05:34:16 YouTube video) Study One, seven subjects
2 received insulin by injection, (inaudible 05:34:22
3 YouTube video) by pump. Study Two, five subjects
4 received insulin by injection (inaudible 05:34:28
5 YouTube video) by pump. They already used basal analog
6 insulin (phonetic 05:34:32 YouTube video). Three
7 subjects used a (inaudible 05:34:35 YouTube video)
8 and/or regular insulin.

9 Due to provided additional (inaudible 05:34:40
10 YouTube video) dosing, majority used sliding scale
11 insulin dosing. One was described to use insulin
12 sensitivity at (inaudible 05:34:53 YouTube video)
13 likely ratio. The basal rates reported for pumps
14 (inaudible 05:34:58 YouTube video). There were no DKA
15 reported in there prior to or in fact any time during
16 the study (inaudible 05:35:07 YouTube video). In all,
17 there were 56 transplants -- 11 subjects receiving 1
18 transplant, 12 subjects receiving 2 transplants, 7
19 subjects receiving 3 transplants (inaudible 05:35:25
20 YouTube video).

1 The reasons no additional transplants were
2 performed were (inaudible 05:35:32 YouTube video) or
3 that they were insulin independent at the time.
4 (Inaudible 05:35:38 YouTube video) lack of a suitable
5 donor organ or was intolerant to immunosuppression or
6 withdrawing from the study within six months. Or they
7 had complications such as infection that required
8 (inaudible 05:35:50 YouTube video) of immunity.

9 The duration of follow up also varied across
10 the subjects. According to notes (phonetic 05:36:02
11 YouTube video), the first transplant for Study One was
12 in 2004. The first transplant in Study Two was 2017.
13 And the last transplant received by any subject was in
14 2016, which resulted in an unequal (phonetic 05:36:17
15 YouTube video) opportunity to follow up. And that all
16 subjects who received their first transplant later in
17 the studies have a shorter available time for follow up
18 compared to those who received their first transplant
19 earlier in the studies.

20 Total duration of follow up ranged from

1 one-third of the year to up to 13 years. (Inaudible
2 05:36:36 YouTube video) mean duration of 7.8 years for
3 Study One, 4.7 years for Study Two.

4 (Inaudible 05:36:44 YouTube video) go over the
5 efficacy (inaudible 05:36:50 YouTube video) safely
6 describe the applicants primary efficacy endpoints. So
7 the success of 19 subjects (inaudible 05:37:03 YouTube
8 video) having success as defined by their primary
9 efficacy (inaudible 05:37:08 YouTube video) reason why
10 others failed was that they had either failed
11 (inaudible 05:37:15 YouTube video) be free from severe
12 hypoglycemia and/or did not achieve (inaudible 05:37:23
13 YouTube video) a hemoglobin A1c less than 6.5.

14 I would like to discuss the two elements of
15 those primary endpoints. The mean time between the
16 measurement of hemoglobin A1c and first transplant was
17 50 days. The minimum was 3 days, and the maximum was
18 41 days. Of the 30 subjects, 11 or 37 percent had a
19 hemoglobin A1c of less than or equal to 7 percent prior
20 to transplant. Sixty or 20 percent had a hemoglobin

1 Alc of less than 6.5 percent, with 5 and 7 being
2 acceptable targets (inaudible 05:38:07 YouTube video).

3 One subject did not have a baseline hemoglobin Alc
4 reported. (Inaudible 05:38:15 YouTube video).

5 (Inaudible 05:38:19 YouTube video) the
6 alternate, that of the 25 to 30 subjects had mild to
7 severe anemia. Depending on the cause of anemia, an
8 increase (inaudible 05:38:29 YouTube video) turnover
9 which can result in a lower hemoglobin Alc that three
10 subjects required transfusions (inaudible 05:38:37
11 YouTube video) study. These facts can interfere with
12 our ability to (inaudible 05:38:43 YouTube video) rely
13 on hemoglobin Alc measurements in some subjects.

14 Next, we will (inaudible 05:38:53 YouTube
15 video) the hemoglobin (inaudible 05:38:55 YouTube
16 video) severe hypoglycemic events. The applicant used
17 severe hypoglycemia as one half of the composite
18 (inaudible 05:39:02 YouTube video) for efficacy.

19 However, 5 of 10 of subjects in Study One, 9 of 20
20 subjects in Study Two did not have hemoglobin

1 (inaudible 05:39:14 YouTube video) -- did not have SHE
2 reported at baseline. This was not required in Study
3 One where two or more SHE (inaudible 05:39:24 YouTube
4 video) hypoglycemic unawareness could be inclusion
5 criteria but was not required.

6 And in Study Two subjects were not to have
7 (inaudible 05:39:37 YouTube video) severe hypoglycemic
8 event in three years. FDA 2009 guidance considers that
9 subjects who are most likely to benefit from islet cell
10 transplant would be those who cannot achieve acceptable
11 metabolic control, (inaudible 05:39:56 YouTube video)
12 experience multiple severe hypoglycemic events in the
13 year prior.

14 The literature describes SHE, as does the
15 applicant, as hypoglycemic event requiring assistance.
16 Many authors further describe that it would be
17 cognitive dysfunction or neuroglycopenia, a (inaudible
18 05:40:14 YouTube video) the patient would be unable to
19 provide care for him or herself. The workgroup on
20 hypoglycemia details inside (phonetic 05:40:23 YouTube

1 video) and again in 2006 (inaudible 05:40:25 YouTube
2 video) further in stating that assistance requires a
3 person to actively administer carbohydrate, glucagon,
4 or other corrective action.

5 With the missing data, we could not show a
6 change from baseline. Therefore, FDA required the
7 applicant to provide (inaudible 05:40:43 YouTube video)
8 for a document review (inaudible 05:40:46 YouTube
9 video) these events in the year prior to transplant in
10 which the subjects required assistance due to cognitive
11 disfunction. One year prior was chosen to allow for an
12 equivalent period of follow up with the one year after
13 transplant.

14 (Inaudible 05:41:00 YouTube video) analysis
15 was done and that of the 30 subjects, 25 did not have a
16 reported SHE event based on this definition. Of the
17 remaining five subjects, two had one, one had two, one
18 had three, one had four, have (inaudible 05:41:25
19 YouTube video) hypoglycemic events. And this let us
20 unable to demonstrate any (inaudible 05:41:33 YouTube

1 video).

2 So we looked at the goal of islet cell
3 transplant, which is restitution of endogenous insulin,
4 (inaudible 05:41:45 YouTube video) improvement or
5 normalization of glycemic control. Restitution of
6 endogenous insulin addresses the deficit in patients
7 with Type 1 diabetes. (Inaudible 05:41:57 YouTube
8 video) of the duration of insulin independence
9 (inaudible 05:42:00 YouTube video) with a reasonable
10 (inaudible 05:42:05 YouTube video) endpoints. Because
11 if endogenous insulin production is restored to the
12 extent that the patient no longer requires (inaudible
13 05:42:15 YouTube video) then the risk of hypoglycemia
14 in SHE would be removed.

15 Again, I remind you that in Study One it would
16 be (inaudible 05:42:25 YouTube video) primary (phonetic
17 05:42:25 YouTube video) endpoint. And in Study Two it
18 was the main secondary endpoint.

19 Total duration of insulin independence
20 achieved ranged from none -- some subjects in study UIH

1 (inaudible 05:42:42 YouTube video) Study Two and up to
2 13 years in Study One. (Inaudible 05:42:48 YouTube
3 video) we chose to look at the dose by the number of
4 transplants (inaudible 05:42:59 YouTube video).

5 Sorry, I don't have an arrow, okay? I will do
6 my best to orient you. On the Y axis is the total
7 duration of insulin independence a year. On the X axis
8 is the number of transplants received by the subjects.
9 Bars on the left, or in blue, represent the experience
10 from subjects in Study One and the red, or on the
11 right, were those subjects in Study Two.

12 (Inaudible 05:43:42 YouTube video) seen
13 there's a wide range of independence across the number
14 of transplants. Insulin independence could not be
15 predicted by the number of (inaudible 05:44:01 YouTube
16 video). That was 21 of 30 subjects received 47 of 56
17 transplants in the first year.

18 We looked at the outcomes of subjects who
19 received all their transplants within that first year.
20 Then for orientation (inaudible 05:44:24 YouTube video)

1 Y axis shows the duration of insulin independence in
2 years. (Inaudible 05:44:32 YouTube video) for the X
3 axis shows the number of transplants in total received.
4 And the colors now show the number of transplants
5 received in the first year with blue being one, red
6 being two, and green being three transplants.

7 We note that there is no blue bar (inaudible
8 05:44:57 YouTube video) this area because no subject
9 who received three transplants only received one
10 transplant (inaudible 05:45:04 YouTube video). Again,
11 just so you cannot (inaudible 05:45:09 YouTube video)
12 predict duration of insulin independence by the number
13 of transplants. (Inaudible 05:45:16 YouTube video).

14 So this is quite a busy slide. So we're
15 (inaudible 05:45:26 YouTube video) person, the sponsor,
16 the applicant did present it earlier. I color coded it
17 for ease of sharing the transplant intervals.

18 Ten subjects in Study One are provided here.
19 The 20 subjects from Study Two here. This shows the
20 duration of follow up, this being approximately a one-

1 year period, this five year, this (inaudible 05:45:59
2 YouTube video). This small arrow, so the time they got
3 an additional (inaudible 05:46:09 YouTube video).

4 But you can also observe that the lighter
5 color (inaudible 05:46:16 YouTube video). The darker
6 color represented here is where they are insulin
7 independent (sic, chart shows "dependent") with blue
8 representing the first transplant, red the second
9 transplant, green the third transplant. This
10 emphasizes the high variability not only in the
11 variation of follow up but also the intervals between
12 transplants and duration of insulin independence and
13 dependence.

14 In all, 25 subjects had insulin independence
15 for any duration, 1 had insulin independence for more
16 than 1 year, 11 were up to 5 years, and 10 greater than
17 5 years. Five subjects were never insulin independent.

18 Reasons why they received a second transplant
19 for 19 subjects (inaudible 05:47:19 YouTube video) were
20 -- or the reason why the 19 subjects were not --

1 received the -- subject -- received a second transplant
2 (inaudible 05:47:30 YouTube video) would not get a
3 second transplant were (inaudible 05:47:35 YouTube
4 video) or were already insulin independent. Three
5 could not find a suitable donor. Four had intolerance
6 to immunosuppression or withdrew from the study within
7 six months.

8 Note that of six did receive a second
9 transplant (inaudible 05:47:56 YouTube video), six
10 still insulin independent at that time. That can be
11 seen easily with this subject and this subject,
12 (inaudible 05:48:10 YouTube video). For those who
13 received a third transplant, all were insulin
14 dependent. No subject was unable to receive a third
15 transplant (inaudible 05:48:25 YouTube video) available
16 organs.

17 Some subjects were unable to receive a
18 (inaudible 05:48:33 YouTube video) transplant because
19 of intolerance or nonadherence to immunosuppression,
20 and one because of an infection. This also shows

1 patients of the applicant's assessment of their
2 outcomes by the year after their first transplant,
3 (inaudible 05:48:51 YouTube video) year after the last
4 transplant and how this resulted in an unequal period
5 of follow up.

6 This subject, who was followed 13 years, had a
7 prolonged duration of insulin independence, only
8 received one transplant. And therefore, all efficacy
9 and safety data would have stopped at (inaudible
10 05:49:12 YouTube video) at this time point. Whereas
11 this subject, who received two transplants, would be
12 followed up (inaudible 05:49:22 YouTube video) this
13 time period. (Inaudible 05:49:26 YouTube video).
14 Therefore, FDA chose to look at all outcomes for the
15 total duration, time of first transplant (inaudible
16 05:49:39 YouTube video) period followed. (Inaudible
17 05:49:42 YouTube video).

18 Data for changes in hemoglobin A1c and the
19 occurrence of SHE after transplant were not supportive
20 of the efficacy (inaudible 05:50:03 YouTube video)

1 transplant. However, insulin independence of greater
2 than one year was achieved by 20 (sic, correct is 21)
3 of 30 subjects. Insulin independence was identified as
4 a key clinical outcome in the 2009 guidance.

5 The FDA examined whether any baseline factors
6 impact the duration of independence. Specifically, we
7 looked at baseline SHE, hemoglobin A1c, duration of
8 diabetes, age, (inaudible 05:50:32 YouTube video) not
9 identify any major differences. Results in these
10 subpopulations were (inaudible 05:50:38 YouTube video)
11 overall data. No conclusions of benefit or lack
12 thereof for subjects who are not fully insulin
13 independent could be drawn as there were (inaudible
14 05:50:51 YouTube video) numbers of subjects and data
15 subset. (Inaudible 05:50:55 YouTube video).

16 We also note with insulin independence,
17 absence of severe hypoglycemic events is an expected
18 benefit. We'll ask the Committee for a discussion of
19 clinically meaningful duration of insulin independence.
20 (Inaudible 05:51:15 YouTube video). We will discuss

1 safety. (Inaudible 05:51:21 YouTube video).

2 Provided by (phonetic 05:51:28 YouTube video)

3 the applicant, there was 1 death, 11 life-threatening
4 adverse events, 124 severe events, 420 moderate events,
5 1,344 mild events with 142 adverse events without an
6 attribution of severity. (Inaudible 05:51:51 YouTube
7 video) possible adverse events related to the islet
8 cell or (inaudible 05:51:59 YouTube video) as
9 suppression (inaudible 05:52:02 YouTube video).

10 Three of thirty subjects experienced four
11 serious procedure-related adverse events, one liver
12 laceration and vascular injury during the second
13 surgery requiring emergency surgery -- two hepatic
14 hematomas. Two of fifty-six transplants were reported
15 to have elevated portal pressures.

16 Transplant protocols have stated that the
17 transplant was not to proceed if the initial portal
18 pressure was greater than 22 millimeters per mercury of
19 if the portal pressure exceeded 22 millimeters per
20 mercury (inaudible 05:52:42 YouTube video) a pause and

1 restart (inaudible 05:52:45 YouTube video) required,
2 and it could only restart if the portal pressure
3 returned to the normal range. Findings were consistent
4 to the procedures described. (Inaudible 05:53:02
5 YouTube video).

6 Adverse events associated with
7 immunosuppression have been described as anemia, bone
8 loss and osteoporosis and increased fracture. More
9 significantly, (inaudible 05:53:21 YouTube video)
10 and/or the increase of cancer and infections and
11 (inaudible 05:53:25 YouTube video).

12 Time from first transplant to detection of
13 cancer are shown on this slide. Each line represents
14 one of the nine subjects (inaudible 05:53:38 YouTube
15 video) had a reported cancer during the study. The X
16 axis shows the years after the first transplant. We
17 note all of these cancers were reported at least six
18 months after the first transplant.

19 (Inaudible 05:53:55 YouTube video) were two
20 episodes of basal cell cancer, six squamous cell cancer

1 and one malignant melanoma. (Inaudible 05:54:09
2 YouTube video) so there was a (inaudible 05:54:18
3 YouTube video) post-transplant lymphoproliferative
4 disease. These are all (inaudible 05:54:26 YouTube
5 video) derived for patients who receive immunotherapy
6 for transplant (inaudible 05:54:32 YouTube video).

7 We also included the breast cancer, papillary
8 thyroid cancer, (inaudible 05:54:39 YouTube video)
9 other conditions were not uncommon, it is unlikely that
10 given that they were described approximately one year
11 after the first transplant (inaudible 05:54:50 YouTube
12 video) have been related to the immunosuppressant
13 (phonetic 05:54:53 YouTube video). (Inaudible 05:54:54
14 YouTube video).

15 We will look at infections. One subject who
16 received only one transplant died from sepsis and
17 multi-organ failure in the second year after
18 transplant. One hundred seventy-eight adverse events
19 of infection were reported for twenty-six of thirty
20 subjects: one life-threatening urosepsis, twelve

1 severe, ninety-four moderate, fifty-nine mild, and
2 twelve without attribution that included two episodes
3 of pneumonia, two of herpes, and one of cellulitis.

4 Herpes infections can cause (inaudible
5 05:55:36 YouTube video) pain especially oral, and this
6 was noted by some of the subjects who were describing
7 their adverse events during the study. This is
8 important because it can not only cause pain, but it
9 can affect eating. And if progressive (inaudible
10 05:55:54 YouTube video) -- cause neurologic sequelae.
11 We note the four subjects who had achieved insulin
12 independence required discontinuation of
13 immunosuppression (phonetic 05:56:03 YouTube video)
14 (inaudible 05:56:04 YouTube video).

15 Renal function is also important not only to
16 patients with diabetes but is said to be affected by
17 the use of immunosuppression. (Inaudible 05:56:25
18 YouTube video) baseline, 10 of 30 subjects had normal
19 renal function, 14 had mild impairment, and 6 had
20 moderate impairment -- those subjects with severe

1 impairment and those subjects with end-stage renal
2 disease (inaudible 05:56:42 YouTube video). At one
3 year after the first transplant no subject changed by
4 more than one category.

5 Six of the thirty subjects had persistent
6 decline from mild to moderate impairment, one had a
7 (inaudible 05:56:55 YouTube video) decline from
8 moderate to severe impairment. Three subjects had a
9 persistent decline to severe impairment or developed
10 (inaudible 05:57:03 YouTube video).

11 At baseline, five subjects had
12 microalbuminuria at baseline (phonetic 05:57:12 YouTube
13 video) and none had macroalbuminuria at (phonetic
14 05:57:14 YouTube video) one year after the first
15 transplant. Six additional subjects had
16 microalbuminuria (phonetic 05:57:14 YouTube video)
17 (inaudible 05:57:16 YouTube video) had macroalbuminuria
18 (phonetic 05:57:22 YouTube video) (inaudible 05:57:23
19 YouTube video).

20 Of those 10 subjects with significant

1 progression of urine albumin, 5 were insulin
2 independent at the time. While renal function does
3 change with age in patients with Type 1 diabetes, these
4 are the results reported for only a one-year period.
5 Therefore, it is unlikely that either age or Type 1
6 diabetes contributed to these changes.

7 (Inaudible 05:57:51 YouTube video) more likely
8 attributable to the use of immunosuppression (phonetic
9 05:57:53 YouTube video), which again, has been well
10 described. This also shows that insulin independence
11 did not preclude worsening or progression to (inaudible
12 05:58:02 YouTube video).

13 In total, there were 1,319 adverse events in
14 the first year, 452 in years 2 through 5, 271
15 (inaudible 05:58:24 YouTube video) point greater than 5
16 years were easily observed. (Inaudible 05:58:30
17 YouTube video) orientation I will show this is the Y
18 axis shows the severity of the adverse event (inaudible
19 05:58:43 YouTube video). The X axis shows the duration
20 in years from time to first transplant.

1 Here we see that the 30 of 30 subjects had at
2 least 1 adverse event (inaudible 05:58:59 YouTube
3 video) first year after transplant. Twenty-two of the
4 twenty-seven subjects who were followed up to five
5 years attributed adverse events. Twelve of the fifteen
6 subjects who were followed up to ten years (inaudible
7 05:59:18 YouTube video) of the four subjects who were
8 followed for greater than ten years. (Inaudible
9 05:59:23 YouTube video).

10 Now, based on the applicant's approach to
11 looking at not only efficacy but safety (inaudible
12 05:59:37 YouTube video) those one year after the
13 (inaudible 05:59:39 YouTube video) last transplant,
14 this death was not captured for this subject because
15 the event occurred one year after their first and only
16 transplant (phonetic 05:59:53 YouTube video).
17 (Inaudible 05:59:54 YouTube video).

18 Our safety conclusion is that procedurally
19 related adverse events were not unexpected and were
20 consistent with those described for other islet cell

1 programs. Immunosuppression related adverse events
2 were not unexpected either and were consistent with
3 those described for patients receiving whole pancreas
4 transplants. (Inaudible 06:00:23 YouTube video).

5 Next, I would like to discuss support for
6 using insulin independence for a benefit assessment
7 (inaudible 06:00:38 YouTube video). To our knowledge,
8 (inaudible 06:00:41 YouTube video) insulin independence
9 without therapeutic intervention in patients with
10 established Type 1 diabetes, i.e. after the so-called
11 honeymoon period, has not been reported outside of
12 errors in diagnosing monogenic diabetes or onset of
13 insulin (inaudible 06:00:58 YouTube video).

14 Therefore the occurrence of insulin
15 independence can provide an objective measure of the
16 in-depth (inaudible 06:01:05 YouTube video) efficacy of
17 the initial cell transplant. Or insulin independence
18 would be expected to resolve glycemic lability in
19 patients whose sole deficit is absolute dependence on
20 insulin.

1 Subjects enrolled in the two subjects (sic)
2 presented today (inaudible 06:01:24 YouTube video)
3 reminds you that (inaudible 06:01:30 YouTube video)
4 donislecel requires donated cadaveric pancreatic
5 (inaudible 06:01:38 YouTube video) transplant material.
6 That the (inaudible 06:01:45 YouTube video) needs to be
7 done, and these are not likely to be redone.

8 And patient population, who we will be
9 discussing, needs an orphan indication. Although there
10 are many Type 1 diabetes, those who have severe
11 glycemic labilities that puts them at risk when we are
12 trying to attempt (inaudible 06:02:09 YouTube video)
13 glycemic control is a small population. We'll ask the
14 Committee to describe the population that they think
15 might be appropriate for this indication.

16 Finally, I will discuss the benefit-risk.
17 (Inaudible 06:02:30 YouTube video) I remind you that 21
18 subjects achieved insulin independence for greater than
19 1 year, 11 (inaudible 06:02:41 YouTube video) 5 years,
20 and more than 5 (inaudible 06:02:45 YouTube video).

1 Procedurally related adverse events were not
2 unexpected. Immunosuppression-related events were not
3 unexpected (phonetic 06:02:54 YouTube video). However,
4 we cannot only compare this to other islet cell
5 transplants or whole pancreas (inaudible 06:03:01
6 YouTube video).

7 When I described this population enrolled to
8 the subject, I reported that the majority of them
9 (inaudible 06:03:10 YouTube video) were using insulin
10 by injection. None were using dose monitors. This has
11 changed in the years since these studies have
12 (inaudible 06:03:20 YouTube video).

13 Now continued use of basal and analog insulins
14 (inaudible 06:03:27 YouTube video) for standard of care
15 and improved flexibility of dosing. (Inaudible
16 06:03:33 YouTube video) also use insulin sensitivity
17 factors and insulin carbohydrate with ratio dosage for
18 a more tailored approach. Portable pumps allow for
19 multiple basal rates. Use of insulin dose calculators,
20 initially only within pumps, now commonly standalones,

1 decrease errors in dose calculation.

2 There was the introduction and continued
3 improvement in personal continuous glucose monitoring
4 devices that alert the patient to possible hypoglycemia
5 and allow them to react proactively. The element of
6 the artificial pancreas systems can pause and even
7 altar delivery based (inaudible 06:04:12 YouTube video)
8 restititional glucose readings and as interpreted in a
9 complex computer algorithm. While none of these
10 devices are perfect and certainly do not resolve all
11 issues, (inaudible 06:04:26 YouTube video) we ask the
12 Committee to consider these when commenting on the
13 benefit-risk discussion.

14 I would like to thank all who have
15 participated and join Dr. Jayachandra in thanking all
16 CBER staff who contributed to the review of this
17 application in preparation for the AC meeting. I would
18 especially like to thank Drs. Elizabeth Hart and Ilon
19 Irony for their thoughtful discussions of applications.
20 Thank you very much for your attention.

1

2

CLARIFYING QUESTIONS TO PRESENTERS

3

4

5

6

7

8

9

DR. LISA BUTTERFIELD: Terrific. Thank you very much, Dr. Beaston. So we now have an opportunity to ask some clarifying questions of both the sponsors and our FDA presenters. So great, I already see some raised hands. So let's start, please, with Dr. Hawkins.

10

11

12

13

14

15

16

17

18

19

20

DR. RANDY HAWKINS: Thank you very much. The demographic questions related to gender, race, and age, directed to the applicant and Dr. Shapiro from the University of Alberta if he's still present and willing to comment on their experience regarding gender and race, please provide insight into gender and race participation in both studies where there are 80 percent female and only the Caucasian race.

Regarding the age, the average age of participants was in the mid-40s. Please comment on suitability of persons in the lower age spectrum and

1 starting at age 18 and potential adverse events in this
2 group related to potential long-term immunosuppressive
3 therapy.

4 **DR. LISA BUTTERFIELD:** And I will ask all the
5 questioners and the respondents to please turn on your
6 cameras when you're speaking if you can. Thank you.
7 Dr. Oberholzer?

8 **DR. JOSE OBERHOLZER:** Yes. And thank you for
9 these questions. And that, of course, we expected to
10 have, and that is something that we have observed from
11 the very beginning. And please do not consider any of
12 my answers as in any way politically motivated or being
13 in any way disrespectful to this country, that they are
14 just realities.

15 But to be part of this clinical trial,
16 patients needed to document that they were seeing their
17 endocrinologist every three months and that they had
18 access to state of the art insulin therapy. And there
19 are even if some patients were using standard insulin
20 that is directed under their endocrinologist because

1 the basis (phonetic 06:07:28 YouTube video) bolus
2 system may not work because of the severe lows that
3 those patients have.

4 So unfortunately, in this country not every
5 patient does have access to standard of care and
6 particularly minority populations. And you saw that we
7 did (inaudible 06:07:43 YouTube video) at the
8 University of Illinois, that it's really the hospital
9 of minority patients in Chicago. And sadly, very few
10 minority patients do have access to standard of care
11 insulin therapy and were precluded.

12 And we think that's unfair, and it's not
13 right. But on the other hand we could not jeopardize
14 their safety by enrolling them without having actual
15 standard of care insulin therapy (phonetic 06:08:10
16 YouTube video). So that's in regard to the ethnicity
17 and race selection that ended up being mostly by
18 Caucasian women.

19 Then in regard to the patient age, you
20 rightfully said that the concentration of safety on the

1 long-term is a very big consideration. And also for
2 the endocrinologists on the call, they are acutely
3 aware that real hypoglycemia unawareness really takes
4 15 to 20 years (inaudible 06:08:39 YouTube video). It
5 is extremely exceptional for somebody to have that
6 before. That's the range. That's just the time it
7 takes for all the autonomic neuropathology to develop.

8 And so for the young patients we were
9 extremely strict in making sure that really nothing
10 else that could be done. And so that's way you see
11 very few young patients. Most have really very long
12 diabetes (inaudible 06:09:04 YouTube video).

13 Then in regard to the gender, also that has to
14 do with the inclusion criteria where normal insulin
15 requirements were expected. And this is, as Dr.
16 Beaston was explaining, length to the body weight and
17 body mass. And so there is a bias in the selection
18 during the clinical trials to more normal rate or
19 lightweight patients with low to normal insulin
20 (inaudible 06:09:36 YouTube video). Did I answer all

1 the points that you had asked?

2 **DR. RANDY HAWKINS:** You did, and I appreciate
3 that very much. And I don't know, though -- I don't
4 know if Dr. Shapiro is able to give any insight
5 relevant to the question (inaudible 06:09:57 YouTube
6 video) asked or not with the long experience?

7 **DR. JAMES SHAPIRO:** Yes. Thank you for the
8 question (inaudible 06:10:08 YouTube video). It's a
9 very excellent question, and Dr. Oberholzer has
10 answered as best he can. I will reflect on our
11 experience in Canada.

12 (Inaudible 06:10:27 YouTube video). We'd said
13 we do have some gender imbalance come into accept
14 (inaudible 06:10:40 YouTube video) more female patients
15 than (inaudible 06:10:48 YouTube video) effect of -- to
16 hypoglycemia and (inaudible 06:10:52 YouTube video)
17 gender based and it was neutralized or not.

18 I'm not an expert to (inaudible 06:11:04
19 YouTube video) just about that it actually can be for
20 inclusion of minority groups and (inaudible 06:11:20

1 YouTube video) there can be challenge specifically in
2 the context of -- requires very intensive monitoring
3 (inaudible 06:11:34 YouTube video) of the blood levels,
4 management of -- and dynamic changing of (inaudible
5 06:11:45 YouTube video). So that does require
6 (inaudible 06:11:54 YouTube video) and available to
7 travel.

8 So as a result of that -- and there are
9 inherent (inaudible 06:12:00 YouTube video) biases in
10 the acceptance for a treatment approach that (inaudible
11 06:12:10 YouTube video) obviate in practice. That's
12 where I would leave my comments and emphasizing that we
13 never intend to (inaudible 06:12:23 YouTube video) any
14 form of transplant.

15 DR. RANDY HAWKINS: Okay. Thank you.

16 DR. LISA BUTTERFIELD: Dr. Hawkins, did that
17 answer your questions?

18 DR. RANDY HAWKINS: Yes, it did. And thank
19 you very much.

20 DR. LISA BUTTERFIELD: Great. Next, Dr.

1 Harlan.

2 **DR. DAVID HARLAN:** There we go. A question
3 for Dr. Oberholzer and Dr. Beaston. I thought when you
4 presented your data, Dr. Oberholzer, that you said that
5 there were two deaths, one, nine years after the first
6 islet transplant, due to dementia. And I'm curious as
7 to the discrepancy between your data and what Dr.
8 Beaston did.

9 **DR. JOSE OBERHOLZER:** Yeah. I can maybe
10 answer that. So as part of the biologic license
11 application there is a 120-day safety update. So once
12 you submit everything, the agency requires that you
13 submit an update of **innovation (phonetic 06:13:20**
14 **YouTube video)**, 3 months of submission of everything --
15 120 days after submission. And so in our safety update
16 we submitted the additional death. And I think the
17 agency did not include that in their analysis for this
18 presentation.

19 **DR. DAVID HARLAN:** Well, then the follow up
20 is, was there any assessment done to ensure that wasn't

1 something related to immunosuppression like progressive
2 multifocal leukoencephalopathy?

3 **DR. JOSE OBERHOLZER:** Yes. So actually for
4 this specific patient, this is a patient who had
5 extraordinary severe hypoglycemia and was actually
6 dependent on a person to be 24/7 next to that person
7 before transplantation. And so our suspicion -- and
8 again, we don't have an autopsy of the brain or
9 anything like that. The family did not want to do
10 that. But our suspicion over the years as we were
11 following this patient was that there was already early
12 on a significant intellectual impairment in this
13 patient, and that progressed.

14 And in the literature -- and you know better
15 than many of us on the call that the recurrence of
16 severe hypoglycemia unfortunately leads to cognitive
17 impairment in patients over the (inaudible 06:14:38
18 YouTube video). And so this was a progression.

19 And, of course, we don't know whether there
20 were additional factors, but it was not like something

1 very rapidly progressing. It was just over the years
2 the intellectual ability was slowly going down. This
3 is a very long process. And to highlight, maybe, the
4 benefit for the family it was a huge relief that at
5 least they didn't have to worry about the lows because
6 it was very difficult for them too and was the main
7 motivation to do (inaudible 06:15:12 YouTube video).

8 **DR. LISA BUTTERFIELD:** Dr. Beaston, did you
9 have anything to add for the FDA's perspective?

10 **DR. PATRICIA BEASTON:** No. So I did pick this
11 up after everything was written. And I reviewed it,
12 and this patient was (inaudible 06:15:36 YouTube video)
13 needed to actually have had the immune therapy
14 continued even though she had only four days of insulin
15 independence during her whole duration of follow up.
16 And she had a number of adverse events and a very
17 complicated medical history. So I didn't have any
18 additional concerns.

19 **DR. LISA BUTTERFIELD:** Thank you. All right,
20 next question, Dr. Opara, please.

1 **DR. EMMANUEL OPARA:** Okay. So I have a
2 question for Dr. Ricordi and the presenter from the
3 University of Chicago, and one question for Dr.
4 Oberholzer. I'll start with the one for Dr. Ricordi
5 and his colleague from Chicago.

6 I'm curious. I would like to explore further
7 the effects that the FDA approval for this BLA would
8 have on islet transplantation at the other academic
9 centers. Do I understand it correctly that you believe
10 that the FDA approval for this BLA would affect the
11 ability of the other medical centers to provide islet
12 transplantation to this certain group of patients that
13 may need it at their centers? So that would be one
14 question.

15 **DR. LISA BUTTERFIELD:** But Dr. Opara, these
16 are questions to the FDA presenters and to the sponsor
17 presenters clarifying their presentations. This is not
18 (inaudible 06:17:40 YouTube video) --

19 **DR. EMMANUEL OPARA:** Oh. I'm sorry.

20 **DR. LISA BUTTERFIELD:** -- like presentations.

1 **DR. EMMANUEL OPARA:** Okay. I'm sorry. All
2 right. So for Dr. Oberholzer, I wonder when the SHE
3 (inaudible 06:17:58 YouTube video) in the patients that
4 you observed them in. And I would imagine -- I think
5 that you'd explained the SHE (inaudible 06:18:08
6 YouTube video) primarily to the graft failure. So how
7 soon did you observe SHE in those patients related to
8 the time of the graft failure?

9 **DR. JOSE OBERHOLZER:** So there is some
10 variability. So we had hoped that if you would achieve
11 normal glycemia for several years and patients
12 eventually would use the transplant, that they would
13 maybe regain hypoglycemic unawareness (sic). And for
14 most patients, sadly, that was not the case.

15 So I gave you an example. We had a patient
16 who was five years off insulin with perfect hemoglobin
17 A1c and then developed a CMV-related pneumonia for
18 which we reduced immunosuppression for safety reasons.
19 The patient lost the islet cell transplant and within a
20 very short period of time, two or three months, the

1 patient had advanced severe hypoglycemia.

2 So in the past we were always thinking that if
3 you increased the hemoglobin Alc of patients, give less
4 insulin, that they could regain some hypoglycemia
5 **unawareness (sic)**. And that may happen in some
6 patients but not to the extent that they would regain
7 complete hypoglycemia awareness. So the hypoglycemia
8 awareness was only present for as long as they had some
9 basal **C-peptide (phonetic 06:19:20 YouTube video)**
10 production.

11 **DR. EMMANUEL OPARA:** Okay. Thank you.

12 **DR. LISA BUTTERFIELD:** Great. Thank you, Dr.
13 Opara.

14 **DR. JOSE OBERHOLZER:** And again, Dr. Opara,
15 you had initially asked me a question about the
16 consequences of this BLA. And I feel it's important
17 for the Committee to understand that we have waived any
18 exclusivity. So it is not true that we are claiming
19 exclusivity. And this was **(inaudible 06:20:08 YouTube**
20 **video)** all that I get the moment of the BLA submission.

1 We shared with the agency we are not claiming -- we are
2 not going to hold back anybody to submit their BLA.

3 And we know that there are other (inaudible
4 06:20:22 YouTube video) campus, other CIT participants
5 that are working on a BLA submission. And we welcome
6 that. This should be available to as many patients as
7 possible (inaudible 06:20:34 YouTube video).

8 **DR. LISA BUTTERFIELD:** Okay. And we are going
9 to restrict our discussion to this particular
10 application. So if there's nothing else, Dr. Oparah,
11 then we will move to Dr. Morrison, please. And we
12 can't hear you yet, Dr. Morrison. Not yet.

13 **DR. SEAN MORRISON:** Can you hear me now?

14 **DR. LISA BUTTERFIELD:** Yes.

15 **DR. SEAN MORRISON:** Sorry about that. A quick
16 clarifying question for the sponsor. If the BLA is
17 approved, will you take it through the United Network
18 for Organ Sharing and continue to abide by their
19 regulations, for example, on organ safety?

20 **DR. JOSE OBERHOLZER:** Absolutely.

1 **DR. LISA BUTTERFIELD:** Okay. That was short.
2 Dr. Feng, question?

3 **DR. SANDY FENG:** Can you hear me? I'm now
4 working. There's a lot to do here. Okay. Now, thank
5 you. I wanted to ask the sponsor in looking at the
6 data as presented it seems as if perhaps the success of
7 the first patients may have been higher than the
8 success in the second batch of patients. And I wonder
9 if this may reflect donor quality changes over time
10 between the first study and the second study?

11 The second question I would like to ask is
12 since you, I believe, stated that all patients must be
13 treated at the University of Illinois for your product,
14 because shipping has not been demonstrated to be
15 efficacious, I'm concerned about what this means,
16 obviously with respect to restriction in assets.
17 Because the need for multiple transplants will really
18 limit the number of people that can be benefitting from
19 this therapy.

20 And then the third point I would make is I

1 would certainly say that solid organ transplant, which
2 also incurs immunosuppression of the exact same ilk,
3 has a much, much broader demographic profile than your
4 (inaudible 06:23:26 YouTube video) you. And so while I
5 appreciate the need for medical contact and management,
6 I think that I would like you to respond to that.
7 Because particularly also if you're restricting it
8 predominately to people who live near you, I find this
9 access issue kind of disturbing all the way around,
10 particularly in light of the demographics of your study
11 population. Thank you.

12 **DR. JOSE OBERHOLZER:** Thank you so much, Dr.
13 Feng. So in regard to the difference in UIH-001 versus
14 002, it is not uncommon, as you know, in clinical
15 research to have extremely exciting results in Phase
16 1/2. And then you broaden it up a little bit and go
17 into a Phase 3 licensure trial, and then you will maybe
18 see a lesser good outcome.

19 So I can only -- given the very small number
20 of patient it could also just be statistical background

1 noise. And so I can only speculate on some of the
2 reasons for a cell product. And so that means that the
3 overall donor quality certainly has seen exactly what
4 our demographics is. There's more obesity. There's
5 more **comorbidities (phonetic 06:25:10 YouTube video)**.
6 Now, to what point this has influenced in this short
7 period of a few years I cannot say. But this could be
8 something that will make it maybe a little bit more
9 difficult to find the optimal **(inaudible 06:25:22**
10 **YouTube video)**.

11 Then there are also some practical
12 considerations that happen, and these are realities of
13 doing clinical research. The second study started in
14 2007. And you know that in 2008 and '09 there was an
15 economic downturn. So funding for doing clinical
16 trials was massively reduced during that time, and we
17 had a little bit less means to be more aggressive with
18 accepting organs. So we had to be -- for a while it
19 was, as Dr. Beaston said, a little bit more difficult
20 to find organs for patients as, for example, some organ

1 procurement agencies ask for very high prices that we
2 could not afford them.

3 **MR. MICHAEL KAWCZYNSKI:** Okay. Give me one
4 second here. I think -- there you are. You there,
5 Lisa?

6 **DR. LISA BUTTERFIELD:** I'm here.

7 **DR. JOSE OBERHOLZER:** Good.

8 **MR. MICHAEL KAWCZYNSKI:** Okay.

9 **DR. JOSE OBERHOLZER:** I apologize. My cell
10 phone gets tired.

11 **MR. MICHAEL KAWCZYNSKI:** Okay. There we go.
12 All right.

13 **DR. JOSE OBERHOLZER:** Okay. My apologies.
14 And then, of course, there is the variability of
15 patient populations. Again as I said, in such a small
16 group it's difficult to say what was the (inaudible
17 06:26:49 YouTube video).

18 Now, in regard to your second question about
19 the concern of a single center. So you are at UCSF,
20 and you have an excellent islet cell transplant

1 program. And I know that UCSF is part of the CIT and
2 can submit a BLA for UCSF and so can UPenn and so can
3 other centers. Of course, it will be an interesting
4 discussion with -- if the agency -- should we get the
5 BLA, what will be a path to facilitate this? And there
6 are open discussions which I think right now are not
7 appropriate to discuss like sublicensing or having
8 other sites under the same BLA. But I think first we
9 need to get through this.

10 And then the last question was -- oh, and in
11 addition to the single center, so Chicago is extremely
12 fortunate by being in the center of the country. So
13 because of the (inaudible 06:27:46 YouTube video) that
14 we accept, we can pretty much accept organs throughout
15 the country. That is a peculiar situation for Chicago
16 that organ availability should not be a major issue.

17 And then the last is pancreas versus islet.
18 And I think it goes a little bit maybe too far, but I'm
19 a pancreas transplant surgeon. And so I think there
20 will be a population for whom islets will not be able

1 to help them. This will be patients with higher body
2 weight, with higher insulin requirements. Those
3 patients I would still direct to our pancreas
4 (inaudible 06:28:19 YouTube video) patients. And
5 islets ultimately will reserved to a small group of
6 patients who pretty much would meet the criteria that
7 we had in our trials.

8 And in regard to addressing the access issue
9 for minority groups and underserved patients, I think
10 (inaudible 06:28:37 YouTube video) we have a lot to do,
11 and especially for Type 1 diabetes, to make access more
12 fair. And then there will be patients that I think can
13 safely have an islet cell transplant (phonetic 06:28:49
14 YouTube video). We have to create this environment.

15 **DR. JAMES SHAPIRO:** May I make (inaudible
16 06:28:56 YouTube video) comment?

17 **DR. LISA BUTTERFIELD:** Yes, Dr. Shapiro.

18 **DR. JAMES SHAPIRO:** Yeah. Just to add to Dr.
19 Oberholzer's and also to respond specifically to Dr.
20 Feng's question about restricting patients to -- that

1 live locally to the transplant center, in our larger
2 experience outside of clinical trials we've happily
3 engaged patients and transplanted them from other
4 provinces and other jurisdictions and certainly back to
5 their jurisdictions, but on the proviso that they have
6 access to an expert transplant physician who can take
7 care of the (inaudible 06:29:35 YouTube video) risks
8 and complications afterwards.

9 So it doesn't necessarily mean, it shouldn't
10 mean that if the UIC group is approved, that patients
11 will only be able to be managed at that center long-
12 term. I think that's a consideration we should think
13 about more broadly and consider that patients will be
14 managed safely just like any other organ transplant as
15 long as they have access to experts in a local
16 transplant center.

17 **DR. LISA BUTTERFIELD:** Okay. Dr. Feng, did
18 that answer your questions? Okay. All right. So I
19 have six more questions from raised hands, and because
20 we're ahead of schedule I think we'll be able to

1 accommodate all of those. Dr. Roos, your question,
2 please? We see you, Dr. Roos.

3 **DR. RAYMOND ROOS:** All right. Yes. Sorry.
4 So I had a question for Dr. Oberholzler. And I do
5 think it would be valuable to define brittle diabetes
6 in very specific, concrete terms. And second, do you
7 think it would be valuable to have a control group that
8 satisfies that definition but doesn't get islet
9 transplantation not necessarily at the University of
10 Illinois, but it could even be a control group from
11 other Chicago institutions.

12 **DR. JOSE OBERHOLZER:** So Dr. Roos, thanks for
13 this question. We do agree with Dr. Beaston and the
14 agency that for the label we need to define this
15 closer. And I think considering all the work that the
16 American Diabetes Association has done, especially a
17 subgroup of experts on hypoglycemia unawareness, we
18 would like to propose to use strictly the ADA criteria
19 for qualifying for a pancreas transplant minus the
20 eligibility for major surgery.

1 So advantage for our procedure would be that
2 if somebody would qualify for a pancreas transplant but
3 does not meet the fitness level that you need for a
4 whole pancreas transplant, that we will be an alternate
5 (inaudible 06:32:07 YouTube video). So we do agree
6 with that.

7 And I think we will work with the agency on
8 defining this in a way that then also would be
9 acceptable -- because that's another hurdle that we'll
10 have to pass -- that we will be acceptable to Medicare
11 for actual reimbursement (phonetic 06:32:23 YouTube
12 video). Medicare right now, for pancreas
13 transplantation alone, uses the ADA criteria.

14 So if I may summarize how this would work, it
15 would pretty much follow an algorithm that UK Diabetes
16 puts together and that American Diabetes Association I
17 think (inaudible 06:32:44 YouTube video) is to go
18 through a line of treatments that the patient needs,
19 absolutely CGMS, insulin pump, try everything that is
20 available today. And then at the end of the algorithm,

1 there would be the option of either pancreas
2 transplantation (phonetic 06:33:01 YouTube video) or
3 islet cell transplantation (phonetic 06:33:02 YouTube
4 video). So I agree with (inaudible 06:33:04 YouTube
5 video).

6 And then the second question about the control
7 group, I cannot impede myself from smiling a little bit
8 because in academia you have sometimes big plans and
9 you do all the things, and then you encounter a
10 practical person at the FDA, and they smash you. So in
11 2007 Dr. Bruce Schneider, who was Dr. Beaston's
12 equivalent, spent months with me on the phone. And we
13 designed this extraordinary clinical trial with
14 enrollment period and controls.

15 And then we had the face-to-face meeting, the
16 pre-Phase 3 trial. And I apologize. I don't remember
17 his name. But he was a statistician, and he asked me,
18 Dr. Oberholzer, how often do patients spontaneously
19 turn insulin independent once they have Type 1
20 diabetes? And Dr. Schneider said well, never. And

1 then he asked so why exactly do you want to have a
2 control group? And in 15 minutes he demolished 6
3 months of work for this beautiful clinical trial.

4 And then together with the agency we then
5 agreed that it was not meaningful and probably not fair
6 considering that during the enrollment period somebody
7 could die from a severe hypoglycemia or have a severe
8 accident. And so we took the control group out then.
9 That's a long explanation for how we got to a single-
10 arm study without control.

11 **DR. RAYMOND ROOS:** But you had mentioned that
12 there were some limits at University of Illinois in
13 enrolling a number of patients into this clinical
14 trial. So I wondered whether that might be an adequate
15 control group in a way?

16 **DR. JOSE OBERHOLZER:** Yes. We did. So in
17 retrospect there is one thing that I do regret -- is
18 for the patients that we turned down, of course, they
19 were no longer part of the study. If I were to redo
20 this again and go back 15 years, I think I would offer

1 them to enroll in an observational study. Because we
2 had actually a few patients who we had denied because
3 we felt they were not severe enough who then actually
4 died in severe hypoglycemia. And that's just feedback
5 we got from the families. So in retrospect if I were
6 to do this over, I would do exactly what you propose.

7 **DR. RAYMOND ROOS:** Thank you.

8 **DR. LISA BUTTERFIELD:** Thank you, Dr. Roos.
9 Dr. Naziruddin, please. And we can't hear you. Now it
10 looks like your phone is muted.

11 **DR. BASHOO NAZIRUDDIN:** Can you hear me now?

12 **DR. LISA BUTTERFIELD:** Yes. Thank you.

13 Sorry. We can't hear you again.

14 **DR. BASHOO NAZIRUDDIN:** Can you hear me now?

15 **DR. LISA BUTTERFIELD:** Yes.

16 **DR. BASHOO NAZIRUDDIN:** So I'm sorry about
17 that technical difficulty. This question is for Dr.
18 Oberholzer. Just like Dr. Feng, there are two trials
19 you are showing, UIH-001 and 002. When compared to the
20 first trial, the hemoglobin A1c reduction after one

1 year in the first trial is very robust when compared to
2 the second one. That's my first question.

3 The second question is in the insulin
4 independence shown in figure number 12, there are 5
5 patients who did not achieve insulin independence
6 **serially (phonetic 06:37:01 YouTube video)** with either
7 1 or 2 infusions. Do you have any comments on either
8 the product release criteria on that or the patient
9 selection? Thank you.

10 **DR. JOSE OBERHOLZER:** Thank you. So I don't
11 have, off the cuff, the data. I can ask my team to
12 pull this up on what the islet equivalents were for
13 those patients. And as Dr. Beaston alluded to, we had
14 discussions about that. There were some patients we
15 just couldn't find an additional organ for.

16 And, typically, patients who don't achieve
17 insulin independence and have side effects from the
18 immunosuppression will have less tolerance to continue
19 in the trial. So we had a couple of patients dropping
20 out, two patients dropping out of the study because

1 they didn't have as much of a benefit and did not
2 achieve insulin independence (phonetic 06:37:57 YouTube
3 video) but had side effects from the immunosuppression
4 (phonetic 06:37:59 YouTube video) (inaudible 06:37:59
5 YouTube video).

6 So let me quickly check with my team whether
7 we have the data. We're looking for those five
8 patients. May I get back to you and answer other
9 questions in the meantime? And as soon as we have
10 pulled this up, I will reply.

11 **DR. BASHOO NAZIRUDDIN:** Sure, thank you.

12 **DR. LISA BUTTERFIELD:** All right. Thank you.
13 Dr. Breuer, your question. We can't hear you yet.

14 **DR. CHRISTOPHER BREUER:** Will then Alc
15 (inaudible 06:38:46 YouTube video) -- can you hear me?

16 **DR. LISA BUTTERFIELD:** Yes.

17 **DR. CHRISTOPHER BREUER:** My question is in
18 regard to the confounding effects of the anemia induced
19 by the treatment. And I was wondering if there is any
20 method for estimating the effect. For example, if you

1 had a 10 percent reduction in the hemoglobin, is that
2 equivalent to a 10 percent reduction of Alc? If that
3 was taken into account at all in looking at your
4 efficacy?

5 **DR. JOSE OBERHOLZER:** Thank you. So we have
6 not corrected for hemoglobin Alc, and it's a phenomenon
7 that is mostly in the first few weeks of the
8 transplant. But for some reason at the beginning the
9 bone marrow seems to be more sensitive to sirolimus or
10 **MMS (phonetic 06:39:33 YouTube video)**. And we see this
11 declining hemoglobin at the beginning, and then somehow
12 the patients get used to it, and it rebounds.

13 In addition, some patients will have a little
14 bit of hemolysis with some of the anti-infectious
15 prophylaxis like Bactrim. But having enough hemolysis
16 to really have a dramatic impact on the hemoglobin Alc
17 is rare, but it does happen. We see this also in
18 pancreas patients. And then typically the **(inaudible**
19 **06:40:04 YouTube video)** hemoglobin Alc is like 4.2
20 percent. And then the endocrinologist tells you well,

1 don't get too excited; they have a little bit
2 hemolysis. But, of course, after a few months I think
3 the reflection of hemoglobin Alc is real. And, again,
4 this does not affect every patient.

5 **DR. CHRISTOPHER BREUER:** Thank you very much.

6 **DR. JOSE OBERHOLZER:** Does it answer some of
7 your questions?

8 **DR. CHRISTOPHER BREUER:** Yeah. Perfect, thank
9 you.

10 **DR. LISA BUTTERFIELD:** Great. And I'll remind
11 everyone not speaking to please mute yourself. And Dr.
12 Wu, your questions.

13 **DR. JOSEPH WU:** Yeah. So I have a question
14 for Dr. Oberholzer. I'm still not clear on the
15 explanation that you give with regard to the low number
16 of Black and Hispanic patients that were recruited, and
17 80 percent was white females. Because if you look at
18 the demographics in Chicago as well as the patient mix
19 at UIC, which is the hospital where you're at, there is
20 quite a large number are underserved population. And I

1 don't think your patient needs to pay for this
2 particular trial if I am not mistaken.

3 So I still don't understand the logic of the
4 explanation that you give why was it that the 80
5 percent was white female. You mentioned something
6 about patient access. But, again, the demographics it
7 doesn't make sense based on your explanation.

8 **DR. JOSE OBERHOLZER:** And so let me maybe take
9 an example of an area very close to UIC, Humboldt Park.
10 So Humboldt Park is about 85 percent Latino population.
11 And we did a study with a public health person there
12 where we just looked at what is the average hemoglobin
13 A1c in that population for diabetic patients. And it
14 was 13.8 percent.

15 To be part of our study you had to have a
16 hemoglobin A1c less than 10 percent. Because we know
17 that if your hemoglobin A1c is above 10 percent and you
18 dramatically drop it after an islet cell transplant,
19 you will have severe progression of retinopathy with
20 bleeding and so on. And patients can go blind. So you

1 have to be careful that you achieve a baseline glyceemic
2 control so that they will tolerate a rapid drop in
3 hemoglobin (inaudible 06:42:32 YouTube video). So
4 patients living in Humboldt Park have very limited
5 access to standard of care. So they couldn't even meet
6 the inclusion criteria to be part of our study.

7 Now let's say those patients go into renal
8 failure and now need a kidney transplant and a pancreas
9 transplant. In that case, they meet the criteria. And
10 then you look at the demographics of kidney-pancreas
11 transplant at the University of Illinois, it represents
12 exactly the population.

13 So it's really an access issue to the first
14 step of getting standard of care that you need to have
15 to qualify for such an islet cell transplant (inaudible
16 06:43:12 YouTube video).

17 Does this help with this rationale? So it's
18 not a question of the cost. All the costs are covered.
19 And we pay for the immunosuppression.

20 But also, as Dr. Shapiro said, those patients

1 need to be followed very closely and have access 24/7
2 to the primary care physicians that are in contact with
3 the transplant physician (phonetic 06:43:35 YouTube
4 video). And sadly, that was just not given at the time
5 for a very large proportion of who we normally would
6 serve. And I'm not that (inaudible 06:43:45 YouTube
7 video) about that. Thank you.

8 **DR. JOSEPH WU:** Maybe as a quick follow up
9 question because this was not a blind study, and I
10 understand because you're giving the patient,
11 immunosuppressive (phonetic 06:43:55 YouTube video)
12 medication, you're following the patients very
13 carefully. I wonder how much of the positive effect is
14 due to the motivation of the patient, meaning that the
15 patients are being seen all the time. The patient
16 believes that they got a curative treatment. They're
17 much more motivated in terms of healthy diet and
18 exercise and so forth.

19 **DR. JOSE OBERHOLZER:** So that's, I think, why
20 it's important to have included metabolic tests. So,

1 for example, the Mixed Meal Test that shows a dramatic
2 increase in C-peptide at basal and stimulated this
3 almost psychological response. That you can provide
4 any kind of follow up, but you won't be able to
5 regenerate endogenous (inaudible 06:44:42 YouTube
6 video). I can, of course, not exclude that there is
7 some additional effect because we took extremely well
8 care of those patients. So that, yes, that surely
9 contributed to the overall wellbeing of (inaudible
10 06:44:59 YouTube video).

11 **DR. JOSEPH WU:** Thank you.

12 **DR. LISA BUTTERFIELD:** Thank you. So I see
13 four final questions for this part. And then we'll
14 move to the Advisory Committee discussion. Dr.
15 Goldstein, please.

16 **DR. LAWRENCE GOLDSTEIN:** Thank you, Dr.
17 Butterfield. I have a question for Dr. Shapiro,
18 please. Dr. Shapiro, during your presentation you
19 stated that the Edmonton protocol, if I remember it
20 correctly, did do tissue typing and tissue matching

1 between donor and recipient. I guess my question is
2 has Canada continued to require that kind of tissue
3 type matching and if not, has it affected the success
4 rate or behavior of disease at all?

5 **DR. JAMES SHAPIRO:** That's an excellent
6 question. We're in the process of analyzing our data
7 on HLA matching right now. I would say with almost 700
8 different transplants and with multiple, different
9 donors, it becomes a very complex analysis. So I don't
10 have all the answers to your questions. Every patient
11 is assessed for their immunoreactivity. We assess the
12 **panel (phonetic 06:46:14 YouTube video)** reactive
13 **antibody whether (phonetic 06:46:15 YouTube video)**
14 preformed antibodies. And we rely very heavily on our
15 HLA teams to screen that out.

16 And we basically follow through standard
17 processes that we're using across all organ
18 transplantation, perhaps with more tolerance in liver
19 transplantation for accepting sensitized recipients.
20 But we follow, essentially, the process that is used in

1 our center for kidney transplantation for selection and
2 the appropriate matching of donors if that makes sense
3 to you.

4 So a lot of times we'll use a virtual cross
5 match. Just from the practical point of view, a donor
6 might be coming from right across the country for islet
7 isolation/donor pancreas. So we can't know when we
8 accept that pancreas that we can't necessarily obtain a
9 prospective cross match. So in those situations we'll
10 often use a virtual cross match. And we've found that
11 over the last several years to be very effective.

12 **DR. JOSE OBERHOLZER:** Just to clarify, so we
13 did a cross match for every patient.

14 **DR. LISA BUTTERFIELD:** All right. Thank you.
15 Dr. Harlan.

16 **DR. DAVID HARLAN:** I'm confused by this
17 concept, Dr. Oberholzer, of not finding a second donor
18 when patients didn't achieve insulin independence. I
19 just don't understand what you mean by that. Was there
20 a time limit to finding the second donor?

1 **DR. JOSE OBERHOLZER:** There was no time limit.
2 It is just the question was specific to the five
3 patients that never achieved insulin independence and
4 why they did not wait because they could have waited to
5 get another islet infusion. And, in general, for two
6 patients it was they got frustrated with the situation
7 of suffering the side effects of immunosuppression but
8 not being off insulin. And at some point, we lost the
9 patients and dropped out. One patient, for example,
10 preferred to get a pancreas transplant, and she was
11 taken off the islet list and received a (inaudible
12 06:48:25 YouTube video). Does this answer your
13 question?

14 **DR. DAVID HARLAN:** Yes. Thanks.

15 **DR. LISA BUTTERFIELD:** Great. Dr. Fox.

16 **DR. BERNARD FOX:** Yes. My question was for, I
17 believe, for Dr. Shapiro. I was really particularly
18 impressed with the dataset that you provided in the
19 long-term follow up on your patients. And it's sort of
20 related to the CMC question because I think you

1 commented that you don't do OCR and you do islet cell
2 number. And my question, really, is there some other
3 CMC component that you do? And I imagine you're
4 familiar with what's happening with the product that
5 we're talking about today. Is there some other CMC
6 type criteria that you employ besides islet cell number
7 that either is or is not being used here?

8 **DR. JAMES SHAPIRO:** Yeah. Thank you, Dr. Fox.
9 We **typed (phonetic 06:49:33 YouTube video)** a lot of
10 data, of course, on the potency and sterility of the
11 islet product. But I would echo the comment that Dr.
12 Oberholzer made earlier on in his presentation that we
13 virtually never see a primary nonfunction of an islet
14 cell graft. So we do not find the oxygen consumption
15 rate -- and we've studied this a lot in our center --
16 we don't find it here a useful or practical measure.
17 We essentially use the, as I mentioned, the islet
18 number. And we do have measures of viability which I
19 must admit are crude, but we use those.

20 And so if we have a viable product with

1 adequate number of islets that are surviving in
2 culture, just from a practical point of view in Canada
3 that has served as the best rather than any specific
4 inline potency test before release. And they are
5 accepted -- I'm talking here to the FDA, and I know
6 that the potency release assay testing is a terribly
7 important component of drug and cell therapies. But in
8 practical terms, it is so incredibly rare to have an
9 islet product that does not function and make C-peptide
10 in the recipient.

11 I've think I've seen that only once in those
12 693 transplants. And that was with a pediatric -- I
13 think it's a 5- or 6-year-old pancreatic donor that was
14 a very unusual donor for us to use. Other than that,
15 I've never seen primary nonfunction in an intraportal
16 islet transplant.

17 So coming from this from a different direction
18 I suppose, coming 20 years later in a practical, well
19 established islet cell transplant program, we've not
20 found the in vitro testing to be particularly valuable

1 over the course of time. And we are certainly open to
2 new and improved measures. And as they evolve and
3 become established, we would certainly consider those.
4 But for the time being we've not found them to be a
5 decisive factor in a go/no go situation for islet cell
6 transplantation.

7 **DR. BERNARD FOX:** If Dr. Butterfield will
8 allow me, I'd ask one more quick question?

9 **DR. LISA BUTTERFIELD:** Yes, please.

10 **DR. BERNARD FOX:** Yes. So also with your
11 long-term follow up I was very impressed with your eGFR
12 rates and how they had stabilized. Do you see other
13 diabetic complications also not developing like ocular
14 complications, retinopathies, other things happening or
15 no?

16 **DR. JAMES SHAPIRO:** Yes. So I would refer you
17 to other studies that have rigorously looked at that in
18 controlled settings in islet and pancreas
19 transplantation. We have studied that but not in the
20 detail that, for example, Dr. Oberholzer's group has

1 done with the (inaudible 06:52:22 YouTube video)
2 fitness measurements and other extensive studies from
3 Italy.

4 So there's a large amount of data, but it has
5 not come from our own group, largely, in terms of
6 protection of renal function, protection of
7 retinopathy, and other secondary complications of
8 diabetes. There's published literature out there that
9 I think is very solid. But we don't own that data. I
10 can't really directly comment from our own group.

11 **DR. BERNARD FOX:** Thank you very much.

12 **DR. LISA BUTTERFIELD:** All right. Thank you.
13 And our final clarifying question before we go to the
14 Committee discussion, Dr. Opara, please. It looks like
15 Dr. Opara has put his hand back down. So that
16 concludes then our clarifying questions.

17

18 **QUESTIONS TO THE COMMITTEE/COMMITTEE DISCUSSION**

19

20 **DR. LISA BUTTERFIELD:** And now we're going to

1 move to the clinical questions to the Committee for
2 Committee discussion. So let's see if we have a slide
3 for that. Okay. We've got a cover slide for that.
4 Great. Thank you very much.

5 So here we're talking about the primary
6 composite efficacy endpoint and the differences between
7 the endpoints in the two studies, and this was covered
8 by Dr. Beaston initially. So you've seen that, and so
9 what we want to discuss here is the minimum duration of
10 insulin independence that the Committee would consider
11 to be clinically meaningful, that would really
12 represent benefit for the individual patient. For that
13 I'll start with Dr. Harlan, please, as primary
14 discussant on this before we open it up to everyone on
15 the Committee.

16 **DR. DAVID HARLAN:** Will the questions be shown
17 like they were before?

18 **DR. LISA BUTTERFIELD:** Yes. So the questions
19 are back up there. That's the first of the two
20 questions.

1 **DR. DAVID HARLAN:** Well, the answer is that
2 it's highly variable. I think anything -- one of Dr.
3 Oberholzer's answers to his question earlier was he
4 wished, if he could go back 15 years, he would have
5 included a control group to see how the control group
6 did relative to patients that got an islet transplant.

7 And part of the difficulty in answering this
8 question is that the standard of care for those with
9 diabetes, as Dr. Beaston pointed out, has changed so
10 dramatically over the last five years with continuous
11 glucose monitors and closed-loop insulin pumps such
12 that I very rarely see someone with uncontrollable
13 hypoglycemia or recurrent DKA anymore. And I actively
14 have seen patients for 35 years. So the bar keeps
15 going up. But I would think anything less than four to
16 five years of insulin independence or complete absence
17 of hypoglycemia with an easily controlled insulin
18 regimen is the current bar.

19 **DR. LISA BUTTERFIELD:** Perfect. Thank you
20 very much for starting us off. So for the rest of the

1 Committee I'm watching for raised hands to address this
2 clinical question. So, in particular, our clinical
3 experienced members. Thank you. Dr. Leschek.

4 **DR. ELLEN LESCHEK:** Okay. I think I'm
5 unmuted, right?

6 **DR. LISA BUTTERFIELD:** Yes. We hear you,
7 thank you.

8 **DR. ELLEN LESCHEK:** Okay. All right. I
9 actually agree with Dave. I think that the bar is
10 continuously changing. And when Dave said that he
11 rarely sees somebody who he can't control and keep from
12 being severely hypoglycemic or severely hyperglycemic,
13 I think that's a really important point. Because a lot
14 of these people who are termed "brittle diabetes",
15 really, they show up for these studies, and the truth
16 of the matter is a really skilled endocrinologist is
17 able to control them and to prevent a lot of this
18 severe hypoglycemia and hyperglycemia.

19 So I agree that the bar is high, and I think
20 you'd really have to have -- in order to outweigh the

1 risks of the immunosuppression, and they are
2 considerable -- I think you really have to have a good
3 amount of time where you're insulin independent maybe
4 four or five years as Dave suggested.

5 **DR. LISA BUTTERFIELD:** Thank you very much.
6 Dr. Opara, what are your thoughts on this first
7 question to the Committee?

8 **DR. EMMANUEL OPARA:** Hello. Can you hear me?

9 **DR. LISA BUTTERFIELD:** We can hear you, thank
10 you.

11 **DR. EMMANUEL OPARA:** Okay. Yeah. So my
12 question is to Dr. Harlan. It's interesting to hear
13 about the ability of current regimens to manage
14 hypoglycemia. Can you speak to the issue of difficulty
15 in controlling the blood glucose on just pure insulin -
16 - on insulin? Because one of the problems that the
17 brittle Type 1 diabetes is characterized, which is the
18 fact that you have this labile glucose -- I mean
19 fluctuations in glucose **level (phonetic 06:59:06**
20 **YouTube video)**.

1 **DR. DAVID HARLAN:** Yes. I don't want to -- I
2 won't use any brand names but with the continuous
3 glucose monitors now hooked up to insulin pumps that
4 sense falling sugars even before they get low and
5 suspend insulin release -- and then, of course, there
6 are pumps and meters coming along that have the ability
7 to infuses doses of glucagon too. And we've tested
8 those in clinical trials. But the closed-loop insulin-
9 only pumps are in current use, and they're game
10 changers.

11 People whose sugars couldn't be controlled
12 coming in with hemoglobin A1cs of 7 percent and -- for
13 instance, patients that had had a previous pancreas
14 transplant that failed and were signed up for another
15 pancreas transplant and they come to see us; and we put
16 them on these things and they say, gosh, I guess I'll
17 avoid the second surgery. It's testimonial that those
18 closed-loop pumps are game changers, Dr. Opara.

19 **DR. EMMANUEL OPARA:** Thank you.

20 **DR. LISA BUTTERFIELD:** All right. Other

1 comments on this first clinical discussion question?

2 Great. Dr. Wu.

3 **DR. JOSEPH WU:** Yeah. So I have a quick
4 question. I'm a cardiologist. I'm not a diabetic
5 specialist.

6 But for somebody who's a brittle diabetic and
7 who's super, super motivated and would join a clinical
8 trial, get the therapy, get the cell, get the
9 (inaudible 07:00:55 YouTube video) injected, follows up
10 with clinic, with coordinators -- I don't know -- a
11 couple times a month or something like that; in that
12 scenario if the same person had been in the placebo
13 group, do you see the brittle diabetics in the placebo
14 group who are very motivated, exercise, healthy diet
15 but undergo placebo treatment would be completely
16 insulin free? Do you see that?

17 **DR. DAVID HARLAN:** Are you directing that to
18 me, Dr. Wu?

19 **DR. JOSEPH WU:** Yeah. The diabetic
20 specialist, yeah.

1 **DR. DAVID HARLAN:** So restate the question
2 because I didn't quite follow it.

3 **DR. JOSEPH WU:** Yeah. So these are brittle
4 diabetic patients, and I assume lifelong they've been
5 using insulin. But they go in a clinical trial because
6 they're super motivated. And I'm just asking in a
7 placebo situation in which the patient got a placebo
8 treatment -- he or she did not know that he or she got
9 a placebo treatment, he would be super motivated, got
10 the treatment placebo, exercises every day and
11 afterwards healthy diet, and monitors the sugar all the
12 time, would that change the person from being insulin
13 dependent to nondependent?

14 **DR. DAVID HARLAN:** Oh no. That person is
15 clearly, as Dr. Oberholzer shared when he met with
16 Bruce Schneider and the statistician, we don't see
17 people with diabetes that come off insulin. They're
18 still on insulin. And I don't discount for a second
19 the real need to come up with curative therapies.

20 I think we started today with saying we're

1 approaching the 100-year anniversary of the first shot
2 of insulin being given. Therapy for Type 1 diabetes
3 hasn't changed, really, in 100 years. It's insulin and
4 diet. Coming off insulin is a game changer if it's
5 safe and long lasting. And that's the difficulty.
6 That's where we have trouble adjudicating the
7 therapeutic equipoise.

8 **DR. JOSEPH WU:** Yeah. So this is very helpful
9 for me to understand because then in that case, there's
10 a biological effect, and then you got to weigh how much
11 you're willing to take the serious adverse events then.
12 Thank you.

13 **DR. DAVID HARLAN:** Absolutely.

14 **DR. ELLEN LESCHEK:** What I would say is that
15 that placebo group will get the benefit, hopefully, of
16 getting close control, close, very intensive care. And
17 their brittle diabetes may not be so brittle anymore,
18 and they may not have all of those extremes that they
19 were having before. And that was kind of the
20 impression I got when he was talking about regretting

1 not having a control group is that a placebo control
2 group getting optimal standard of care may very well do
3 a lot better than what they were doing before they got
4 into the study.

5 **DR. JOSEPH WU:** Yeah. And that was my concern
6 as well, meaning that how much of this is due to
7 treatment and how much of this is due to patient
8 education, motivation? Yeah.

9 **DR. LISA BUTTERFIELD:** All right. Thank you
10 for this discussion. So we'll go next to Dr. Feng, and
11 then Dr. Hatipoglu from the sponsor's group will make a
12 comment. Dr. Feng, please.

13 **DR. SANDY FENG:** Yes. I actually have a
14 question for Dr. Harlan on availability of these new
15 therapies. Since I'm in the transplant world, I'm very
16 familiar with the immunosuppression and all that. But
17 it seems to me that in the islet transplant field we
18 have sort of this vicious cycle. The people who can't
19 achieve some reasonable control are also those who
20 can't get the islet therapy because they aren't

1 achieving some reasonable control.

2 Another vicious cycle is people who are less
3 compliant, which are not the people who are enrolled in
4 the study but may be people who benefit or take
5 advantage of the therapy if it were approved. Those
6 who are less compliant are also potentially more likely
7 to lose their islet graft function or to have
8 deteriorating graft function. So we're sort of back to
9 the best patients can get the best treatments and then
10 can get the best outcomes.

11 And so my question is what is the availability
12 of these closed-loop gadgets in terms of disseminating
13 to not the best patients who don't have the best care
14 and who are currently getting the worst outcomes?
15 Because that seems to be an important thing.

16 And I guess one of the slides also said that
17 no more trials are going to be done; these are so long,
18 these are so expensive. I mean, rather than the **blind**
19 **(phonetic 07:06:13 YouTube video)** control group, the
20 control group is really the best possible therapy. And

1 it's the problem that everybody has identified is that
2 the best possible therapy has changed over 15 years,
3 and we don't have any comparison directly to that
4 group. So it's sort of the availability of the current
5 best possible therapy.

6 **DR. DAVID HARLAN:** My general comment is this
7 has been a fantastic day, and a lot of smart people
8 have said a lot of really good things. Nobody has said
9 a word about that 80 percent of patients that you're
10 talking about that aren't getting good control because
11 there's no resources. None of this is going to apply
12 to those people. And, unfortunately, I think as a
13 healthcare system that should be our goal. But islet
14 transplant, pancreas transplant, closed-loop pumps in
15 our current healthcare finance system, none of those
16 things are going to reach that patient population in
17 greatest need.

18 **DR. LISA BUTTERFIELD:** Okay. So we are going
19 to have a brief comment from the sponsors team.

20 **DR. BETUL HATIPOGLU:** Can you hear me? This

1 Dr. Hatipoglu.

2 **DR. LISA BUTTERFIELD:** Yes. Yes, please.

3 **DR. BETUL HATIPOGLU:** Yes. And I wanted to
4 just comment as an endocrinologist who has been
5 treating a lot of Type 1 diabetes in my life and I
6 actually made my career, a few comments that I would
7 like to make. One is when it comes to minorities as we
8 do take care of them, we have to also consider that
9 Type 2 diabetes is much more common in minorities than
10 Type 1. And that their obesity rates are much higher
11 than the white ethnic groups, which also excludes them
12 from this kind of enrollment.

13 Second of all -- at least in Ohio where I
14 practice -- perhaps where Dr. Harlan practices is not
15 the same -- but I could write these closed-loop pumps
16 or other technology to our underserved population
17 because our Ohio CareSource, which is a **public aid**
18 **(phonetic 07:08:44 YouTube video)**, and Medicare both
19 pay for it. The challenge is even though I have seen
20 in my career -- just reminding you that I come from a

1 background where we boiled the needles for insulin
2 because where I was actually trained in my country, we
3 didn't have disposable needles -- to see where we came
4 today with closed-loop is like a miracle in my own
5 career.

6 Nevertheless, I also have to admit that they
7 are not perfect. During the times my patients,
8 unfortunately, wearing those devices **who (sic)** are
9 supposed to save my patients, I lost a few of them.
10 Which is very sad for a physician who indeed becomes a
11 friend with their patients who chronically need
12 management. And these say -- these six --

13 **DR. LISA BUTTERFIELD:** Dr. Hatipoglu, I'm
14 going to ask you to cut it short because this is mostly
15 Committee discussions so very briefly your point.

16 **DR. BETUL HATIPOGLU:** Sure. These were the
17 things that I wanted to -- even though there's the
18 technology, it doesn't always work. And there's still
19 subgroup of patients who -- we need an alternative.
20 And pancreas transplant is currently the only

1 alternative, which is not ideal for everybody. And I
2 just wanted to clarify that it doesn't sound like
3 technology out there is going to save everybody. I
4 wish. But it doesn't unfortunately, yet at least.
5 Thank you.

6 **DR. LISA BUTTERFIELD:** All right. Thank you.
7 All right. So I still see hands up from Drs. Wu and
8 Feng, but we've heard from them. So we're going to Dr.
9 Hawkins, please.

10 **DR. RANDY HAWKINS:** I'm okay, actually. Drs.
11 Feng and Wu raised the points I was interested in.

12 **DR. LISA BUTTERFIELD:** Thank you. All right.
13 Well, we've talked a good bit about Question number 1.
14 So why don't we move to Question number 2? And here is
15 that question that's now up on the board.

16 So this is about the designation treatment of
17 brittle Type 1 diabetes as the indication. And so we
18 want to discuss the benefit-risk profile for the
19 product in general and if we can, define subset of the
20 diabetics that would be most appropriate as a target

1 population. So I will watch -- okay. Let's hear from
2 Dr. Hawkins, please, on this second question.

3 **DR. RANDY HAWKINS:** Okay. Can you hear me?
4 It's a question. Can you hear me? I'm not getting --

5 **DR. LISA BUTTERFIELD:** Yes. Quality is
6 imperfect, but we can hear you.

7 **DR. RANDY HAWKINS:** Okay. This is a slide
8 shown by Dr. Oberholzer regarding the adverse effects.
9 And it appears that those adverse effects occurred
10 relatively early. And I couldn't find the slide to see
11 what duration we're talking about over a year.

12 So really asking the transplant experts, the
13 folks who (inaudible 07:11:53 YouTube video) these
14 patients early on, the duration of these adverse
15 effects? I couldn't see if they're happening in the
16 first two or three months and they're gone, and the
17 adverse events trail off for the years and years that
18 the person is (inaudible 07:12:07 YouTube video)
19 transplant (inaudible 07:12:10 YouTube video).

20 **DR. LISA BUTTERFIELD:** (Inaudible 07:12:16

1 YouTube video). Thank you.

2 **DR. RANDY HAWKINS:** I don't know if my
3 question came through. I was trying to get an idea
4 about the duration of these adverse effects related to
5 the immunosuppressive therapies. I have a patient who
6 has had a combined pancreatic-renal transplant. She's
7 five years out, and she has had no side effects from
8 immunosuppressants. So just getting any kind of feel
9 (phonetic 07:12:45 YouTube video) from the experts
10 about this duration of adverse effects which appeared
11 to be very, very low when we looked at that curve.

12 **DR. LISA BUTTERFIELD:** Dr. Oberholzer,
13 (inaudible 07:12:58 YouTube video)?

14 **DR. JOSE OBERHOLZER:** Is the question
15 addressed to me or to the Committee?

16 **DR. RANDY HAWKINS:** Actually, I'm trying to
17 get information from anyone. Particularly, I would
18 like to hear from some of those people who actually do
19 this on a daily basis, the members of the panel that
20 actually are treating patients, following patients.

1 **DR. JOSE OBERHOLZER:** So, as I said, I am a
2 pancreas transplant surgeon. Dr. Feng, please go ahead
3 first. I apologize.

4 **DR. SANDY FENG:** Oh, so it is pretty well
5 accepted that the toxicities of immunosuppression are
6 cumulative. The longer you're on them, the more
7 overall risk they pose. Certainly, I think you saw
8 that the cancer risk is -- for example, skin cancers.
9 It's pretty well known that as you spend 5, 10, 15, 20
10 years on immunosuppression your risk of skin cancer
11 continues to escalate along with other cancer.

12 The proteinuria is again, something that is
13 likely, as was attributed by Dr. Beaston, related to
14 the immunosuppression. And that can also take its toll
15 over time. So while your personal patient doesn't
16 exhibit any signs or complain of any symptom, the
17 cumulative nature of the immunosuppression is what is
18 widely believed to result in cumulative toxicity over
19 time.

20 I think the other piece of it that I was

1 raising is as one loses organ function, then one is
2 less interested in maintaining the immunosuppression
3 because now you're on drugs that are not helping your
4 organ if it's, now, they're beginning to fail or
5 failing. And so that actually is when you face an
6 increased risk of potentially becoming sensitized to
7 the organs because while they're not working, they're
8 still in your body and displaying HLA.

9 And so even if -- so there's a downside to
10 staying on immunosuppression indefinitely because of
11 cumulative toxicity. But if your organ has stopped
12 working, there's also a downside to reducing
13 immunosuppression potentially because of the
14 sensitization that would make it difficult for you to
15 get another islet or some other transplant.

16 **DR. RANDY HAWKINS:** Thank you.

17 **DR. LISA BUTTERFIELD:** Dr. Harlan, did you
18 want to weigh in on this specific question about the
19 risk-benefit profile or defining the subset of
20 diabetics for this therapy potentially? Or perhaps

1 while Dr. Harlan is considering Question number 2, we
2 can go to Dr. Walters who is also wanting to make a
3 point and ask a question.

4 **DR. MARK WALTERS:** Yes. Thank you. I needed
5 some help both from the sponsor and the experts in
6 endocrinology diabetes about the mortality risk. The
7 two patients who died on the study, one of whom
8 appeared to have an infection perhaps related to the
9 immunosuppression -- and whether the mortality risk in
10 best available therapy is comparable to that observed
11 in this period of time of follow up in the two studies.

12 In particular, I recognize that the transplant
13 itself may carry a higher mortality risk in the short-
14 term but because of the reduced symptomatology and need
15 for insulin replacement, result in benefits and quality
16 of life that are hard to compare to mortality risk --
17 and how the experts and the sponsor consider that risk-
18 benefit aspect of the therapy? Thanks.

19 **DR. LISA BUTTERFIELD:** Thank you. Dr. Harlan,
20 do you want to weigh in? Not hearing you, Dr. Harlan.

1 **MR. MICHAEL KAWCZYNSKI:** Dr. Harlan, hold on a
2 second. Let's see if I can help you out here. You're
3 muted in Adobe as well. Yep. Here we go. Here you
4 go, sir.

5 **DR. DAVID HARLAN:** Can you hear me now?

6 **MR. MICHAEL KAWCZYNSKI:** Yes.

7 **DR. DAVID HARLAN:** Okay. Yeah. I was trying
8 -- I was commenting earlier too after Dr. Feng spoke.
9 Because I echo what she said, the effects of the
10 immunosuppression are cumulative, and they span any
11 organ that's transplanted.

12 As long as you're on a calcineurin phosphatase
13 inhibitor you are at risk for decreasing kidney
14 function. The decreased kidney function and the
15 microalbumin and macroalbuminuria that was seen in
16 these studies is entirely predictable. And,
17 unfortunately, that's a very significant prognostic
18 factor for cardiometabolic outcomes. I think it's more
19 meaningful than **intraparotid intimal (phonetic 07:18:36**
20 **YouTube video)** thickness that they do have data for.

1 So the risk-benefit ratio is tough here. I
2 can tell you that for solid pancreas transplantation,
3 which is done for the same indications, there were 600
4 of those done in 2005. But then as the toxicity
5 associated with immunosuppression became more apparent,
6 last year there were only 125 solitary pancreas
7 transplants done. So it's a tricky balance,
8 immunosuppression versus properly administered insulin.
9 My input.

10 **DR. LISA BUTTERFIELD:** Thank you. Any
11 thoughts, while we have you, on the definition for the
12 brittle Type 1 diabetes or the (inaudible 07:19:33
13 YouTube video)?

14 **DR. DAVID HARLAN:** Yeah. For me it's -- and I
15 have seen some -- they exist -- patients that you say
16 the word "insulin" and they can go low. I don't
17 understand it, but they're very rare. And when I say
18 very rare, not the 80,000 number that we heard. I
19 suspect it's maybe a few hundred in this country.

20 But then the other point is -- and this hasn't

1 come up yet -- there's only about 6,000 organ donors in
2 this country every year. So even if every pancreas
3 went to an islet isolation and were to be transplanted,
4 the isolation procedure is not perfect. We may be
5 talking about treating 1,000 patients or so per year,
6 maybe. So I think it would take a large group to
7 discuss what the appropriate definition is of someone
8 who would be a good candidate for this therapy. But
9 for me, it's uncontrollable, recurrent, severe
10 hypoglycemia.

11 **DR. LISA BUTTERFIELD:** Thank you. So I think
12 looking at the hands up, we've heard from Dr. Hawkins.
13 We've heard from Dr. Walters. Dr. Breuer?

14 **DR. CHRISTOPHER BREUER:** Is there a subset of
15 patients that would be candidates for pancreas
16 transplantation but it's contraindicated because they
17 can't tolerate a major operation, that would be
18 candidates for this (inaudible 07:21:10 YouTube video)?
19 And if so, how big is that population?

20 **DR. DAVID HARLAN:** Yes. My view is that they

1 exist. But it's a very small population. And it would
2 require -- I think I would suggest that a group be
3 convened to say who exactly are these patients. And
4 the trouble with these randomized, controlled studies -
5 - and we've talked about it already -- is the studies
6 that Dr. Oberholzer enrolled for getting best current
7 medical therapy, that's dark ages medical therapy that
8 they got then compared to what's available now.

9 **DR. LISA BUTTERFIELD:** Okay. Is there any
10 further discussion on this question? Dr. Goldstein,
11 please.

12 **DR. LAWRENCE GOLDSTEIN:** Okay. Thank you. I
13 have a question that perhaps both Dr. Harlan and Dr.
14 Oberholzer would have an opinion about. Which is given
15 all these questions about risk-benefit and
16 immunosuppression risk and all the rest, what's your
17 opinion from interacting with your patients? What kind
18 of choice would they make if they had well-regulated
19 disease using one of these new pump systems but had the
20 opportunity for an islet transplant but with heavy

1 immunosuppression? Would they want to do that even?
2 Or is this something that a license might be issued
3 for, but there would be no consumers?

4 **DR. DAVID HARLAN:** I have a few patients, and
5 I can count them on one hand, who for one reason or
6 another just find the technology inconsistent with how
7 they want to live. And the imponderable is that none
8 of them know what life is going to be like with an
9 islet transplant and immunosuppression.

10 As we heard from Dr. Oberholzer and from Dr.
11 Beaston, some patients get the transplant and then they
12 get on immunosuppression, and they think -- a lot of
13 them love it. And I've transplanted patients. As Dr.
14 Oberholzer and Dr. Shapiro know, I've given islet
15 transplants to some patients in a previous life. Some
16 patients just love it. But there's others who say this
17 is not what I thought I was going to get. And it's the
18 imponderable.

19 **DR. LISA BUTTERFIELD:** Dr. Oberholzer.

20 **DR. JOSE OBERHOLZER:** Yes. So thanks for

1 asking this question. So you saw in the video one
2 patient who has the PTLD, and you would think that a
3 PTLD would scare you a lot. And so this patient went
4 on a closed-loop system on the latest technology and
5 continued to experience severe lows. This is a very
6 smart, very intelligent and compliant patient. And
7 through working with her oncologist and everything had
8 convinced us that she would like to have an islet cell
9 (inaudible 07:24:42 YouTube video).

10 And she was off insulin for 10 years, and she
11 experienced the side effects of it with the PTLD. And
12 in her risk-benefit analysis she absolutely wants
13 another islet cell (inaudible 07:24:53 YouTube video).
14 That is a single patient you would say.

15 But when you look at the Type 1 diabetes
16 exchange data -- and this is maybe not perfect. It's
17 reported by the patients and (inaudible 07:25:03
18 YouTube video). But right now in the United States
19 only 21 percent of patients meet the ADA criteria for
20 hemoglobin A1c goal, for example. And then you look at

1 the clinical trials with the latest pump technology,
2 the closed-loop system published in the *New England*
3 *Journal of Medicine*, an excellent journal, patients
4 still have a certain percentage of time in hypoglycemia
5 below 70 milligrams per deciliter.

6 And to give you just an insight from academia,
7 so we work with Boris Kovatchev who developed the
8 mathematical algorithms for the closed-loop system and
9 founded the company now that has the most advanced
10 closed-loop system. And I asked him well, is my job
11 finished? Should I stop doing islet cell transplant?
12 He said absolutely not. Now your job is starting
13 because now they can define some of the patients.

14 And we do have patients that still continue to
15 have severe lows. They have less lows, much better
16 than it used to be. We are not any more in the dark
17 ages. But highly compliant patients in clinical trials
18 under very close surveillance, they will experience a
19 significant amount of time in hypoglycemia (phonetic
20 07:26:14 YouTube video).

1 And then lastly when, again, you look at the
2 most recent Type 1 diabetes exchange, only 36 percent
3 of patients use a CGMS in the United States. And when
4 you look at the period before CGMS where only about 10
5 percent used CGMS, and now with CGMS there is actually
6 an increase in the average hemoglobin A1c in young
7 adults. So while this technology is great and has
8 contributed dramatically to the improvement of quality
9 of many Type 1 diabetic patients, there will still be a
10 small group of patients for whom those technologies are
11 just not fast enough to pick a rapid drop in (inaudible
12 07:27:01 YouTube video).

13 **DR. LISA BUTTERFIELD:** Thank you for that
14 perspective. Dr. Goldstein, did that address your
15 questions? And then we'll go to Dr. Harlan.

16 **DR. LAWRENCE GOLDSTEIN:** Absolutely. I
17 thought those were very helpful answers. Thank you.

18 **DR. LISA BUTTERFIELD:** Thank you. Dr. Harlan.

19 **DR. DAVID HARLAN:** I agree with Dr. Oberholzer
20 that I'm not going to defend the American healthcare

1 system and its care for patients with Type 1 diabetes.
2 I'm not. It's terrible. But I do think it's a little
3 disingenuous to say that with insulin pumps they're
4 still having -- closed-loop -- that we're still having
5 hypoglycemia when you use the less than 70 milligram
6 per deciliter threshold because it doesn't become
7 serious requiring help of others until the blood sugar
8 falls below 54. And for those patients that use them,
9 the closed-loop insulin pumps are really quite
10 effective.

11 **DR. JOSE OBERHOLZER:** But I apologize for
12 using the 70 milligram per deciliter. We actually
13 looked at the 340 patients enrolled in these trials and
14 put the bar at 55 milligram per deciliter to see are
15 there any patients in that study population that could
16 benefit from a transplant? And out of all those
17 patients -- I think 340 -- there were about 40 patients
18 who still spent more than 2 to 3 percent below 55
19 milligrams per deciliter.

20 **DR. DAVID HARLAN:** Did they require the

1 assistance of others? Or did they have seizures? Did
2 they lose consciousness? Those things I just -- I
3 don't know. I don't see them anymore in people on
4 those systems very often. They happen.

5 **DR. LISA BUTTERFIELD:** All right. Thank you
6 both. So Dr. Fox, did you have a quick question, or
7 has that been answered?

8 **DR. BERNARD FOX:** Thank you, Dr. Butterfield.
9 It comes back to the discussion again too -- for me not
10 being quite the expert in this area -- that I was
11 hearing from Dr. Shapiro, I think, and from the results
12 of the clinical trial that we're talking about, that
13 the patients who were insulin dependent post
14 transplant, was the inference that they're better
15 controlled than they would have been if they had never
16 had the transplant? And has that got a benefit or not?

17 **DR. DAVID HARLAN:** Their glycemic control is
18 better and easier in general. But the larger question
19 is -- I tell my patients I'm not a numbers doctor. I'm
20 a people doctor. And I want to know if your risk of

1 heart attacks and strokes and kidney failure has been
2 significantly improved. And that's a tougher question
3 with modern medical technologies because modern
4 insulin-based technologies do not include the
5 calcineurin phosphatase inhibitors.

6 **DR. BERNARD FOX:** Okay.

7 **DR. LISA BUTTERFIELD:** All right. So as we
8 bring this to a close does anyone on the Committee want
9 to make any final comments before I make an attempt to
10 sum up some of the key discussion points? All right.
11 I see three hands. Dr. Goldstein? Is your hand still
12 up? No. Dr. Roos?

13 **DR. RAYMOND ROOS:** Yes. I had a question for
14 Dr. Oberholzer, and it relates, I guess, to the
15 transplant itself and my concern that a number of
16 patients required two and some even three islet cell
17 transplants. And what do you think the explanation for
18 this is? And do you think that knowing the cell
19 composition more precisely of the islet cell transplant
20 would make them more effective?

1 DR. LISA BUTTERFIELD: Thank you. Dr.
2 Oberholzer?

3 DR. JOSE OBERHOLZER: Can you hear me?

4 DR. LISA BUTTERFIELD: Yes.

5 DR. JOSE OBERHOLZER: (Inaudible 07:31:41
6 YouTube video). For some reason my camera doesn't want
7 to start up so I apologize.

8 So the reasons why patients need two to three
9 transplants I think is in the number of islets that can
10 be isolated of the (inaudible 07:31:53 YouTube video).
11 But during the manufacturing process there is
12 invariably a loss and that you count the islets that we
13 have at the end, they often correspond to about what a
14 half pancreas would be.

15 Now, there is also variability in how much
16 insulin a patient needs. And that's why insulin is not
17 given as a fixed (phonetic 07:32:13 YouTube video)
18 dose, like blood pressure medication needs to be
19 adjusted with the patient's need and metabolic
20 situation. To some patients even if they don't have a

1 super high insulin requirement, some will still need
2 more than others. So some patients you can give a
3 relatively small amount of islets, and they will be off
4 insulin within a few (inaudible 07:32:35 YouTube
5 video). And others you have to give more and,
6 ultimately, we don't understand why that is.

7 Now, knowing the cell composition currently
8 would not be helpful because I would not know -- I
9 don't have any data, and there's no good data in the
10 literature that would tell me how many beta cells or
11 alpha cells or delta cells you would need. I think
12 that's something that I think we will need more
13 experience and more data with a much larger patient
14 population (inaudible 07:33:07 YouTube video). I wish
15 that I had a marker that would tell me this is going to
16 work or not.

17 The last point I want to make is insulin
18 independence is a great goal. But for some patients
19 having endogenous insulin secretion will at least cut
20 off the number of hypoglycemia-hyperglycemia (inaudible

1 07:33:28 YouTube video). And as Dr. Shapiro said, we
2 have not had any patients with primary nonfunction.
3 All patients had significant C-peptide production
4 (inaudible 07:33:38 YouTube video).

5 DR. RAYMOND ROOS: Thank you.

6 DR. LISA BUTTERFIELD: Thank you. And then a
7 final question from Dr. Berns.

8 DR. KENNETH BERNS: Can you hear me?

9 DR. LISA BUTTERFIELD: Yes.

10 DR. KENNETH BERNS: So the question that I had
11 was (inaudible 07:34:07 YouTube video) Dr. Witkowski
12 made two statements that I could not -- I just didn't
13 know for sure that I understood what he was saying.
14 One was that if the BLA were granted, nobody else could
15 do an islet cell transplant? I don't know if that's
16 correct or not. I'm just it's a question that was
17 raised. And secondly, why are islet cell transplants
18 different than all other transplants as far as the FDA
19 is concerned? And are we the only country where that's
20 (inaudible 07:34:54 YouTube video)?

1 **DR. LISA BUTTERFIELD:** So that's a bigger
2 question than we have on our plates today. We're going
3 to keep it focused just on this particular product and
4 this particular discussion point. But thank you for
5 raising it. There were many, many interesting
6 questions that were raised today. But I think what
7 we're going to do now is I will make an attempt to
8 summarize the major discussion points. Then I'll ask
9 the members of the Committee with regards to these two
10 clinical questions if I've covered the opinions and
11 comments that were made.

12 So these are challenging questions because
13 over the time -- over the several recent years and the
14 times that the studies were conducted there's been
15 radical changes in therapies. So there's a lot of
16 variables in terms of the patients and the products and
17 the lack of a control group to try to make decisions
18 compared to.

19 And there have been significant changes in
20 standard of care since these data have been collected.

1 The target population of patients is quite possibly
2 reduced from where it was when these studies were
3 started. And when thinking about a bar for Question 1
4 for what would be the clinically meaningful benefit of
5 insulin independence, four to five years was the
6 benchmark that was mentioned and agreed to by some of
7 the members.

8 The pumps and continuous monitoring have
9 really changed the landscape, but that still doesn't
10 cover all patients. So it could be a very rare subset
11 of patients who are truly uncontrolled. And those
12 numbers are a matter of some debate.

13 In terms of the second question about the
14 risk-benefit ratio, the lifelong immunosuppression is
15 certainly a major toxicity. And the longer the patient
16 is on these immunosuppressive regimens, the greater the
17 chance of secondary toxicities, other drugs, loss of
18 compliance, and increased mortality risks.

19 So in terms of the patient perspectives, there
20 were a number of examples given of patients who have

1 benefitted and are delighted that they went for the
2 transplant. Others whose personal experience and
3 lifestyle learned that that wasn't perhaps the best
4 choice for them compared to trying to manage with
5 insulin. So lifestyle, even the patient is another
6 thing that makes it perhaps a more personal doctor-
7 patient choice.

8 And the level of efficacy of these current
9 therapies is also a matter of debate, exactly where the
10 line is, exactly what percentage of patients are
11 benefitting. And then another point that was raised is
12 about really linking the CMC questions to the clinical
13 questions, and might better characterization of the
14 product and the cells in it -- might that improve some
15 of the clinical decisions and the clinical outcomes?
16 But, again, the patient variables and even their need
17 for insulin on a personal level makes that a challenge
18 and a debatable question.

19 That is what I took from the discussion.
20 Would anyone on the Committee like to add something or

1 comment further, anything I missed? I'm looking for
2 any hands. Dr. Zaia. We can't hear you yet, Dr. Zaia.

3 **DR. JOHN ZAIA:** Can you hear me now? I'm
4 sorry. So the issue is -- from what I've heard -- is
5 that we want to use this new risk, namely a lifetime of
6 immunosuppression, to counterbalance the risk of
7 basically having a disease that could be lethal, which
8 would be hypoglycemic unawareness. So the question is
9 if the study didn't focus on that as the issue, that
10 there were only, as was pointed out here, 37 percent of
11 subjects had that problem going into the study, then
12 did the study data actually prove that the product
13 meets that risk-benefit analysis? Do you understand
14 what I'm saying?

15 I'd like to hear from the endocrinologists,
16 not being an endocrinologist. But if I were -- I'm a
17 virologist. If I were to study a drug to prevent
18 chronic herpes infection, I wouldn't be enrolling
19 anyone except those that had chronic herpes infection.
20 So what is the weakness of the studies' data that we're

1 looking at relative to answering this question about
2 risk-benefit?

3 **DR. LISA BUTTERFIELD:** Is there a member of
4 the Advisory Committee that would like to respond?

5 **DR. DAVID HARLAN:** Well, I'll try, but it is
6 basically unanswerable. I can tell you that if you
7 look at patients in the United States who are listed
8 for a pancreas transplant and typically the solitary
9 pancreas transplant -- pancreas transplant alone, their
10 kidney function is normal -- the most common reason for
11 listing for a pancreas transplant is brittle diabetes.
12 Their mortality over a 4-year period is about 4 percent
13 or about 1 percent per year or less.

14 So some way to put some guardrails on this
15 would be to say are the benefits achieved by an islet
16 transplant, how risky is the immunosuppression relative
17 to that overall risk? It's a pretty small risk even --
18 1 percent is not nothing. But it's not 20 percent.
19 We're trying to improve on something that's not a huge
20 problem, and the islet function itself only lasts for

1 as we saw, three or four or five years in general.

2 **DR. JOHN ZAIA:** Thanks.

3 **DR. LISA BUTTERFIELD:** All right. With that I
4 thank everyone on the Advisory Committee, and I will
5 turn this over to Ms. Christina Vert from the FDA.

6

7

VOTING

8

9 **MS. CHRISTINA VERT:** Thank you, Dr.
10 Butterfield. I am Christina Vert, the Designated
11 Federal Officer, and I will explain the voting process
12 and conduct the vote. Only members and temporary
13 voting members, excluding the industry representative,
14 will be voting in today's meeting. No one else should
15 vote.

16 In regard to the voting process Dr.
17 Butterfield will read the question for the record. And
18 afterwards all members and temporary voting members,
19 excluding the industry representative, will cast their
20 vote by selecting one of the voting options which
21 include "Yes," "No," or "Abstain."

1 You will have two minutes to cast your vote
2 after the question is read. Once all the votes have
3 been placed, we will broadcast the results and read the
4 individual votes aloud for the record. Please note
5 that once you cast your vote, you can change your vote
6 within the two-minute timeframe. However, once the
7 poll has closed, all votes will be considered final.

8 So does anyone have any questions related to
9 the voting process before we begin? Okay. I don't see
10 any questions. There is the voting question on the
11 slide. Dr. Butterfield, if you could read the voting
12 question for the record?

13 **DR. LISA BUTTERFIELD:** Sure. "Does donislecel
14 delivered by intraportal administration have an overall
15 favorable benefit-risk profile for some patients with
16 Type 1 diabetes? In considering this question, please
17 incorporate the risks of the transplantation
18 procedure(s) and long-term immunosuppression as risks
19 of the product."

20 **MS. CHRISTINA VERT:** You may go ahead and

1 please cast your vote. And we'll start the timer.
2 (07:44:38 to 07:45:53 no voice). You have less than a
3 minute left. (07:45:54 to 07:46:15 no voice). Thirty
4 seconds. (07:46:16 to 07:46:38 no voice). Okay. It
5 looks like I have received all the votes. At this
6 time, the two minutes are up so if we could please end
7 the vote by closing the poll and then broadcast the
8 results? Okay. We have a majority vote with 12 "Yes"
9 votes, 4 "No" votes and 1 "Abstain." The vote passes.

10 And I will read the voting responses for the
11 record. Dr. Hawkins, yes. Dr. Fox, yes. Dr.
12 Goldstein, yes. Dr. Butterfield, yes. Dr. Opara, no.
13 Dr. Berns, yes. Dr. Naziruddin, no. Dr. Harlan, no.
14 Dr. Feng, yes. Dr. Roos, yes. Dr. Breuer, yes. Dr.
15 Leschek, yes. Dr. Walters, yes. Dr. Lee, abstain.
16 Dr. Morrison, yes. Dr. Zaia, yes. Dr. Wu, no. And
17 those are all the votes.

18 Okay. So this concludes the voting portion of
19 the meeting. And I will now hand the meeting back over
20 to Dr. Butterfield for the voting explanation.

1

2

MEMBER REMARKS

3

4

5

6

7

8

DR. LISA BUTTERFIELD: Okay. And so I know we're supposed to go around to the 17 voting members to have a brief explanation of your vote. It would be very helpful to have a list of those voting members in front of me and to just run down that list.

9

10

11

12

13

14

15

16

17

18

Sadly, I'm at the top of that list. So I will use the -- I will begin and say that my "yes" vote was due to the data from the Canadian experience, the written comments that were submitted from the patients. I do, however, support a post-approval gathering of data to learn more about the product as some other assays are available. And I don't know how many patients will really benefit, but I think that is to be determined. That is the reason for my vote. Dr. Berns, what's the reason for your vote?

19

20

DR. KENNETH BERNIS: The same as your reasons. I just couldn't -- it wasn't clear to me what "some"

1 really implied. I decided that some did need the
2 benefit (inaudible 07:50:24 YouTube video).

3 **DR. LISA BUTTERFIELD:** Thank you. Dr. Breuer?

4 **DR. CHRISTOPHER BREUER:** Yeah. I would
5 reiterate the same reasons that you said too. But the
6 thing that put me over the top was I think there's two
7 very small subpopulations that it would provide the
8 only viable therapy. And those would be the ones that
9 I mentioned that the patients that were eligible for
10 transplantation but couldn't tolerate a big operation
11 so this provided the only potential therapy. And those
12 that were on the best standard of care, the feedback
13 responsive pumps that were not tolerating those for
14 (inaudible 07:50:59 YouTube video). Thank you.

15 **DR. LISA BUTTERFIELD:** Thank you. Dr. Fox?

16 **DR. BERNARD FOX:** Yeah. I agree with the
17 comments made so far. But also, I was impressed --
18 kind of one of the questions that Dr. Sandy Feng has
19 mentioned about the concern about sensitizing the
20 subsequent transplant. But seeing the eGFR results

1 from the long-term study it seemed like that's less of
2 a risk, and so in addition to everything else I thought
3 that also swayed me. Plus the patient who has the
4 post-transplant proliferative disorder who would go
5 back and do it again speaks of the patient quality of
6 life issue. So that's why I voted "yes" for some of
7 those patients.

8 **DR. LISA BUTTERFIELD:** Thank you. Dr.
9 Hawkins.

10 **DR. RANDY HAWKINS:** Yes. Thank you. So as a
11 consumer representative I really appreciate the
12 opportunity to be involved in this high-level
13 discussion and exposure, something I would not do
14 normally in a private practice.

15 I voted "yes" because I believe that the study
16 did show, and I believe there's a benefit from insulin
17 independence, with improved safety in severe
18 hypoglycemic events. I do have concerns about the
19 adverse effects of immunosuppressants. I think we
20 should keep this in a toolbox, but I believe the

1 patients need to be given strict informed consent about
2 the risk.

3 And I think that, what I heard, I don't expect
4 a large number of patients actually get this product.
5 But ongoing research will follow, and we'll learn
6 things that we don't know yet. I did appreciate the
7 discussion about the -- and recognition of healthcare
8 inequities thanks to -- how we take our patients, what
9 we have available to us. Thank you.

10 **DR. LISA BUTTERFIELD:** Thank you. Dr. Lee?

11 **DR. JEANNETTE LEE:** I'll just say that I
12 struggled with the study since I looked at it a couple
13 weeks ago. As a biostatistician and clinical trialist
14 I'm actually more used to seeing protocols where
15 there's sort of a clear cut you've either met your
16 endpoint or you haven't. And so this seems to be
17 shifting sand. And not least at this point they're
18 trying to figure out what the endpoint is and how to
19 make the decision. And amidst all the erudite
20 discussions today I really still couldn't come to a

1 decision so that's where I am, thanks.

2 **DR. LISA BUTTERFIELD:** Thank you. Dr.
3 Morrison.

4 **DR. SEAN MORRISON:** Can you hear me okay?

5 **DR. LISA BUTTERFIELD:** Yes.

6 **DR. SEAN MORRISON:** Okay. I voted "yes"
7 because I found the data on sustained insulin
8 independence was compelling even if we set the bar at
9 more than four years after the patient treated by
10 CellTrans would meet that bar. The point is well taken
11 the bar is going up over time as the closed-loop
12 devices confer better control and the risks of
13 immunosuppression are better recognized. Finally, as I
14 think the evidence currently suggests that many
15 patients have benefitted from islet (inaudible 07:53:49
16 YouTube video) patients. So I voted "yes" even if the
17 market size for this therapy might decline over time.

18 I'd make two quick suggestions for the FDA to
19 consider. One is that I don't think we know whether
20 other cellular components in the graft influence

1 durability or efficacy, and so I would also like to see
2 them collect post-market data on those other cellular
3 components and then compare to efficacy over time to
4 see if it correlates. And the second thing is the
5 FDA's comments about the need to better define the
6 approved indication beyond brittle diabetes are well
7 taken. So I'd like to see them work with CellTrans
8 (inaudible 07:54:28 YouTube video).

9 **DR. LISA BUTTERFIELD:** Thank you. All right.
10 Dr. Nichol is a nonvoting member. So Dr. Walters.

11 **DR. MARK WALTERS:** Yes. Thank you. I voted
12 "yes" because of the therapeutic effect in a group of
13 patients who had difficult to manage diabetes and
14 ultimately because I thought that the decision about
15 whether or not to pursue this therapy should be made by
16 patients with their physicians. So for those reasons I
17 voted "yes."

18 **DR. LISA BUTTERFIELD:** Thank you. Dr. Wu.

19 **DR. JOSEPH WU:** I voted "no" because I have
20 some concerns about the study design, the lack of

1 control group, and in particular, the serious adverse
2 events, 53 percent serious adverse events in 1 year, 65
3 percent serious adverse events in long-term follow up,
4 10 percent procedure-related serious events, and then
5 also two deaths. That's why I voted "no."

6 **DR. LISA BUTTERFIELD:** Thank you. Dr. Zaia.

7 **DR. JOHN ZAIA:** I voted "yes" because the
8 question was so narrowly framed that namely could this
9 help some people? And I know that there are some
10 people with hypoglycemic unawareness that really have a
11 lethal disease that could benefit from this. I think
12 the question will be for the FDA how to develop the
13 eligibility criteria for use of this product.

14 **DR. LISA BUTTERFIELD:** Thank you. Another
15 temporary voting member is Dr. Feng.

16 **DR. SANDY FENG:** Yes. It's a pleasure to
17 follow Dr. Zaia because my first comments would echo
18 his. Who should really get the therapy? I think that
19 we would all agree that people who are insulin
20 independent and even those who are not would be likely

1 protected from severe hypoglycemic events. And so if
2 that were the criteria to be eligible for receiving
3 this therapy, which could be determined subsequently,
4 then I think that the "success rate" would be
5 relatively high.

6 One or two other comments, first of all, I
7 think that I would look forward to further developments
8 in immunosuppression that would mitigate the current
9 toxicities that we are facing. And I think that this
10 is something we did not discuss that we're concerned
11 about the toxicity of what we currently use. But there
12 are definitely additional therapies that are being
13 developed that might mitigate those toxicities that
14 would be beneficial to this population.

15 A second comment I would make is I agree with
16 the concerns raised by some of the guest speakers
17 related to the monitoring of these patients and the
18 fact that these patients may or may not -- and I don't
19 know the answer to that -- be under the UNOS/OPTN
20 rubric in terms of reporting the toxicities and

1 outcomes, et cetera. And I would look to the FDA for
2 further guidance because I think this post-approval
3 monitoring is a critical component.

4 And then the final thing I would contribute to
5 why I voted "yes" is I have taken care of patients. I
6 do do pancreas transplants, and I can tell you that
7 there is nothing that a person likes more than their
8 pancreas transplant and the freedom from dealing with
9 the entire insulin issue. And I think that that has
10 made a large impression on me over the last 20 plus
11 years of clinical practice. So I do think this can
12 help some people and will be incredibly meaningful to
13 those people. Thank you.

14 **DR. LISA BUTTERFIELD:** Thank you. Dr.
15 Goldstein.

16 **DR. LAWRENCE GOLDSTEIN:** Yes. Thank you. I
17 voted "yes." I think it was a close call for me, but
18 it's clearly a situation where this would be an
19 improved additional option for some patients,
20 potentially, at their own choice. But I share many of

1 the panel members concerns about variability issues,
2 and I would like to see those continued in post-
3 marketing analyses, including other cell types and
4 perhaps just the compatibility antigens.

5 I'll note that, though, the modified figure
6 two that we were sent shows a very clear threshold of
7 the data. So once you get to higher levels of islet
8 equivalents, things look better. And then finally, I
9 think this is a step in the development of the field.
10 We need to have these sorts of treatments become
11 regularized. Better things are coming down the pipe,
12 but for right now this looks pretty reasonable. Thank
13 you.

14 **DR. LISA BUTTERFIELD:** Thank you. Dr. Harlan.
15 Dr. Harlan, we can't hear you.

16 **DR. DAVID HARLAN:** Oh, I'm sorry. I was on
17 mute. I agree with what Dr. Zaia said about the
18 question being so narrowly focused that it was a
19 difficult one for me. But I ultimately -- and the
20 reason is could someone in the United States benefit

1 from this was the way you would read that question.
2 And there may be a few. But it's a few. As I say,
3 there's only 100 pancreas transplants done in this
4 country every year, and that's very effective. So
5 we're talking about patients that are not candidates
6 for pancreas transplants that might get this.

7 And I voted "no" because I too have taken -- I
8 take care of patients with diabetes and I've
9 transplanted islets before. I've done both, and I've
10 seen them both pre and post transplant. And I've seen
11 the awful things that can happen in post-transplant
12 recipients that it's really hard to get that informed
13 consent from someone when you're asking them to
14 consider a future that they don't know. When it works,
15 it's great. When it doesn't work, it's catastrophic.
16 It can be catastrophic.

17 So I just was worried about opening Pandora's
18 box with the advent of stem-cell-derived beta cells and
19 a greater supply of cells that can be transplanted,
20 this will be worked out. But I do implore the FDA to

1 come up with very strict criteria for who gets this
2 therapy. And I think it was very telling that very few
3 of the patients even in these trials truly had severe
4 hypoglycemia unawareness. It just -- you open the box
5 and patients get it unknowingly and then are surprised
6 that it's not always what they thought it would be.
7 That's my comment.

8 **DR. LISA BUTTERFIELD:** Thank you. Dr.
9 Leschek.

10 **DR. ELLEN LESCHEK:** Yes. Hi. I very
11 reluctantly voted "yes" for exactly the same reasons
12 that they voted "no." I voted "yes" because of the way
13 that the question was posed that it was could a few
14 people benefit? Yes. There are some people that could
15 benefit. I believe, though, that it's a much smaller
16 number than maybe the company believes.

17 I am concerned that if this (inaudible
18 08:01:53 YouTube video) is approved that too many
19 people will get treated this way when in fact for a lot
20 of those people the risks will outweigh the benefits.

1 And so I am very, very concerned about that. The other
2 thing I will say is that I am also worried that
3 approval may hamper future study in this area because I
4 don't see the studies that we heard about today as
5 being definitive. I think that a lot more studies are
6 needed, and I worry that with an approval those studies
7 won't happen.

8 **DR. LISA BUTTERFIELD:** Thanks very much. Dr.
9 Naziruddin?

10 **DR. BASHOO NAZIRUDDIN:** I voted "no" because
11 primarily the patient selections in these two trials
12 permitted by CellTrans are not really the best. So I'm
13 not very -- I mean that the patients really benefited.
14 So a vigorous selection of patients should have been
15 done. And that was my number one. But because the
16 hemoglobin A1c and the absence of severe hypoglycemic
17 episodes are not really impressive.

18 And the second thing was concerning about the
19 side effects from prolonged immunosuppression in
20 patients. Now with the new technology coming up, can

1 patients avoid neoplasms? So that is something that
2 also was very important for my answer. So no. Thank
3 you.

4 **DR. LISA BUTTERFIELD:** Thank you. Dr. Roos.

5 **DR. RAYMOND ROOS:** I voted "yes," but there
6 were problems answering the question. The studies that
7 we heard most about were small studies, no real control
8 group, and not as standardized as one might want. And
9 clearly, the field and standard of care is changing.
10 And there are health resource issues that impact
11 answering this question. But at present I think this
12 direction may be a reasonable one for what probably is
13 a small number of diabetic patients.

14 **DR. LISA BUTTERFIELD:** Thank you. And Dr.
15 Opara.

16 **DR. EMMANUEL OPARA:** Okay. I too, like Dr.
17 Harlan and Dr. Leschek, I was actually sitting on the
18 fence on this question because of the way it was
19 framed. But I finally voted "no" because I'm really
20 very seriously concerned about the effects of long-term

1 immunosuppression, particularly the effect on kidney
2 function.

3 And then, of course, with that you also
4 consider the fact that these patients may be sensitized
5 because of the long-term immunosuppression, and then
6 they would need a kidney down the road. So I think
7 it's going to be really very difficult to deal with
8 such patients. And then consider the fact that we have
9 these improved management protocols that were
10 considered in the discussions today, which diminishes
11 the number of patients that would get this treatment.
12 And I thought that the risks outweighed the benefits.

13 **DR. LISA BUTTERFIELD:** Thanks very much. And
14 that is the end of the discussion of the reasons behind
15 the voting, and so I turn the meeting over now to
16 Jarrod Collier.

17 **MR. JARROD COLLIER:** I would like to introduce
18 Dr. Peter Marks, Director for the Center for Biologics
19 Evaluation and Research to give a few closing remarks.
20 Dr. Marks? Your phone is on mute, Dr. Marks.

1

2

CLOSING REMARKS

3

4

DR. PETER MARKS: Yes. I got it. Thanks very

5

much. I was double muted. Thanks very much. I don't

6

want to belabor things. Thank you for a -- I know it's

7

been a very long day. I really just want to say thank

8

you so much for taking the time. We really appreciate

9

all of your input. It makes a tremendous difference,

10

and it's tremendously helpful for us. Thanks to Dr.

11

Butterfield for chairing a very well-run meeting here.

12

And thank you to all for your input, and thanks to all

13

the stakeholders who have joined us and listened in.

14

So I wish you a very good evening and thanks again.

15

16

ADJOURNMENT

17

18

MR. JARROD COLLIER: All right. Thank you

19

very much, Dr. Marks. I would also like to give

20

special thanks to our wonderful chair, Dr. Lisa

1 Butterfield for doing such an outstanding job
2 conducting today's meeting. I also would like to thank
3 the CTGTAC (inaudible 08:06:54 YouTube video) team, the
4 FDA participants, the members and consultants, our
5 guest speakers, sponsor speakers, and OPA (phonetic
6 08:07:00 YouTube video) speakers for their time and
7 effort in conducting this virtual meeting. And with
8 that the 69th meeting of the Cellular Tissue and Gene
9 Therapy Advisory Committee is now adjourned. Thank you
10 all very much and enjoy the rest of your day.

11

12

[MEETING ADJOURNED FOR THE DAY]