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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUG ADVISORY COMMITTEE (ODAC)

Thursday, August 13, 2020

8:06 a.m. to 11:41 a.m.

Morning Session

Virtual Meeting

Meeting Roster**ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)****Joyce Yu, PharmD**

Division of Advisory Committee and
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Office of Executive Programs, CDER, FDA

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1 P R O C E E D I N G S

2 (8:06 a.m.)

3 **Call to Order**

4 **Introduction of Committee**

5 DR. HOFFMAN: Good morning and welcome. I
6 would first like to remind everyone to please mute
7 your line when you are not speaking. For media and
8 press, the FDA press contact is Kristin Jarrell.
9 Her email address is kristin.jarrell@fda.hhs.gov,
10 and her phone number is 301-796-0137.

11 My name is Philip Hoffman, and I will be
12 chairing today's meeting. I will now call the
13 morning session of today's Oncologic Drugs Advisory
14 Committee to order. Dr. Joyce Yu is the acting
15 designated federal officer for today's meeting, and
16 we'll begin with introduction of this morning's
17 meeting roster.

18 DR. YU: Good morning. My name is Joyce Yu,
19 and I am the acting designated officer for today's
20 meeting of the Oncologic Drugs Advisory Committee.
21 When I call your name, please introduce yourself by
22 stating your name and affiliation. I'll start. My

1 name is Joyce Yu, acting designated federal officer
2 for the Oncologic Drugs Advisory Committee.

3 Dr. Hoffman?

4 DR. HOFFMAN: My name is Philip Hoffman.
5 I'm a medical oncologist at University of Chicago.

6 DR. YU: Dr. Garcia?

7 DR. GARCIA: Jorge Garcia, chief medical
8 oncology, University Hospitals, Seidman Cancer
9 Center, Case Western Reserve University, Cleveland,
10 Ohio.

11 DR. YU: Thank you.

12 Dr. Halabi?

13 (No response.)

14 DR. YU: Dr. Halabi, can you unmute your
15 line, please?

16 DR. HALABI: Yes. Good morning, everyone.
17 Susan Halabi, biostatistician, Duke University.

18 DR. YU: Thank you.

19 Dr. Hinrichs?

20 DR. HINRICHS: Christian Hinrichs, senior
21 investigator, NCI.

22 DR. YU: Thank you.

1 Dr. Sung?

2 DR. SUNG: Anthony Sung, hematopoietic stem
3 cell transplant physician, Duke University.

4 DR. YU: Thank you.

5 Dr. Cheng?

6 DR. CHENG: Good morning. I'm Jon Cheng,
7 medical oncologist. I'm the industry rep and I
8 work for Merck Pharmaceuticals.

9 DR. YU: Thank you.

10 We'll be skipping Dr. Finestone. She's not
11 yet on the line.

12 Dr. Morrison?

13 DR. MORRISON: Sean Morrison. I'm a stem
14 cell biologist at the University of Texas,
15 Southwestern Medical Center.

16 DR. YU: Thank you.

17 Ms. Pearl?

18 MS. PEARL: Good morning. My name is Diane
19 Pearl. I am the mother of two Fanconi anemia
20 post-bone marrow transplant patients, and I live in
21 Park City, Utah.

22 DR. YU: Thank you.

1 Dr. Robey?

2 DR. ROBEY: Pam Robey, stem cell biologist
3 and senior investigator at the National Institutes
4 of Health, dental research.

5 DR. YU: Thank you.

6 Dr. Singec?

7 DR. SINGEC: Ilyas Singec. I'm a stem cell
8 scientist at NIH.

9 DR. YU: Thank you.

10 We'll now introduce our FDA participants.

11 Dr. Bryan?

12 DR. BRYAN: Wilson Bryan. I'm director of
13 the Office of Tissues and Advanced Therapies, in
14 the FDA's Center for Biologics Evaluation, and
15 Research.

16 DR. YU: Thank you.

17 Dr. Puri?

18 DR. PURI: Good morning. My name is Raj
19 Puri. I'm the director of the Division of Cellular
20 and Gene Therapies in the Office of Tissues and
21 Advanced Therapies in the Center for Biologics
22 Evaluation, and Research.

1 DR. YU: Thank you.

2 Dr. Oh?

3 DR. OH: I'm Steven Oh. I'm the deputy
4 director at the Division of Cellular and Gene
5 Therapies at the Office of Tissues and Advanced
6 Therapies in CBER.

7 DR. YU: Thank you.

8 Dr. Bauer?

9 DR. BAUER: Good morning. Steve Bauer. I'm
10 a branch chief in the Division of Cell and Gene
11 Therapies.

12 DR. YU: Thank you.

13 And Dr. Klinker?

14 DR. KLINKER: Morning. I'm Matt Klinker. I
15 am a product reviewer in the cell therapy branch in
16 the Division of Cellular and Gene Therapies and the
17 primary product reviewer for this application.

18 DR. YU: Thank you. That concludes our
19 morning introductions.

20 DR. HOFFMAN: For topics such as those being
21 discussed at today's meeting, there are often a
22 variety of opinions, some of which are quite

1 strongly held. Our goal is that today's meeting
2 will be a fair and open forum for discussion of
3 these issues and that individuals can express their
4 views without interruption.

5 Thus, as a gentle reminder, individuals will
6 be allowed to speak into the record only if
7 recognized by the chairperson. We look forward to
8 a productive meeting.

9 In the spirit of the Federal Advisory
10 Committee Act and the Government in the Sunshine
11 Act, we ask that the advisory committee members
12 take care that their conversations about the topic
13 at hand take place in the open forum of the
14 meeting.

15 We are aware that members of the media are
16 anxious to speak with the FDA about these
17 proceedings, however, FDA will refrain from
18 discussing the details of this meeting with the
19 media until its conclusion. Also, the committee is
20 reminded to please refrain from discussing the
21 meeting topic during breaks or lunch. Thank you.

22 Dr. Joyce Yu will read the Conflict of

1 Interest Statement for the meeting.

2 **Conflict of Interest Statement**

3 DR. YU: The Food and Drug Administration is
4 convening today's meeting of the Oncologic Drugs
5 Advisory Committee under the authority of the
6 Federal Advisory Committee Act, FACA, of 1972.

7 With the exception of the industry representative,
8 all members and temporary voting members of the
9 committee are special government employees, SGEs,
10 or regular federal employees from other agencies
11 and are subject to federal conflict of interest
12 laws and regulations.

13 The following information on the status of
14 this committee's compliance with federal ethics and
15 conflict of interest laws, covered by but not
16 limited to those found at 18 U.S.C. Section 208, is
17 being provided to participants in today's meeting
18 and to the public. FDA has determined that members
19 and temporary voting members of this committee are
20 in compliance with federal ethics and conflict of
21 interest laws.

22 Under 18 U.S.C. Section 208, Congress has

1 authorized FDA to grant waivers to special
2 government employees and regular federal employees
3 who have potential financial conflicts when it is
4 determined that the agency's need for a special
5 government employee's services outweighs his or her
6 potential financial conflict of interest or when
7 the interest of a regular federal employee is not
8 so substantial as to be deemed likely to affect the
9 integrity of the services which the government may
10 expect from the employee.

11 Related to discussions of today's meeting,
12 members and temporary voting members of this
13 committee have been screened for potential
14 financial conflicts of interest of their own as
15 well as those imputed to them, including those of
16 their spouses or minor children and, for purposes
17 of 18 U.S.C. Section 208, their employers. These
18 interests may include investments; consulting;
19 expert witness testimony; contracts, grants,
20 CRADAs; teaching, speaking, writing; patents and
21 royalties, and primary employment.

22 Today's agenda involves biologics license

1 application, BLA, 125706 for remestemcel-L, ex-vivo
2 culture-expanded adult human mesenchymal stromal
3 cells suspension for intravenous infusion,
4 submitted by Mesoblast, Incorporated.

5 The proposed indication or use for this
6 product is for the treatment of steroid refractory
7 acute graft versus host disease in pediatric
8 patients. This morning session will discuss issues
9 related to the characterization and critical
10 quality attributes of remestemcel-L as they relate
11 to clinical effectiveness.

12 This is a particular matters meeting during
13 which specific matters related to Mesoblast's BLA
14 will be discussed. Based on the agenda for today's
15 morning meeting and all financial interests
16 reported by the committee members and temporary
17 voting members, no conflict of interest waivers
18 have been issued in connection with this meeting.
19 To ensure transparency, we encourage all standing
20 committee members and temporary voting members to
21 disclose any public statements that they have made
22 concerning the product that issue.

1 With respect to FDA's invited industry
2 representative, we would like to disclose that. Dr.
3 Jonathan Cheng is participating in this meeting as
4 a non-voting industry representative acting on
5 behalf of regulated industry. Dr. Cheng's role at
6 this meeting is to represent industry in general
7 and not any particular company. Dr. Cheng is
8 employed by Merck & Company.

9 With regard to FDA's guest speaker, the
10 agency has determined that the information to be
11 provided by the speaker is essential. As a guest
12 speaker, Dr. Sally Temple will not participate in
13 committee deliberations nor will she vote.

14 We would like to remind members and
15 temporary voting members that if the discussions
16 involve any other products or firms not already on
17 the agenda for which an FDA participant has a
18 personal or imputed financial interest, the
19 participants need to exclude themselves from such
20 involvement and their exclusion will be noted for
21 the record. FDA encourages all other participants
22 to advise the committee of any financial

1 relationships that they may have with the firm at
2 issue. Thank you.

3 DR. HOFFMAN: We will now proceed with FDA
4 opening remarks from Dr. Wilson Bryan.

5 **FDA Opening Remarks - Wilson Bryan**

6 DR. BRYAN: Good morning. On behalf of the
7 FDA, I want to thank the members of this advisory
8 committee for taking the time to consider this
9 biologics license application, or BLA, for
10 remestemcel. This product is proposed to treat
11 pediatric patients with steroid-refractory acute
12 graft-versus-host disease.

13 Throughout our consideration of this BLA, it
14 is critical that we remember that these are highly
15 vulnerable patients. They are vulnerable because
16 they have a life-threatening disease. They are
17 vulnerable because as infants and children, they
18 are not able to fully participate in or give
19 informed consent for decisions regarding their
20 medical care. And they're vulnerable because for
21 the patients who are less than 12 years old, there
22 is no FDA-approved therapy for steroid-refractory

1 acute GVHD, so there is a substantial unmet medical
2 need. It is critical that we make our regulatory
3 decisions with these patients and their
4 vulnerability in mind.

5 The FDA is bringing this BLA for
6 consideration by this advisory committee because
7 this is a first-in-class product and because we
8 have substantial concerns regarding this
9 application. Remestemcel is a mesenchymal stromal
10 cell or MSC product. There are a large number of
11 ongoing clinical trials of MSC products, but no MSC
12 product is FDA approved for the treatment of any
13 disease or condition in the United States.

14 The FDA is concerned that a wide variety of
15 MSC products are being marketed and sold illegally
16 in the United States to treat diverse conditions,
17 including but not limited to orthopedic,
18 rheumatologic, cardiac, pulmonary,
19 neurodegenerative, and oncologic disorders, and
20 COVID-19. These products have not been shown to be
21 safe and effective but are marketed to vulnerable
22 and desperate patients who are often charged

1 thousands of dollars.

2 The FDA believes that the field of cell
3 therapy has the potential to address many unmet
4 medical needs, but that potential must be reached
5 through rigorous science with regulatory oversight
6 and not by exploiting vulnerable patients. For
7 these reasons, we very much appreciate the efforts
8 of Mesoblast to undertake clinical studies and
9 develop their products to address an unmet need.

10 In today's discussions, we ask this
11 committee to consider the rigor of the evidence,
12 both the product's characterization data and the
13 clinical trial data, in this first application for
14 an MSC product. This afternoon, Drs. Bindu George
15 and Kristin Baird will outline some of the FDA's
16 concerns regarding the clinical trial data. For
17 this morning's discussion, Dr. Steve Bauer will
18 describe some of our concerns related to product
19 characterization.

20 Because MSCs and all cell therapies are
21 highly complex products, the FDA often finds that
22 chemistry, manufacturing, and controls, or CMC

1 issues, can be particularly challenging, but it is
2 our responsibility to address these challenges. If
3 remestemcel receives marketing approval, it is
4 critical that every pediatric patient receives a
5 product that has the same safety and effectiveness
6 as is seen in the clinical trial or trials that
7 supported that marketing approval.

8 The discussion this morning focuses on
9 product characterization issues that are at the
10 core of providing this assurance to patients and
11 their parents. I am very much looking forward to
12 hearing the perspectives of this committee on these
13 critical product characterizations and clinical
14 issues.

15 I am also looking forward to the
16 presentations from our guest speakers, to reviewing
17 the public comments submitted to the docket, and
18 the statements that we will hear today in the open
19 public hearing. All of your deliberations and
20 comments will assist the FDA in our consideration
21 of this license application. I will stop there and
22 turn it back over to Dr. Hoffman.

1 DR. HOFFMAN: We now have a guest speaker
2 presentation by Dr. Sally Temple.

3 **Presentation - Sally Temple**

4 DR. TEMPLE: Thank you. I'd like to thank
5 you for the opportunity to speak about some of the
6 challenges surrounding assessment of therapeutic
7 cell products. I'm going to use some of the
8 literature on MSC use for graft-versus-host disease
9 as examples, and the presentation will be in four
10 sections: an introduction; discussion of the
11 sources of variability in cell product and patient
12 response; cell product characterization covering
13 morphology, markers, and function; and then
14 conclude with some suggestions regarding approaches
15 to determine critical quality attributes, that is
16 the --

17 DR. YU: Hi --

18 DR. TEMPLE: Hello?

19 DR. YU: Dr. Temple?

20 DR. TEMPLE: Yes?

21 DR. YU: Hi. I'm very, very sorry. Could I
22 just pause for one moment and allow Dr. Hoffman to

1 inform the committee about the conflicts?

2 DR. TEMPLE: Okay.

3 DR. HOFFMAN: I'm sorry. I got out of order
4 here.

5 DR. TEMPLE: No worries.

6 DR. HOFFMAN: Both the Food and Drug
7 Administration and the public believe in a
8 transparent process for information gathering and
9 decision making. To ensure such transparency at
10 the advisory committee meeting, FDA believes that
11 it is important to understand the context of an
12 individual's presentation.

13 For this reason, FDA encourages all
14 participants, including the applicant's
15 non-employee presenters, to advise the committee of
16 any financial relationships that they may have with
17 the applicant such as consulting fees, travel
18 expenses, honoraria, and interests in the
19 applicant, including equity interests and those
20 based upon the outcome of the meeting.

21 Likewise, FDA encourages you at the
22 beginning of your presentation to advise the

1 committee if you do not have any such financial
2 relationships. If you choose not to address this
3 issue of financial relationships at the beginning
4 of your presentation, it will not preclude you from
5 speaking.

6 We will now proceed with presentations from
7 the guest speaker, immediately followed by
8 presentations from Mesoblast, Incorporated and FDA.

9 DR. YU: Thank you so much.

10 Dr. Temple, please proceed.

11 DR. TEMPLE: Thank you.

12 I'm going to use, as I said, some of the
13 literature on MSC use for graft-versus-host disease
14 as examples; and the presentations in four sections
15 covering an introduction, discussion of the sources
16 of variability in the cell product, and the patient
17 response; and then cell product characterization
18 covering morphology, markers, and function; and
19 then conclude with some suggestions regarding
20 approaches to determine critical quality
21 attributes, which are attributes of the cell
22 product that indicate efficacy and that can be used

1 to assess differences in cell product preparation.

2 Allogeneic stem-cell transplant of
3 hematopoietic stem cells is the treatment of choice
4 for patients with several high-risk malignancies
5 and other life-threatening, non-malignant
6 disorders.

7 Acute graft-versus-host disease is a leading
8 cause of mortality and morbidity. While steroids
9 remain the first-line treatment, about half the
10 patients don't respond. So second- and third-line
11 treatments are needed cryopreserved unmatched. Our
12 generic mesenchymal stromal cells, or MSCs, are
13 currently used in several European countries to
14 treat graft-versus-host disease.

15 So why MSCs? MSCs can be derived from
16 different sources, including from bone marrow, and
17 they have been shown to exhibit plasticity, taking
18 on the features of cells such as fat, bone
19 cartilage, and muscle. They've been shown to
20 secrete numerous factors that can be beneficial in
21 an injured environment, and some of these factors
22 have immunomodulatory properties.

1 For example, they can suppress the
2 proliferation and activity of T cells, B cells,
3 natural killer cells, and they can positively
4 regulate activated regulatory T cells.

5 In this review, acute graft-versus-host
6 disease mechanism is laid out as shown in this
7 figure, and they describe it in three phases.
8 First, there's initial tissue damage and antigen
9 presenting cell activation. Then the donor T cells
10 from the graft are primed, differentiate, and
11 migrate. Then there's a third stage. When the
12 activated immune cells destroy the host tissue,
13 especially in the gut, liver, and skin, after
14 infusion, the MSCs become activated and are thought
15 to inhibit processes at each of these three phases.

16 However, there are several sources of
17 variability that can affect outcome. There's donor
18 variability that's shown here on the left of the
19 slide. That includes genetics, age, health,
20 medications, et cetera. Then once the MSCs are
21 isolated, they enter a multistep manufacturing
22 process with several opportunities for variations

1 such as cell plating density, the vessel type used
2 for culture; the culture components that are used;
3 the length of time in culture; and the number of
4 passages.

5 All of these factors can affect the specific
6 cells and the final cell product, their
7 characteristics and properties, and how they
8 interact with the disease environment. The
9 recipient patient is also a source of variability,
10 having different genetics depending on the stage of
11 disease, the specific tissue locale, and prior
12 treatment they have received, all potentially
13 affecting outcome.

14 Now, I'd like to delve a bit more into these
15 sources of variability and product effectiveness
16 because understanding these factors is critical to
17 understanding therapeutic efficacy. I have to
18 point out that the data that I'm going to show were
19 collected from several different studies using MSCs
20 and they do not reflect a single product or a
21 single manufacturing process.

22 There's good evidence that the MSC donor

1 impacts outcome, and in this experiment using a
2 T-cell proliferation assay, two of the donors,
3 indicated by 303 and 308, had significantly lower
4 inhibition of T-cell proliferation at the 1 to 9
5 ratio of MSCs to peripheral blood mononuclear
6 cells. Dr. Bauer will go into more detail about
7 donor variability in his presentation, but it's
8 clear from studies in the literature that we need
9 to have a better understanding of the impact of
10 donor on cell product characteristics.

11 This figure describes the basic steps in MSC
12 manufacture from tissue collection, cell isolation,
13 expansion, harvest, and then release testing prior
14 to patient administration. In addition, the cells
15 may be frozen and cryopreserved during this
16 process. So a significant challenge is knowing how
17 to optimize this multistep complex process and how
18 to make sure it's standardized and reproducible.

19 As agents, reagents, supplies, and donor are
20 changed, how do we determine that the product is
21 sufficiently similar to one that previously
22 demonstrated efficacy and safety?

1 In this study from 2012, the impact of
2 passage number was assessed, and it was
3 demonstrated that if MSCs are used at early
4 passages, they were more effective in patients than
5 late passage cells. So again, we need to
6 understand how MSC properties change with time and
7 culture, with passage, and different culture
8 conditions.

9 There are numerous different culture modes
10 for MSC production whether you're using a
11 particular type of multi-layered spec system or
12 bioreactor, and as I mentioned different culture
13 components. The impact of these on the cell types
14 produced and the cell therapy success is important
15 to determine.

16 I mentioned previously that MSCs are used in
17 Europe for graft-versus-host disease, and in this
18 review from 2018, data from 17 European centers
19 were analyzed to assess differences in product
20 manufacturing, including the tissue source, how the
21 MSCs were isolated, the growth factors that were
22 used to expand the product, and the methods used

1 were different at different centers, as you can
2 see. Further details were taken, including the
3 markers that are used for acceptance criteria,
4 which also varied substantially.

5 Given we have different manufacturing
6 protocols, different criteria to characterize the
7 product, and there is information on how the
8 patients responded, it may be worth while analyzing
9 these data and potentially studying the cell
10 product and any retained locks, and relate this to
11 patient outcome.

12 I also talked about variation that comes
13 from the particular recipient. The recipient
14 varies in genetics and stage of disease, and the
15 same product can elicit different responses in
16 patients. These are typically recorded as
17 complete, partial, or non-response.

18 Clearly, we need to understand how
19 differences in the recipient patient impact the
20 cell therapy outcome. An important question is
21 whether we can identify responders versus
22 non-responders for a particular treatment by using,

1 for example, genomic sequencing of patient or
2 assessing parameters related to stage of disease.

3 Going on, building further into impact of
4 recipient, we know that after the MSCs are infused,
5 the allogeneic MSCs live for a short while in the
6 host. This occurs in mouse models, and in this
7 study, it was shown that MSCs infused into mouse
8 models of graft-versus-host disease underwent cell
9 death, as shown in B. Further, in these
10 graft-versus-host disease models, the MSCs
11 successfully reduced the graft-versus-host disease
12 effector cells in both the spleen as shown here and
13 in the lung and another one.

14 They also then went on to ask whether the
15 MSC death was important. They compared the outcome
16 and second mouse model, which was mutant for
17 perforin, in which the MSCs did not die. What they
18 found now is that, as shown here, these
19 graft-versus-host disease effector cells were not
20 reduced in the spleen or in the lung. So in this
21 model, then, it appears that the MSC death is
22 critical for beneficial response.

1 Importantly, they also showed that the
2 peripheral blood mononuclear cells, the PBMCs, from
3 the patients with graft-versus-host disease could
4 kill MSCs in vitro, while those from healthy
5 controls did not. Moreover, as shown in B, the
6 cell death in vitro correlated with patient
7 response as shown here. In this case, then,
8 there's an in vitro assay that appears to protect
9 clinical outcome in different patients, which is
10 very valuable information.

11 So how do we better define the cell product
12 characteristics that are related to clinical
13 benefit? We typically characterize cell products
14 with three main areas of assessment: cell
15 morphology, markers, and functional tasks.
16 Assessment of morphology is a fundamental aspect of
17 cell culture method.

18 Experienced researchers can look down the
19 microscope at growing cells and rapidly tell
20 whether a particular culture is on track. So
21 integrating this fundamental method of assessment
22 into the manufacturing process is very important.

1 Cell morphology depends on many different
2 factors on the cell type, the substrate, the
3 culture medium, the growth factor, and the passage
4 number. Morphology is a powerful indicator of cell
5 type, cell health, and state, and therefore it can
6 inform about cell identity, purity, and potency,
7 but we need methods to assess morphology that
8 ideally are operator independent.

9 Computer-based image analysis has advanced
10 to very sophisticated levels, and in this study led
11 by Dr. Bauer, MSC images were collected, segmented,
12 and captured by computer software and then analyzed
13 in depth. This digitized information about the
14 cell features can then be used to predict MSC
15 properties relevant to patient outcome such as
16 degree of mineralization or immunosuppressive
17 activity.

18 Recent analytical methods use deep learning
19 with large sets of training images to assess cell
20 properties, as shown in this study led by Dr. Kapil
21 Bharti at the National Eye Institute.

22 Here, induced pluripotent stem cells were

1 used to generate a monolayer of retinal pigment
2 epithelial cells. Image analysis and deep learning
3 methods then enabled prediction of important
4 features of this cell, including the tightness of
5 the monolayer and the polarized secretion of
6 vascular endothelial growth factor.

7 Analyzing images by non-invasive methods
8 combined with customized software programs can be
9 very valuable tools to assess the cell product
10 during the manufacturing process.

11 Stem and progenitor cells divide and they
12 produce progeny of different types, and dynamic
13 features such as division mode, cell migration, and
14 process outgrowth, these can help indicate cell
15 health and properties.

16 In this paper from 2010, computer-based
17 analysis of time-lapse movies was used to predict
18 the retinal progenitor cell fate from the movies,
19 and in fact the successful prediction rate, as
20 shown here, was very high. Static images or movies
21 can be captured by non-invasive methods during
22 manufacturing and provide critical information that

1 improves the efficiency and the reproducibility of
2 the manufacturing process.

3 The marker expression is another key
4 characteristic used to assess cell products, and
5 numerous markers have been identified on MSCs,
6 including cell-surface markers that are valuable to
7 identify and also select cells.

8 However, despite extensive study, no markers
9 have yet been identified that accurately predict
10 clinical outcomes, so how do we know whether we
11 have correctly identified the key markers to
12 follow? We need a comprehensive understanding of
13 cell markers, including cell-surface markers, that
14 can be used as a reference to correlate with
15 product performance.

16 An understanding of the molecules expressed
17 on the cell surface is especially useful, as these
18 are the molecules that will interact with the host
19 environment. For example, the surfaceome
20 encompasses specific receptors, surface ligands,
21 and adhesion molecules, which could impact product
22 performance after transplantation. The surface

1 proteome is a small percentage of the total genes
2 expressed in a cell.

3 This figure from Dr. Rebecca Gundry shows
4 the method she uses, that the surface glycoproteins
5 are captured, and then mass spec is used to
6 sequence the associated peptides. Dr. Gundry has
7 also developed sophisticated bioinformatic tools to
8 analyze the surfaceome and identify which molecules
9 are unique to a particular cell type.

10 Just as an example, she's used this system
11 to identify a cell-surface transporter, which one,
12 that is expressed on the surface of pluripotent
13 stem cells and can be used to remove residual stem
14 cells during cell culture to improve product purity
15 and safety.

16 Any cell product has a degree of
17 heterogeneity due to different numbers of cell
18 subtypes or two different cells being different
19 states. How many different subtypes of cells are
20 present? We need to know also whether the
21 heterogeneity is actually important for product
22 success. Are some populations beneficial and

1 others harmful?

2 Selecting subpopulations could improve
3 product performance. Are some subpopulations
4 inert? This could impact dosing. So for many
5 reasons, we need to have a good understanding of
6 the heterogeneity of cell products.

7 Single-cell analysis has greatly advanced
8 our understanding of cell population heterogeneity.
9 For example, single-cell transcriptomics has become
10 routine to define the diverse cell types in a
11 mixture and provide information on gene expression
12 in individual cells that can inform about cell
13 state and cell health.

14 In this study, adipose cells were isolated
15 and cultured, and then thousands of the cultured
16 cells were analyzed with RNA sequencing. In this
17 case they used a 10x platform, then a
18 bioinformatics analysis was performed as shown in
19 B. After correcting for cell proliferation,
20 several subpopulations of cells were revealed.

21 Currently there are a number of different
22 platforms to perform single-cell sequencing and

1 there are several bioinformatic tools. Both of
2 these impact outcome. So in order to use this
3 technology to provide information on the
4 heterogeneity of a cell product, it's crucially
5 important to standardize the platform and the
6 bioinformatic analysis pipeline that is used.

7 It's also valuable to use the single-cell
8 technology to understand more about the original
9 cell isolate. I already mentioned that the cell
10 product can vary with different donors, and in this
11 recent paper, bone marrow mesenchymal cells were
12 studied using single-cell transcriptomics, and this
13 revealed several different cell subpopulations with
14 distinct gene expression pattern.

15 Hence, defining the composition of the cell
16 isolate, which we can consider the starting
17 material in this cell manufacturing protocol, can
18 be informative and potentially valuable to predict
19 the performance of the final cell product.

20 I previously mentioned that MSC preparations
21 can vary in its efficacy with passage. In this
22 study, bone marrow stromal cells were sequenced at

1 single-cell level and found to change gene
2 expression with passage, and some of these markers
3 are selected in seq. This information could
4 potentially explain how passage impacts clinical
5 outcome.

6 Note that in addition to the single-cell
7 sequencing that I have mentioned, other methods are
8 available and are being developed to analyze
9 features of cell population. These include, for
10 example, single-cell ATAC-seq, which gives
11 information about chromatin state. New
12 technologies that are coming online have great
13 potential to improve our understanding of cell
14 products.

15 Overall then, it would be useful to gain
16 deeper information about cells at several stages of
17 the manufacturing process, at the beginning in the
18 original cell isolate; during manufacture to track
19 changes that occur with time and culture and
20 passage; to assess the impact of critical steps
21 such as cryopreservation; and then to more fully
22 characterize the final formulated product. A

1 challenge is determining what tests should be done,
2 and when, and how that information will be used to
3 assess the product.

4 In addition to morphology and markers,
5 functional testing plays an important role in
6 product characterization. MSCs are known to
7 exhibit plasticity and acquire features as adipo-,
8 osteo-, and chondrogenic lineage cells. This
9 plasticity is induced, for example, by using
10 specialized inductive culture media that push the
11 cells down these different pathways.

12 However, MSCs are not the only cell type
13 with this property. In a paper we published in
14 2012, we demonstrated that retinal pigment
15 epithelial cells, that were derived either from
16 adults themselves or from pluripotent stem cells,
17 were able to acquire features with these lineages
18 after exposure to the same inductive media that was
19 used for MSCs. Even single identified RPE cells
20 could take on these different phenotypes. Retinal
21 pigment epithelial cells are central nervous system
22 cells and not an MSC, so this feature is not unique

1 to MSCs. It may be an important and necessary to
2 define them, but it's not sufficient.

3 An important property of MSCs is cytokine
4 secretion, and typically one or two factors are
5 used to assess a particular cell production
6 process. But we can now take advantage of larger
7 scale methods, such as using cytokine arrays to
8 determine the secretome more completely and be able
9 to define differences between one production
10 process or another production run -- one process or
11 a different production run and another.

12 Functional tests that predict outcome in
13 patients would be ideal. In this study, a typical
14 in vitro test was performed to assess whether MSCs
15 could inhibit patient PBMCs. The outcome of this
16 in vitro test was then compared to clinical outcome
17 with the patients classified as responders or
18 non-responders.

19 It's notable that this test did not predict
20 the patient response. So we need to identify
21 functional tests that can be used to assess the
22 cell product that ideally are demonstrated to be

1 predictive.

2 Just as a reminder, I talked earlier about
3 this cytotoxic in vitro assay that was found to be
4 predictive of patient response. So such tests will
5 be useful to help identify cell populations that
6 would benefit specific patient populations.

7 In conclusion, defining the critical quality
8 attributes of a cell product is an iterative
9 process that demands knowledge about the cells and
10 how they perform in patients. It would be best to
11 gather wide knowledge about the cell product. It's
12 very important to consider which data to gather,
13 which methodologies to use, and at which time
14 points in the production process.

15 Similarly, it's important to consider what
16 information to gather about the patients and their
17 clinical responses, and correlating the two in an
18 iterative manner may be used to identify the
19 critical quality attributes and the patient
20 population that the product is best suited for.

21 Finally to summarize, the field of cell
22 therapy is growing and has great potential to

1 produce new medicines and that we acknowledge that
2 it is a relatively new field and that cells are
3 complex, and dynamic, and it is challenging to
4 define identity, purity, and potency assays. I
5 mentioned the MSCs are being used for
6 graft-versus-host disease in Europe with a variety
7 of manufacturing processes and markers used to
8 identify and release the product, so it may be
9 worthwhile to delve further into existing data.

10 The MSC mechanism of action is likely
11 multifactorial, so there is value in gathering wide
12 information on the product to correlate with
13 patient outcomes in order to define critical
14 quality attributes.

15 Finally, we're at an exciting time when
16 multiple technologies are maturing that enable us
17 to characterize cells in depth and the key stages
18 of the manufacturing process to better understand
19 how these novel therapeutic agents work and may
20 benefit patients. Thank you.

21 DR. HOFFMAN: Thank you, Dr. Temple. We'll
22 now move on to the applicant's presentation,

1 Dr. Storton.

2 **Applicant Presentation - Geraldine Storton**

3 MS. STORTON: Yes, I'm here.

4 Good morning, Mr. Chairman, members of the
5 advisory committee, and the FDA. I'm Geraldine
6 Storton, the head of regulatory affairs and quality
7 management at Mesoblast. We're pleased to be here
8 today to discuss remestemcel-L, which I'll refer to
9 as remestemcel throughout the presentation.

10 Here is the agenda for this morning's
11 presentation. I will introduce remestemcel and
12 elaborate on the manufacturing process and quality
13 controls in place.

14 Dr. Silviu Itescu will then provide
15 background on the pathophysiology of acute GVHD, a
16 disease caused by cytokine storm and T-cell
17 activation. He will also speak to the mechanism of
18 action and the ability of remestemcel to reduce the
19 cytokine release and inhibit T-cell activation. He
20 will conclude by explaining how our clinical trial
21 outcomes have been able to validate and demonstrate
22 the selection of appropriate potency assays.

1 Remestemcel is an allogeneic cell product
2 that comprises culture-expanded mesenchymal stromal
3 cells isolated from bone marrow of healthy adult
4 donors. Since the mesenchymal stromal cells are
5 hypo-immunogenic, cells from a single donor can be
6 used in recipients without tissue matching.

7 Remestemcel is an off-the-shelf product that can be
8 readily available to treat patients when needed.

9 Remestemcel is manufactured in Mesoblast's
10 contracted GMP manufacturing facilities over a
11 three-stage GMP compliant process. In the first
12 stage, the bone marrow is obtained from healthy
13 donors. The bone marrow then goes through the
14 process to isolate and purify the cells, which then
15 proceed through the initial steps of expansion into
16 a cell bank. At this point, the quality is
17 confirmed and the banks can be stored for some
18 time.

19 In the second stage of the process, cells
20 are further expanded and formulated into the final
21 drug product and undergo cryopreservation. In the
22 third stage, the product is packaged, stored, and

1 distributed under strict quality control. As the
2 product is cryopreserved, it can be stored in
3 distribution centers ready to be sent to hospitals
4 when a patient needs treatment.

5 Let me elaborate on the donor program, and
6 then I'll walk you through each of the
7 manufacturing stages in more detail. The donor
8 program is well established with potential donors
9 evaluated for eligibility and safety. The donors
10 must be prescreened and blood testing undertaken up
11 to a week prior to donation to check for a full
12 infectious disease profile.

13 In addition to meeting all the requirements
14 for good tissue practice, we have added additional
15 criteria to donors such as body mass index, age,
16 and bone marrow cell count. The screening process
17 works to prevent introduction of possible
18 communicable diseases, and the additional measures
19 are included to reduce the variability in the
20 attributes of the cells such as their proliferative
21 capacity, leading to more consistency in the yields
22 of the manufacturing process.

1 The first stage of manufacturing is the
2 production of the donor cell bank from the bone
3 marrow aspirate. The nucleated bone marrow cells
4 are isolated from the bone marrow aspirate. They
5 are then culture expanded in a process using two
6 passages of expansion.

7 Following passage 2, the cells are harvested
8 and cryopreserved as the donor cell bank. Each
9 donor cell bank lot is derived from a single donor,
10 which following culture expansion generates
11 multiple containers of donor cell banks per lot.
12 Several donor cell bank lots are currently
13 available for continued manufacture of drug
14 products.

15 The second stage involves the continued
16 production of drug substance and formulation and
17 fill of the final drug product. One vial from a
18 donor cell bank is stored and further culture
19 expanded for three more passages. The cells are
20 harvested following passage 5.

21 These cells are the active drug substance,
22 and they are then formulated in a cryoprotectant

1 solution and filled to create the final drug
2 product. The drug product is cryopreserved and
3 stored below negative 135 degrees C in liquid
4 nitrogen vapor phase. For each manufacturing
5 campaign of drug product, a single container of
6 donor cell bank is used. Overall, one donation of
7 bone marrow can manufacture enough drug product to
8 treat more than 400 patients.

9 Throughout manufacturing, there are a number
10 of in-process controls to monitor the quality of
11 the cell and the manufacturing environment to
12 ensure that the process is being executed
13 consistently. Cell count and viability are
14 routinely monitored to assess consistency of cell
15 growth throughout the process. Attributes such as
16 sterility are also periodically monitored to ensure
17 the process maintains an aseptic environment
18 throughout.

19 In addition, quality control release testing
20 is performed on the donor cell banks and the final
21 drug product. As the drug substance is immediately
22 processed, the tests on the drug substance are

1 focused on in-process sterility and mycoplasma
2 testing to ensure the aseptic environment has been
3 maintained. Our critical quality attributes, which
4 are attributable to safety, efficacy, and yield,
5 have been established, and we have consistently
6 carried them through the development process,
7 including multiple manufacturing site and raw
8 material changes.

9 The characteristics and attributes of
10 mesenchymal stromal cells are well understood, and
11 robust quality assurance processes ensure final
12 product with batch-to-batch consistency and
13 reproducibility. Once manufactured and packaged,
14 the third stage of the process involves shipping
15 the final drug product to distributors, where
16 remestemcel is packaged into cartons containing
17 either 1 or 4 vials. The product is held at
18 distribution centers until it is requested by a
19 treating hospital.

20 The product quantities are prepared and
21 shipped under strict temperature conditions to the
22 treating hospital to ensure the quality of the

1 product at the time of treatment. Products can be
2 stored for up to four years under cryostorage
3 conditions. This gives hospitals the ability to
4 have off-the-shelf product available when needed to
5 treat a patient.

6 To prepare for administration, the required
7 number of vials are thawed based on the patient's
8 body weight, resuspended, and transferred into an
9 infusion bank with 40 mls of Plasma-Lyte A or an
10 equivalent solution, and infused. The infusion
11 typically takes no longer than 30 minutes.

12 Mesoblast works with the hospitals to ensure the
13 staff are trained in the handling, thawing, and
14 administration procedures for the drug product.

15 To understand the quality attributes that we
16 use to ensure a quality product is distributed to
17 these patients, you need to understand a bit of the
18 pathophysiology of GVHD and the mechanism of
19 remestemcel in this disease. To describe this, I
20 will now pass to Dr. Silviu Itescu to explain the
21 mechanism by which remestemcel functions in the
22 treatment of patients with graft-versus-host

1 disease.

2 **Applicant Presentation - Silviu Itescu**

3 DR. ITESCU: Thank you. My name is
4 Dr. Silviu Itescu. I'm the chief executive officer
5 of Mesoblast. Remestemcel is a novel cellular
6 therapy for the multimodal mechanism of action. It
7 modulates in terms of excessive immune response to
8 foreign tissues, autoantigens, or infections,
9 allowing resolution and recovery of healthy
10 tissues.

11 Due to these characteristics, we have
12 developed remestemcel for the treatment of acute
13 graft-versus-host disease in pediatric patients
14 when they have failed to respond to treatment with
15 systemic corticosteroids.

16 Acute graft-versus-host disease is a serious
17 and life-threatening complication of allogeneic
18 hematopoietic stem cell transplantation that occurs
19 when alloreactive donor T cells within the
20 hematopoietic stem cell graft recognize the
21 recipient's tissues as foreign and trigger an
22 immunological response.

1 The pathophysiology of acute GVHD disease is
2 complex and is characterized by three phases:
3 tissue damage from conditioning treatment; immune
4 cell activation and cytokine storm; and end-organ
5 damage, primarily involving the skin, the gut, and
6 the liver.

7 In phase 1, the bone marrow transplant
8 conditioning regimen causes profound damage to host
9 issue, which leads to the release of inflammatory
10 stimuli. This activates antigen-presenting cells.
11 In phase 2, following the bone marrow transplant,
12 there is substantial immune activation of donor
13 macrophages and T cells, which results in a
14 cytokine storm that mediates tissue damage.
15 Phase 3 is the end-organ damage involving the gut
16 and the liver that results from the macrophage and
17 T-cell cytokine storm and is frequently fatal.

18 This slide demonstrates two major
19 characteristics of remestemcel's mechanism of
20 action. Firstly, the cells use surface receptors
21 such as tumor necrosis factor receptor type 1, or
22 TNFR1, to sense the presence of high levels of

1 inflammatory cytokines such as TNF-alpha produced
2 by the inflammatory macrophages and T cells within
3 the micro environment.

4 TNF signaling through TNFR1 activates
5 cytoplasmic NF-kappaB, which moves into the nucleus
6 and is the master regulator of multiple
7 anti-inflammatory factors, which ultimately result
8 in polarization of inflammatory M1 macrophages to
9 M2, anti-inflammatory macrophages, switching off
10 TNF-alpha production and inducing production of the
11 anti-inflammatory cytokine, interleukin 10.

12 Measuring surface levels of TNFR1 is a
13 sensitive predictor of the ability of the cell to
14 respond to the inciting inflammatory stimulus, in
15 this case TNF-alpha, and orchestrate an
16 anti-inflammatory response, and is a good upstream
17 assay to quantify the ability of the cell to evoke
18 a downstream, anti-inflammatory matrix response.

19 The measure of the cell's bioactivity is its
20 ability to inhibit CD4 T cell activation and
21 proliferation, the end result of multiple
22 anti-inflammatory factors produced either in

1 response to signaling through TNFR1 or via other
2 surface cytokine receptors, including interferon
3 gamma. Measuring the cell's ability to inhibit CD4
4 T cells provide the qualitative bioactivity that
5 reflect the combined effects of multiple
6 anti-inflammatory factors and pathways.

7 The next slide shows the ability of
8 remestemcel to inhibit production of high levels of
9 TNF alpha produced during an active cytokine storm.
10 Shown in the second panel, significant induction of
11 TNF alpha, lymphotoxin, and interferon gamma is
12 seen following activation of peripheral blood
13 mononuclear cells with anti-CD3 and anti-CD28
14 monoclonal antibodies.

15 Co-culture with remestemcel from two
16 distinct product lots result in potent inhibition
17 by over 90 percent of both TNF alpha and
18 lymphotoxin production, both ligands for TNFR1 but
19 not interferon gamma, indicating a specific and
20 selective pattern of proinflammatory cytokine
21 depression within both T cells and macrophages.

22 This suggests a feedback loop whereby high

1 levels of TNF alpha activate remestemcel via its
2 surface receptor to secrete paracrine factors
3 responsible for specific shut down of the inciting
4 TNF alpha produced by inflammatory M1 macrophages
5 and T cells.

6 To evaluate whether specific levels of
7 surface TNFR1 are indeed related to the
8 intracellular bioactivity following TNF alpha
9 signaling of remestemcel, we used siRNA technology
10 to establish remestemcel lots expressing reduced
11 TNFR1 expression levels, as seen here. The
12 right-side panel shows the effect of TNFR1
13 knockdown on phosphorylation of NF-kappaB following
14 TNF alpha stimulation.

15 When remestemcel is activated with TNF
16 alpha, there is significant phosphorylation of
17 NF-kappaB as shown in black. This response is
18 dependent on the level of TNFR1 expressed by
19 remestemcel, providing a direct link between TNFR1
20 levels on the surface of the cells and
21 intracellular bioactivity as measured by NF-kappaB
22 activation.

1 This process ultimately results in nuclear
2 translocation of the activated NF-kappaB, where the
3 complex is able to initiate transcription and use
4 expression of multiple target genes. This
5 translocation is inhibited when TNFR1 is
6 downregulated, as shown in the middle panel, but
7 not when TNFR2, the second receptor for TNF, is
8 downregulated, as shown in the right-hand panel.
9 This demonstrates the critical requirement for
10 signaling via TNFR1 in NF-kappaB translocation and
11 its bioactivity.

12 We next sought to directly show the effect
13 of TNFR1 signaling on secretion by remestemcel stem
14 cell of NF-kappaB regulated immunomodulatory
15 factors. In the left-hand panel is shown the
16 dose-dependent induction by TNF alpha of CCL2
17 secretion by remestemcel, an immunomodulatory
18 factor which is regulated by NF-kappaB. Maximal
19 induction is seen when using 10 nanograms per ml of
20 TNF alpha.

21 In the right-hand panel, we show that
22 progressively increasing concentrations of siRNA

1 targeting TNFR1 abrogated the effect of TNF alpha
2 at 10 nanogram per ml to induce CCL2 secretion.
3 This shows that there is direct relationship
4 between the level of TNFR1 expression and CCL2
5 secretion by remestemcel.

6 A similar response is seen for secretion by
7 remestemcel of another immunomodulatory factor
8 regulated by NF-kappaB, in this case, M-CSF. On
9 the left is shown dose-dependent induction by
10 TNF alpha of M-CSF secretion by remestemcel, while
11 in the right panel there is again a progressive
12 reduction in the secretion of M-CSF with increasing
13 knockdown of TNFR1.

14 Collectively, these data demonstrate that
15 TNFR1-dependent induction of at least two factors
16 regulated by NF-kappaB, CCL2 and M-CSF, both of
17 which play the key role in polarizing macrophages
18 to an anti-inflammatory M2 state.

19 In summary, these data very clearly
20 demonstrate that the absolute level of TNFR1
21 expressed by remestemcel determines the response to
22 TNF alpha, and in turn NF-kappaB activation and the

1 secretion of immunomodulatory molecules.

2 We next sought to directly show whether CCL2
3 production by remestemcel, a TNFR1-dependent and
4 NF-kappaB regulated factor, result in M1 to M2
5 macrophage polarization. Purified CD14 positive
6 monocytes co-cultured with remestemcel in the
7 presence of TNF alpha showed significant increase
8 in IL-10 secretion. This IL-10 production was
9 inhibited in the presence of a blocking antibody to
10 CCL2. These results were seen consistently when
11 using distinct remestemcel product lots.

12 So these data show TNFR1-dependent signaling
13 of remestemcel leads to production of CCL2, which
14 plays a key role in the polarization of macrophages
15 to an IL-10 producing immunomodulatory state.

16 In addition to the level of surface TNFR1
17 expression being an upstream measure of the
18 integrity of remestemcel's ability to regulate
19 NF-kappaB dependent immunomodulatory factors, it is
20 important to measure the cell's downstream
21 bioactivity to inhibit CD4 T cell activation and
22 proliferation since these are important in the

1 clinical outcome of GVHD.

2 Shown in the right-hand panel is a
3 reproducible inhibition of multiple remestemcel
4 lots of the ability of CD4 T cells to proliferate
5 following activation with anti-CD3 and anti-CD28
6 monoclonal antibodies. Measuring the cell's
7 ability to inhibit CD4 T cells provides a
8 qualitative bioactivity that reflects the combined
9 effects of multiple anti-inflammatory factors and
10 pathways, either in response to signaling through
11 TNFR1 or other surface cytokine receptors such as
12 the interferon gamma receptor.

13 Given our understanding of the multimodal
14 mechanisms of action by which remestemcel inhibits
15 T cell proliferation and inhibits macrophage
16 polarization and retains the M1 phenotype, we
17 utilized the matrix-based approach to develop our
18 potency assays.

19 This approach is consistent with FDA
20 guidance, which recommends the use of one
21 quantitative bioassay and one qualitative bioassay,
22 which together are sufficiently robust in terms of

1 reproducibility as indicators of product quality
2 and stability.

3 In summary, our in vitro understanding of
4 the multimodal mechanisms of action of remestemcel
5 has informed the selection of our potency critical
6 quality attributes. TNFR1 is upstream of NF-kappaB
7 signaling and secretion of immunomodulatory
8 cytokines, and can be determined quantitatively.

9 IL-2 receptor alpha inhibition on activated
10 peripheral blood mononuclear cells is an early
11 marker of T cell activation and was selected as a
12 qualitative bioassay based on our knowledge that
13 inhibition of T cell activation is critical to the
14 immunomodulatory activity of remestemcel, both
15 directly and via macrophage polarization.

16 As I'll show you, data from the broad and
17 long clinical development program has further
18 informed on the absolute levels of these potency
19 measures and the correlation with clinically
20 meaningful outcomes in patients with
21 steroid-refractory acute graft-versus-host disease.

22 Our clinical program has included three

1 studies in patients with steroid-refractory acute
2 graft-versus-host disease: Protocol 280, a
3 randomized-controlled phase 3 trial; Protocol 275,
4 an expanded access program in children; and Study
5 001, the pivotal, single-arm phase 3 trial in
6 children.

7 During the yellow-shaded period in 2009,
8 several manufacturing enhancements were made to
9 optimize and streamline the overall manufacturing
10 process of remestemcel, which Mesoblast has
11 consistently carried forward. The most important
12 change was to set a limitation on maximal
13 trypsinization time, a process modification that
14 has been shown to significantly impact the surface
15 expression of TNFR1.

16 In this figure, pale blue indicates product
17 made using the original manufacturing process
18 resulting in a lower level of TNFR1 potency. The
19 product made using the original process was used in
20 clinical studies 280 and about three-quarters of
21 the Expanded Access Protocol 275. The dark blue
22 shows the product made using the optimized

1 manufacturing process, which has a much higher
2 level of TNFR1 potency. This product was used in
3 about a quarter of the Expanded Access Protocol 275
4 and in the pivotal trial Study 001.

5 Shown in this slide are the changes in the
6 two key potency critical quality attributes between
7 critical product lots made with the original
8 process in light blue above and with the optimized
9 process in dark blue below. The product made with
10 the optimized process demonstrated a significantly
11 higher mean TNFR1 expression level and a shift to
12 the right in the overall distribution of TNFR1
13 expression levels. Additionally, the product made
14 with the optimized process demonstrated a
15 significantly reduced variability in mean IL-2
16 receptor inhibition than product made with the old
17 process.

18 An assessment of the measured potency
19 attributes on product used in the three
20 steroid-refractory acute GVHD trials showed that
21 patients treated with remestemcel in trials after
22 2009 received product with higher critical quality

1 attributes as a result of the optimized
2 manufacturing process.

3 This table shows that mean TNFR1 levels and
4 percent inhibition of IL-2 receptor expression will
5 both increase in product used to treat all patients
6 in Study 001. Cell viability was consistently high
7 throughout this period.

8 We next examined whether these observed
9 differences in potency attributes in products used
10 in each of the study protocols had an impact on day
11 28 overall responses and on day 100 survival. As
12 you can see, our pivotal Study 001, where all
13 patients received optimized product, showed the
14 highest day 28 overall response and the highest
15 overall survival. Study 271 only measured survival
16 through day 100. That's why we're showing here
17 day 100 survival only.

18 Stratifying patients across all
19 steroid-refractory graft-versus-host disease trials
20 on the basis of having received only product made
21 with the original or the optimized process
22 demonstrated that patients who received only

1 product made with the optimized process had
2 significantly higher mean levels of TNFR1 and
3 IL-2Ra inhibition, IL-2Ra percent inhibition, and
4 significantly higher day 100 survival.

5 In pediatric study Expanded Access 275,
6 children who received a single-donor lot of product
7 made with the optimized process had a significantly
8 better survival than those who received the product
9 made for the original process. This demonstrates
10 the relationship between optimization of critical
11 attributes on a single-product lot and survival
12 benefit within one single trial and consistency of
13 patient demographics.

14 In pivotal study phase 3 001, where only
15 product made with the optimized process was used,
16 there was an almost identical survival outcome at
17 day 100 of 74 percent, demonstrating a second
18 trial, which confirmed the survival benefit
19 associated with the optimized manufacturing process
20 seen in the 275 study.

21 An analysis of donor lots from single donor
22 used in patients treated in the phase 3 Trial 001

1 showed, in fact, that all of these lots have
2 consistently high TNFR1 levels, on the left, and
3 high T cell inhibitory function, as shown on the
4 right.

5 Shown in the next slide is the relationship
6 between in vitro inhibition of IL-2 receptor
7 expression for lot and reduction in activated CD4 T
8 cells in vivo after 28 days of treatment with
9 remestemcel in the phase 3 Trial 001 in patients
10 who received a single product lot. Activated CD4 T
11 cells were defined as expressing IL-2 receptors in
12 HLA-DR. The inverse relationship is significant
13 using linear regression. Change in activated CD4
14 T-cell levels was seen in all patients for 28 days
15 of treatment, indicating that this is a consistent
16 in vivo measurement of the product's bioactivity.

17 Taking into consideration our understanding
18 of the manufacturing process and controls and being
19 further informed through the clinical outcomes,
20 we've revised our specifications to ensure the
21 commercial product lots will consistently reflect
22 the potency and activity of the product used in the

1 001 phase 3 study.

2 In conclusion, remestemcel has a
3 well-considered consistent and robust manufacturing
4 process that uses well-defined release criteria.
5 We've identified two important product attributes,
6 TNFR1 expression and IL-2 receptor inhibition, that
7 have demonstrated a relationship to the clinical
8 performance of specific drug product lots. The
9 survival outcomes in our clinical development
10 program further inform determination of TNFR1
11 specification and IL-2 receptor inhibition in vitro
12 associated with in vivo reduction of immune
13 activation.

14 The optimization of product manufacturing
15 for remestemcel has resulted in greater potency of
16 these assays and improved clinical outcomes over
17 time. Data from our clinical development program
18 support that TNFR1 and IL-2 receptor inhibition
19 correlate with clinical outcomes and highlight the
20 importance of these clinical quality attributes to
21 ensuring the manufacturing process consistently
22 produces remestemcel lots of acceptable quality.

1 This concludes our presentation. Thank you.

2 DR. BAUER: Good morning. This is Steve
3 Bauer. Shall I proceed?

4 DR. HOFFMAN: Please.

5 DR. BAUER: Thank you.

6 **FDA Presentation - Steve Bauer**

7 DR. BAUER: As I said, I'm Steve Bauer. I'm
8 the chief of the Cellular and Tissue Therapies
9 Branch in the Division of Cell and Gene Therapies
10 in the Office of Tissues and Advanced Therapies,
11 and I'll be giving the FDA presentation on product
12 characterization for remestemcel-L. In FDA
13 terminology, product characterization is also
14 referred to as chemistry manufacturing and controls
15 or CMC for short.

16 (Pause.)

17 DR. BAUER: Before going further, I would
18 like to acknowledge my fellow CMC experts, our
19 office leadership, and our colleagues in OCE and
20 ODAC for their assistance with this presentation.
21 I also want to thank our special government
22 employees and advisory committee panel for their

1 participation today. We look forward to the
2 discussion and input from you folks.

3 The purpose of my talk is to discuss the
4 quality attributes of remestemcel-L and their
5 relationship to product quality and effectiveness.
6 In plain language, this product can be described as
7 an off-the-shelf product, and the assumption is
8 that each batch of product will have the same
9 quality.

10 So we can ask this question. How do you
11 know that the next batch has the same activity as
12 the batches used in the clinical trial? What we
13 rely on to answer this question is overall control
14 of the manufacturing and testing for quality
15 attributes as explained in the next two slides.

16 We rely on three key types of control as
17 part of our strategy to ensure product quality and
18 consistency. For each type of control, we
19 determine characteristics to assess or measure and
20 specifications for those measurements. One key is
21 source control, meaning that we control the quality
22 of the starting materials used in manufacturing.

1 Another key is process control of manufacturing,
2 but the focus for today is control of product
3 testing. At the end of manufacturing, we want to
4 test the product to make sure it has the same
5 characteristics from batch to batch or lot to lot.
6 Product testing focuses on properties of the
7 product that we call quality attributes.

8 DR. YU: Hi, Dr. Bauer. This is Joyce Yu.

9 DR. BAUER: Yes?

10 DR. YU: I'm sorry to interrupt you. Do you
11 see the left-right arrows at the bottom left of
12 your screen on your slides?

13 DR. BAUER: I did. Yes. I was pressing
14 those and nothing seemed to be happening.

15 DR. YU: Okay. If it's not working for you,
16 then I can move them for you as well.

17 DR. BAUER: Yes. I will try next time, but
18 if it doesn't work, I'll ask you to do it. Thanks.

19 DR. YU: Sure. Please proceed.

20 DR. BAUER: So what are quality attributes?
21 A quality attribute is a molecular or other
22 characteristic of the product that is selected for

1 its ability to help indicate the quality of the
2 product, and we also identify critical quality
3 attributes, or CQAs, which consist of a physical,
4 chemical, biological, or microbiological property
5 or characteristic that should be within an
6 appropriate limit, range, or distribution to ensure
7 the desired product quality. Collectively, quality
8 attributes define the safety, purity, potency,
9 identity, and stability of the product.

10 In contrast to small molecule inhibitors, or
11 monoclonal antibodies that target specific
12 molecules, remestemcel-L is a cellular product.
13 And as we heard earlier, cellular products and MSCs
14 are inherently complex since cells express
15 thousands of proteins, thousands of genes, and
16 respond to their environment, both during
17 manufacturing and in patients.

18 So how do we determine what are useful
19 quality attributes and critical quality attributes
20 for a cellular product? Quality attributes can be
21 developed and established through understanding the
22 characteristics and biological properties of the

1 product. The applicant has defined many
2 characteristics of remestemcel-L as shown in this
3 slide. This chart is from the applicant briefing
4 document.

5 These characteristics overlap considerably
6 with characteristics the scientific literature and
7 stakeholder community have developed as consensus
8 markers and properties that define mesenchymal
9 stromal cells or MSCs.

10 These characteristics include morphology,
11 the cell surface markers that are present and
12 absent; the ability of MSCs to undergo trilineage
13 differentiation; their ability to proliferate;
14 their ability to evade host immunity and to be
15 immunomodulatory, which is the key functional
16 attribute of remestemcel-L that we focus on today;
17 and finally their karyotype, which should remain
18 stable through culture expansion as an indication
19 that they will not likely be tumorigenic.

20 Among the characteristics the applicant
21 chooses the characteristics they identify as being
22 essential for product quality, this slide shows a

1 list of these critical quality attributes. Each
2 product is tested for these CQAs, and each lot must
3 meet acceptance criteria or values for these tests.

4 These tests of the CQAs are called release
5 tests. This means that lots that pass the release
6 test and meet predefined specifications are
7 accepted, while lots that don't meet these values
8 are rejected. The CQAs include tests for identity,
9 purity, potency, activity, and safety.

10 I've highlighted the CQAs for identity,
11 potency, and activity because they are the focus of
12 our discussion this morning. The identity tests
13 define what is in the product. CD105 and CD166 are
14 markers that should be present on the cell surface.
15 The products that pass the identity tests should
16 then meet all the other release criteria to be
17 considered an acceptable product lot.

18 The potency and activity tests measure the
19 biological activity of the product and are
20 attributed to the cells that meet the identity
21 criteria. Tumor necrosis factor receptor 1, or
22 TNFR1, is expressed by the product, and

1 interleukin-2 receptor alpha, or IL-2R alpha, is
2 measured on T cells that have been activated, then
3 co-cultured with the product. The applicant has
4 based acceptance criteria as minimal threshold
5 level specifications for both TNFR1 and IL-2R
6 alpha.

7 The regulatory definitions of potency are
8 found in the U.S. Code and Code of Federal
9 Regulations, and a biological license application
10 may be approved on the basis of a demonstration
11 that the biological product that is subject of the
12 application is safe, pure, and potent.

13 For biological products, potency refers to
14 the specific ability or capacity of the product as
15 indicated by appropriate laboratory tests or by
16 adequately controlled clinical data obtained
17 through the administration of the product in the
18 manner intended to affect a given result. The
19 laboratory tests for remestemcel-L are the ones
20 I've described in the previous slide on
21 product-release testing.

22 In recognition that cellular products are

1 extremely complex, FDA published a guidance
2 document on potency tests for cell and gene therapy
3 products. Ideally, the potency assay will
4 represent the product's mechanism of action.
5 However, for cellular products such as remestemcel-
6 L, the mechanisms of action may be very complex.

7 To test for potency of many biological
8 products, we rely on bioassays, including in vivo
9 animal studies; in vitro organ tissue or cell
10 culture systems; or any combination of these. But
11 we can also rely on non-biological analytical
12 assays, which are methods that measure
13 immunochemical, molecular, or biochemical products
14 of the product outside of a living system. We
15 refer to these as surrogate measurements, and these
16 surrogate measurements can be substantiated by
17 correlation to a relevant product-specific
18 biological activity.

19 Our potency guidance included the use of
20 multiple potency assays also called the Matrix
21 approach. Because of the product's biological
22 complexity, one assay may not be sufficient to

1 measure potency. In this situation, we consider
2 the use of multiple complementary assays that
3 measure different product attributes associated
4 with quality consistency and stability.

5 Such matrix assays can consist of
6 combinations of biological assays, or biological
7 and analytical, or analytical assays alone. They
8 also can have a quantitative or qualitative
9 readout, however, a qualitative assay should be
10 accompanied by one or more quantitative assays.
11 The applicant's potency and activity test for TNFR1
12 and IL-2R alpha constitute such a matrix approach
13 to potency testing.

14 This slide reminds us of the proposed CQAs
15 for remestemcel-L that are the focus of our
16 discussion today. Identity is assessed by
17 expression of CD105 and CD166, and the activity and
18 potency are attributed to the MSCs in the lot.
19 Tests for TNFR1 and IL-2R alpha comprise the matrix
20 test for potencies. These tests include a
21 quantitative measurement of TNFR1 expression and a
22 qualitative measurement of activity based on the

1 inhibition of IL-2R alpha expression on the
2 activated T cells that are co-cultured with the
3 MSCs. For both assays, as I said earlier,
4 acceptance criteria are based on a threshold
5 minimum value.

6 The potency proposed by the applicant is
7 based on a reasonable proposal for mechanism of
8 action and employs a matrix approach that is in
9 line with FDA's guidance. However, as we heard in
10 Dr. Temple's presentation this morning, MSCs are
11 complex and have multimodal biological activities.
12 Also, Dr. Temple's talk and the scientific
13 literature describe considerable heterogeneity of
14 MSCs due to differences in biological activity and
15 donor-related effects.

16 This raises the essence of the question we
17 wish to discuss today, are the potency tests and
18 other critical quality attributes for remestemcel-L
19 sufficient to ensure the quality of the product
20 from batch to batch? This question is important
21 not only because there have been manufacturing
22 changes during the course of the clinical trials,

1 but also because if the product is approved for
2 marketing, future manufacturing may need to make
3 remestemcel-L from new donors.

4 We begin to address this question and look
5 at the evidence to support the proposed MoA of
6 remestemcel-L. The applicant states that
7 remestemcel-L has immunomodulatory properties and a
8 multimodal mechanism of action that counteract
9 inflammatory processes associated with
10 steroid-refractory acute graft-versus-host disease.

11 Subjects receiving remestemcel-L in
12 MSB-GVHD001 showed reduced markers of inflammation
13 at day 180 post-treatment, but there was no placebo
14 group control for comparison to bolster this
15 proposed MoA.

16 Also, remestemcel-L has demonstrated
17 in vitro immunomodulatory activity, but this MoA
18 has not been demonstrated in vivo. While
19 remestemcel's MoA might be related to
20 immunomodulatory effects, the FDA believes that the
21 MoA remains unknown.

22 As you've heard earlier this morning, the

1 applicant is proposing that there is a positive
2 relationship between TNFR1 levels and overall
3 survival, but here's why we do not agree with that
4 conclusion. In the BLA, the applicant presented
5 data to correlate the potency of lots with clinical
6 outcomes, but some limitations of the data were not
7 discussed in the applicant's briefing document.

8 In the BLA, the applicant presented data
9 correlating clinical outcomes with mean TNFR1
10 levels from lots used to individual patients.
11 There were no differences between TNFR1 levels in
12 the product lots received by responders and
13 non-responders in MSB-GVHD001, and now I will refer
14 to this as Study 001. That is the clinical trial
15 that provides the primary evidence of
16 effectiveness.

17 There was no association between survival on
18 day 100 and the mean TNFR1 levels in lots used in
19 Study 001. Similarly, there was no association
20 between day 28 overall response, the primary
21 outcome in Study 001, and the mean TNFR1 levels in
22 the lots used in Study 001.

1 Using pooled data from three clinical
2 studies, 275, 280, and Study 001, the applicant
3 found a statistically significant association
4 between TNFR1 results and survival on day 100,
5 however, these studies had different study
6 populations and concomitant medications. This
7 significance is not observed in Study 001 and most
8 subjects received product from multiple remestemcel
9 lots. Therefore, the interpretation of such a
10 pooled analysis is challenging.

11 Also, there's no clear relationship between
12 TNFR1 levels and the proposed MoA. Since this
13 slide was made, the applicant provided additional
14 data, and the bullet point here about their
15 knockdown study needs some correction.

16 Although studies in early product
17 development showed that knockdown of TNFR1
18 expression in the product reduced in vitro
19 immunomodulatory activity, similar knockdown
20 studies using the current version of the product
21 found that inhibition of T cell activation was not
22 affected by TNFR1 knockdown.

1 These new results suggest the in vitro
2 modulatory activity of the product is largely
3 independent of TNFR1 expression. Also, TNFR1
4 levels of the product lots without knockdown do not
5 correlate with in vitro immunomodulatory activity.
6 Although these assays are consistent with the
7 hypothesized immunomodulatory mechanism of action,
8 this has not been demonstrated in the clinical
9 trials submitted to support licensure.

10 While remestemcel-L and other MSC-based
11 investigational products have demonstrated apparent
12 immunomodulatory effects in in vitro experiments,
13 the ability of remestemcel-L to reduce
14 inflammation, as measured by inflammatory
15 biomarkers in humans receiving the product, has not
16 been demonstrated.

17 Steroid-refractory acute GVHD is thought to
18 be an immune-mediated disorder, but its etiology is
19 complex, and many cell types are likely to be
20 involved in its pathogenesis. Therefore, any
21 efficacy remestemcel-L might have in treating this
22 disease is not sufficient to demonstrate the

1 product's mechanism of action.

2 These analyses raise the concern expressed
3 in this first bullet, the CQAs for remestemcel-L
4 may not by themselves ensure adequate control of
5 clinical effectiveness of individual lots of
6 product. Also, although I won't present details,
7 the applicant submitted a product comparability
8 study under the IND and used the same critical
9 quality attributes to assess changes to
10 manufacturing, and we did not accept that this
11 study demonstrated comparability.

12 FDA understands the complexity and
13 challenges in understanding and developing CQAs for
14 cell therapy products. However, it's important to
15 continue efforts to develop critical quality
16 attributes that demonstrate product quality and
17 predict sustained quality for future manufacturing.
18 Based on our experience as regulators and
19 scientists, we often discuss with stakeholders the
20 importance of characterization studies and how they
21 can support identification and development of
22 release tests for CQAs that are predictive of

1 effectiveness.

2 Such characterization studies may be
3 sophisticated, powerful, slow, finicky,
4 labor-intensive, often expensive, comprehensive,
5 and time consuming, and we realize that these
6 characterization studies may necessitate an
7 iterative process in order to reach the goal of
8 developing lot release tests that are predictive.

9 In the end, what we want is to assist
10 stakeholders to develop release tests that are
11 robust, rapid, GMP friendly, so they're easy to
12 validate and operator independent, and that are
13 economical and focused.

14 But to help achieve this goal, FDA also
15 supports research on strategies to find CQAs that
16 correlate with in vitro and in vivo assays on
17 safety and effectiveness. This slide gives an
18 overview of FDA's MSC consortium. We manufactured
19 large batches of bone marrow derived MSCs from a
20 variety of commercially available sources and
21 harvested them at passages 3, 5, and 7, then
22 employed a variety of analytical methods to

1 characterize these MSC batches.

2 One overarching goal of this research is to
3 correlate product characteristics with bioassay
4 outcomes. Such product characteristics could then
5 potentially be used as predictive CQAs for
6 lot-release testing. At the same, FDA's goal is
7 not to develop tests that must be done by
8 developers of MSCs or any other products, but
9 instead to illustrate strategies that may be useful
10 to find CQAs that are predictive of effectiveness.

11 One of the key strategies we would use was
12 to develop functional quantitative bioassays for
13 MSCs based on the biological functions shown here,
14 the trilineage differentiation and
15 immunomodulation. So we developed ways to measure
16 the amount of these activities quantitatively. We
17 also developed a method for the immunomodulatory
18 activity as well as the trilineage differentiation.

19 These methods are sufficiently sensitive and
20 reproducible so that we can detect differences in
21 activity of MSCs from different batches and from
22 different lengths of time in tissue culture or

1 passaging. These are all specific outcomes based
2 on the way we manufactured the cells that we used
3 so are not necessarily true for all MSCs grown in
4 all conditions. But our techniques were similar to
5 those used by stakeholders who employ MSCs,
6 including the applicant.

7 This summarizes the method to determine how
8 many cells can undergo adipogenesis after
9 stimulation. In the microscope image on the left,
10 the blue color shows nuclei of the cells and the
11 green indicates the presence of lipid in the cells.
12 These were fluorescent dyes, so we could automate
13 cell counting and determine the percentage of cells
14 that differentiated.

15 On the right, the bar graph shows that there
16 are large differences in the fraction of cells that
17 turn into adipocytes from different MSC batches,
18 ranging from 0.5 to 14 percent. The purple,
19 orange, and green bars were measurements taken at
20 passages 3, 5, and 7. This data shows that the
21 ability of MSCs to differentiate into adipocytes is
22 different in MSCs from different donors and that

1 this ability decreases with cell passage.

2 The results suggest that MSC batches have
3 different numbers of adipocyte precursors. With
4 this degree of difference between batches, one
5 might be able to identify the subpopulation of
6 cells that respond and to find a corresponding
7 molecular signature that correlates with this
8 biological function.

9 This slide describes a quantitative assay we
10 develop for immunosuppressive activity of MSCs.
11 The assay is based on the co-culture of MSCs with
12 activated T cells. A constant number of activated
13 T cells are co-cultured with increasing doses of
14 MSCs, then 16 different markers associated with
15 T cell activation were measured by flow cytometry
16 and principal component analysis is conducted on
17 this multi-parameter data set.

18 In principal component analysis, one takes
19 high dimensional data and finds a mathematical
20 description of the variability along the different
21 dimensional axes. If you envision all of the data
22 as a cloud where individual cells fall at different

1 points within this multidimensional data, principal
2 component 1 describes the line between the farthest
3 separated data points.

4 So in the graph on the left, we plotted
5 principal component 1 versus the number of MSCs
6 added to the activated T cells, and you can see
7 that the activity of T cells decreases as you
8 increase the number of MSCs. So we calculated the
9 area under this curve from this plot, and we use
10 this as a single number to represent
11 immunosuppression of MSCs.

12 On the left, you see analysis for one MSC
13 line that was done at an early passage, and the
14 area under the curve, or AUC, is shown in blue, and
15 just to its right, you see the analysis done on
16 MSCs from a late passage, and the area under the
17 curve is shown in red. So in this type of
18 analysis, less area under the curve indicates more
19 immunosuppression. This tells us that the
20 immunosuppressive activity of this MSC line
21 decreased with passage.

22 On the right, you see a bar graph that shows

1 the area under the curve value for 6 different MSC
2 lines measured as early and late passage. The
3 take-home message is that MSC immunosuppressive
4 activity can be quantified and that there are
5 differences between MSCs from different donors, and
6 the immunosuppressive activity decreases as the
7 number of passages increases.

8 We also found that stimulation with
9 interferon gamma could induce greater amounts of
10 immunosuppressive activity and change the
11 morphology of MSCs, so we followed the morphology
12 changes of using up to 96 parameters of cell and
13 nuclear morphology, and then used a machine
14 learning analysis of this high dimensional data to
15 identify subpopulations of cells based on their
16 morphological footprint.

17 The figure on the upper left shows this
18 multidimensional, the data reduced to two
19 dimensions. We could count the number of cells
20 that fall into the different regions of this
21 display as shown in the middle figure where we were
22 able to gate on cells in these regions. The images

1 around this show the shapes of cells in three of
2 these morphological subpopulations, including those
3 with the most immunosuppressive cells on the left
4 and images of cells that did not correlate with
5 immunosuppressive activity shown on the right.

6 In the end, we could correlate the amount of
7 immunosuppressive activity with the number of cells
8 in specific morphological subpopulations present in
9 different MSC batches.

10 I want to emphasize that we do not expect
11 stakeholders or an applicant to use these specific
12 assays I've described, but I do want to emphasize
13 that there can be approaches and strategies that
14 might be useful in facing the challenge of
15 identifying cell therapy critical quality
16 attributes that correlate with in vitro bioassay
17 outcomes.

18 This slide shows that the significant
19 functional heterogeneity I've just shown you that
20 was associated with different donors and different
21 passages is not revealed using community consensus
22 cell surface markers for MSC identity. Our

1 analysis included CD105 and CD166, the two markers
2 used for identity by the applicant.

3 Shown in these 6 panels that show analysis
4 for six different MSC markers, all of our cell
5 lines at all passages express all of these markers
6 at high levels, and this did not correlate with or
7 reveal any of the functional differences I've shown
8 you in the last several slides or other
9 quantitative assays I did not have time to talk
10 about.

11 To summarize, the consensus MSC surface
12 markers we used do not identify the significant
13 heterogeneity and biological activity of different
14 MSCs from different donors or cells that were
15 cultured for different numbers of passages.

16 This slide summarizes the challenging issue
17 for today's discussion. Our research and the
18 research of others touched on in Dr. Temple's talk
19 suggest that the common MSC identity markers and
20 those of the applicant do not capture the
21 substantial functional heterogeneity that has been
22 observed in MSC batches. This raises the concern

1 that potency tests for remestemcel-L may not detect
2 functionally important differences between batches,
3 or what the applicant calls drug product lots,
4 since they do not correlate with clinical
5 effectiveness.

6 Our purpose is to facilitate the committee
7 discussion of the applicant's proposed potency
8 assays and to provide some potential alternative
9 approaches to assess quality attributes that may
10 correlate with clinical effectiveness.

11 We will talk about these questions later.
12 I'll just read these quickly. These are the points
13 for discussion by the advisory committee later.
14 The first is, the product quality attributes
15 measured for remestemcel-L are intended to ensure
16 that key qualities of the drug product are
17 maintained consistently from lot to lot. Please
18 discuss the adequacy of the potency assay
19 established by the applicant for remestemcel-L.

20 The second is, in addition to discussing
21 potency, please propose and discuss other possible
22 product quality attributes or characteristics that

1 could be controlled to better assure consistent
2 quality of remestemcel-L with regard to safety or
3 effectiveness of the product.

4 With that, I'll conclude my presentation and
5 turn back over to the chair. Thank you.

6 **Clarifying Questions to Presenters**

7 DR. HOFFMAN: Thank you very much.

8 We will now take clarifying questions for
9 the presenters for about 15 minutes, and then we'll
10 probably resume afterwards. Please use your
11 raised-hand icons to indicate that you have a
12 question.

13 Please remember to put your hand down after
14 you have asked your question, and please remember
15 to state your name for the record before you speak.
16 Please direct your question to a specific presenter
17 if you can. It would be helpful to acknowledge the
18 end of your question with a thank you and end of
19 any follow-up question with "That is all for my
20 questions," so we can move on to the next panel
21 member.

22 Dr. Morrison?

1 DR. MORRISON: Yes. Hi. A couple of
2 questions for Mesoblast first. On slides 27 and
3 28, you suggested that the improved clinical
4 results across all clinical trials correlated with
5 increased TNF receptor expression and IL-2 receptor
6 inhibition, but you had also altered the trial
7 design based on experience to focus on patients
8 more likely to respond in the later trial.

9 So given those changes in the trials were
10 intended to increase response rates, do you think
11 that the correlation with increased TNF receptor
12 expression can really be interpreted to demonstrate
13 improved product quality based on that attribute,
14 rather than just a change in patient selection?

15 MS. STORTON: Thank you. It's Geraldine
16 Storton here.

17 Dr. Itescu, I'll ask you to address this
18 question.

19 DR. ITESCU: Sure. Thank you very much.

20 We've done various analyses, but first of
21 all, looking right across the three trials, we've
22 done a regression analysis that took into account

1 severity of the patients, age of the patients,
2 other attributes, and certainly TNFR1 levels and
3 IL-2 receptor expression level.

4 If we could go please to MA-23 slide? In a
5 multivariable regression analysis looking at day
6 180 survival, the only variable that was
7 significantly associated was in fact TNFR1, and
8 neither disease severity nor age of the patients
9 were significant when looking at the analysis by
10 single product lot. That type of an analysis says
11 that irrespective of selecting the type of patient,
12 TNFR1 is the driver of survival outcomes.

13 Now, in addition to that, we also showed
14 data within one single trial, 275, where all the
15 children were of the same severity. They were all
16 patients who had received multiple biologic agents
17 and had failed where remestemcel was used to
18 salvage therapy.

19 Here we see that when we looked at a single
20 product lot, as we showed in the earlier slide,
21 patients who received the optimized process with a
22 significantly higher level of TNFR1, approximately

1 50 percent higher, had a substantial improvement in
2 survival through day 100 in those same children,
3 same severity of disease, and the only difference
4 being the receipt of the older product.

5 DR. MORRISON: When you did these analyses
6 that showed the strongest correlation with TNF
7 receptor 1, were you looking genome-wide with some
8 dense data set like RNA seq or something like that
9 or were you looking at a modest number of
10 candidates based on your experience with the
11 biology?

12 DR. ITESCU: The analyses were limited to
13 the existing quality attributes that have been in
14 place for about 10 years, which allows us to have a
15 wide population-based relationship correlation.
16 But there's no doubt that moving forward, it would
17 be good to introduce additional genome-wide
18 analyses as well, as we continue to optimize
19 manufacturing.

20 DR. MORRISON: If I could just ask a couple
21 of final quick questions.

22 I assume that the MSCs in each lot that you

1 manufacture are not clonally derived.

2 DR. ITESCU: That's correct.

3 DR. MORRISON: And I don't think you showed
4 us any data on how much variability you observed
5 between donors, between lots of the same donor, or
6 between passages. Can you comment on that?

7 MS. STORTON: Dr. Itescu, would you like me
8 to take that question?

9 DR. ITESCU: Certainly.

10 MS. STORTON: We obviously have strict
11 qualification of our donors, and what we do see in
12 regard to donor variability is attributes that have
13 more of an impact on yield that are impacted by
14 that donor-to-donor variability rather than
15 quality.

16 In addition to that, we have quality
17 attributes fit and tested at the donor cell bank
18 stage, which gives us an early indication of
19 whether there are substantial differences between
20 donors, and we have an acceptance criteria at that
21 point so that we can determine appropriate donor
22 cell banks that should move forward to

1 manufacturing of the drug product.

2 DR. MORRISON: One last question. You
3 describe these cells as being hypoimmunogenic. In
4 the briefing materials that you supplied in
5 advance, the reference that was cited in support of
6 that only did in vitro assays. We know these cells
7 are cleared once they're transplanted in vivo. So
8 what's the evidence that they're actually
9 hypoimmunogenic in vivo?

10 MS. STORTON: Dr. Itescu, would you like to
11 take that question?

12 DR. ITESCU: Sure. Thank you.

13 We've performed extensive in vivo studies
14 across different trials from indications where
15 we've followed anti-HLA antibodies, for example.
16 We see in some cases a low level of anti-class 1
17 antibodies that are transient, not associated with
18 any kind of clinical sequelae, and generally within
19 12 months are no longer observed, of the order of
20 less than 10 percent of patients develop such
21 antibodies. We do see anti-class 2 antibodies.
22 And more importantly, in those situations where

1 we've measured T-cell responses against donor
2 cells, we do not see donor T-cell responses.

3 So given that these cells express class 1
4 HLA but not class 2, this suggests that the class 1
5 HLA antigens can induce, in some patients,
6 alloantibody response and does not appear to have
7 any clinical sequelae and do not appear to be
8 T-cell or antibody responses against class 2
9 antigens.

10 DR. MORRISON: Thank you.

11 DR. HOFFMAN: Dr. Robey?

12 DR. ROBEY: Yes. This is Pam Robey. I have
13 two questions.

14 When you measured the TNF receptor 1, you're
15 measuring it in the whole population. You add this
16 as the whole population, but it could be that there
17 are cells that are very actively producing that
18 receptor and other cells that are not.

19 Do you have a sense of how homogeneous TNFR1
20 expression is across your donor population?

21 MS. STORTON: Dr. Itescu, would you like to
22 comment on that question?

1 DR. ITESCU: Look, that is an excellent
2 question. It's a very complex question. I think
3 you're suggesting that within a heterogeneous
4 cultured population there may be different levels
5 of expression from cell to cell to cell. That's
6 certainly possible. We're not analyzing single
7 cells here; we're analyzing population-based
8 analyses.

9 It's certainly possible there are
10 differences, but those differences are unlikely to
11 be very large given that the population of cells
12 that we have, they're all treated the same way and
13 cultured the same way. At the end of the day, this
14 is an overall cultured process targeting the entire
15 population that's harvested.

16 MS. STORTON: And I will add to that.
17 Geraldine Storton here. I'll just add that we have
18 a specific dose per vial. So even though there may
19 be differences between cells, what we're looking at
20 is an amount per dose for the patient that has been
21 dosed based on their body weight.

22 DR. ROBEY: Right. But the point is that

1 you could have one cell in a hundred making tons
2 and the others not making very much, and that could
3 impact upon the effectiveness. It's just some food
4 for thought.

5 Another question that I have about your
6 presentation is that even though you've mentioned
7 colony-forming efficiency, you don't really have
8 that as one of your critical quality attributes,
9 and it would seem to me that that would be a very
10 important measure of the viability and
11 healthfulness of the cell cultures.

12 Do you actually do colony-forming efficiency
13 on a routine basis?

14 MS. STORTON: I will start and see if
15 Dr. Itescu wants to add anything. It is a measure
16 that we use as part of our extended
17 characterization panel at both the donor cell bank
18 stage.

19 Dr. Itescu, would you like to add?

20 DR. ITESCU: Yes. We certainly do routinely
21 measure see CFU-Fs, absolutely, and it's part of
22 the criteria we use to select the appropriate

1 donors that go through the donor cell bank stage.
2 And then of course we verify the CFU-F levels at
3 the donor cell bank stage, as well as the final lot
4 release; a very important attribute, no doubt. We
5 agree.

6 DR. ROBEY: Okay. Thank you very much. I
7 have no further questions.

8 DR. HOFFMAN: Okay. Dr. Cheng?

9 DR. CHENG: Good morning. Jon Cheng,
10 industry rep. I appreciate the presentation. I
11 have two clarifying questions. The first is, how
12 many distinct drug product lots were used in
13 Protocol 01, GVHD001, and how many donors does that
14 represent? I have a similar question for 280, your
15 randomized study. How many drug product lots were
16 used and how many donors?

17 Then my second question is Dr. Bauer stated
18 that the TNFR1 levels did not correlate with
19 response or clinical outcome in GVHD 1, and I was
20 interested in the sponsor's perspective as to why
21 that may be.

22 MS. STORTON: I will address the first

1 question. The number of lots in GVHD001, I don't
2 have the specific number, but I can bring that back
3 after the break. But those lots were made with
4 three distinct donors. That was for the pivotal
5 study, GVHD001. The second question in regard to
6 the correlation of TNFR1, I will turn to Dr. Itescu
7 to address that question.

8 DR. ITESCU: Sure. I think this is a very,
9 very important question. When one looks and tries
10 to provide correlations between biomarkers and
11 clinical outcomes, it's essential that you have
12 sufficient patients, large numbers of
13 population-based patients, to be able to make those
14 correlations.

15 We have a very, very large database. We're
16 fortunate, in fact, that we've treated more than
17 400 patients with remestemcel across multiple
18 trials over 10 years. We can only demonstrate and
19 we can only identify correlations when you have
20 enough patients. By the fact that changes in
21 manufacturing and optimization has occurred, we're
22 able to look across those timelines and learn.

1 In fact, when you do that, you see that the
2 product that was used in some of the failed trials
3 10 years ago, trial 280, 265, et cetera, you used a
4 product that had about a 50 percent lower level of
5 TNFR1.

6 When you have that degree of variability,
7 you can actually see correlations in patients. The
8 optimized product, which has now got a 50 percent
9 higher level of TNFR1, was used entirely in the
10 pivotal trial phase 3 and in a good portion of
11 patients in the Expanded Access Protocol 275.

12 When you have such a high, high level of
13 consistency, as we saw in 001, the phase 3 trial,
14 and I showed you that between lot variability it
15 was very low, when you have that degree of
16 consistency and reproducibility in a level that is
17 50 percent higher than a previously used product,
18 it is of course very difficult to show within only
19 50 patients a relationship between minor
20 differences in TNFR1 and survival outcomes. Those
21 are very, very important clinical outcomes and
22 requires hundreds, if not thousands, of patients to

1 relate.

2 The fact that we've been able to demonstrate
3 that in 400 patients is precisely because we've
4 improved the potency by 50 percent, and those
5 variabilities between old product and new product
6 allow us to make those conclusions. But within
7 50 patients only, or 54 patients only, in the
8 pivotal phase 3 trial where the product has been
9 significantly improved and the variability is very
10 small, it is not possible to show a relationship
11 with survival. Nonetheless, we have very
12 significant outcomes in terms of biomarkers and
13 immunomodulation that appears to be very important
14 and related to the outcomes in these patients.

15 DR. CHENG: Thank you.

16 DR. HOFFMAN: This is Dr. Hoffman. I have a
17 question. I apologize if this was covered at the
18 very beginning for the sponsor. How many donors go
19 into producing one lot, or does one lot represent
20 multiple donors, or does one donor's cells, which
21 are then expanded, cover multiple lots? I'm just
22 not sure. Are there thousands of donors or there

1 are a few? It's a very basic question, I realize.

2 MS. STORTON: Geraldine Storton here. I'll
3 address that question. One bone marrow aspirate
4 generates a number of donor cell bank vials. So
5 one donor cell bank, of which there are numerous
6 vials, and one vial is used for every manufacturing
7 lot, and then you obviously result in a certain
8 number from that manufacturing lot. So one bone
9 marrow aspirate can provide enough finished product
10 to treat over 400 patients.

11 DR. HOFFMAN: So within a given lot, a given
12 lot only represents one donor.

13 MS. STORTON: Yes, always you can trace back
14 to one donor from a given lot.

15 DR. HOFFMAN: Okay. Thank you.

16 Dr. Singec?1

17 DR. SINGEC: Yes. Hi. This is Ilyas Singec
18 from NIH. I have a question regarding the use of
19 animal serum, such as fetal bovine serum. Also,
20 based on the provided materials, it seems that
21 animal serum is required to be used.

22 Could you please clarify at what stage

1 throughout manufacturing or I saw that it's being
2 used also in some potency assays?

3 MS. STORTON: Yes. I will address that
4 question for you. Fetal bovine serum is used in
5 the culture media both for the expansion of the
6 cells for the donor cell bank and the expansion
7 passages for the drug product. So it is a
8 component of our growth medium.

9 Does that answer your question? 1

10 DR. SINGEC: Yes, it does. How do you
11 control lot-to-lot variability across animal serum
12 batches?

13 MS. STORTON: Sure. We actually have quite
14 strict acceptance criteria in relation to the fetal
15 bovine serum, and it needs to meet, obviously,
16 certain tests. We ensure that it's safe and it's
17 been irradiated, et cetera. We look at things like
18 the proliferative capacity of the fetal bovine
19 serum as well to try and ensure as best consistency
20 as possible each time.

21 DR. SINGEC: Okay. Thank you.

22 DR. HOFFMAN: How about if we take the last

1 question before the break. Dr. Garcia?

2 DR. GARCIA: Thank you, Dr. Hoffman.

3 Jorge Garcia. I have a clarifying question
4 for Dr. Bauer from the FDA. I do understand the
5 heterogeneity and the concerns perhaps raised by
6 the group as to, again, the difference in
7 manufacturing each lot or product at the time and
8 the concerns that there may be variation between
9 the products used in clinical trials and protocols
10 against the commercial product.

11 My question relates simply to the release
12 testing. The applicant used phenotype, the CD166
13 and the 105. For potency they used a TNF receptor
14 1 expression and for activity they used the
15 inhibition of IL-2 receptor. Are these acceptable
16 for the FDA as release testing or is the FDA, the
17 agency, asking for additional testing to be done
18 prior to release of the product?

19 DR. BAUER: Yes. We don't describe or
20 prescribe what tests the manufacturers have to rely
21 on for these assays, so we don't really say we
22 can't use these or we need to use something in

1 addition. We're asking the question in a different
2 way. Are those assays the way the applicant has
3 used them sufficient to say each batch is going to
4 be the same?

5 Our concern is as we stated the issue. We
6 don't see a correlation of individual patient
7 outcomes with individual lots. Are they doing this
8 assay or are they using a quality attribute that
9 will associate or predict that quality attribute
10 with a clinical outcome? We're not saying that
11 those aren't useful or informative assays as a
12 general class of assay, but in the particular case
13 here.

14 Does that answer your question?

15 DR. GARCIA: Yes. Thank you.

16 Perhaps if I can expand my question for the
17 applicant. It wasn't really clear to me throughout
18 the morning that I truly understand -- I understand
19 GVHD is a complex and multifactorial, and perhaps
20 multifaceted, biological issue, but does the
21 company really know what is the true MoA of this
22 agent? MSCs

1 MS. STORTON: I'm going to ask Dr. Itescu to
2 respond to that question in regards to mechanism of
3 action.

4 DR. ITESCU: Certainly.

5 So as we tried to show you, remestemcel has
6 surface receptors that are able to sense inciting
7 inflammatory cytokines. The TNF receptor is a very
8 important one. Interferon gamma receptor is
9 another one. You put the cells into an
10 inflammatory micro environment where you have high
11 levels of TNF alpha, and through these receptors,
12 the cell senses the inflammation and is activated.
13 The activation pathway goes through TNFR1, through
14 NF-kappaB, which is a master regulator of multiple
15 factors, and it's well established that this cell
16 then secretes the anti-inflammatory mediators that
17 are downstream, resulting from NF-kappaB
18 activation.

19 Those factors, and they include CCL2 and
20 M-CSF, act on the proinflammatory macrophage, which
21 has made TNF in the first place and is the M1
22 macrophage, and switches it off, and turns it into

1 an M2 macrophage, which is an immunomodulatory
2 long-lived cell that produces interleukin 10.
3 Interleukin 10 is a very important cytokine that
4 immunomodulates an inflammatory micro environment
5 as occurs in GVHD.

6 In addition, through parallel pathways,
7 including interferon gamma, the remestemcel cell
8 also secretes factors that switch off T-cell
9 activation. So a downstream measurement of
10 multiple factors, some through regulators through
11 TNFR1 and some through additional pathways, is the
12 measurement of a matrix that measures the ability
13 of a cell to inhibit T-cell activation. T cell
14 activation is important also in disease
15 pathogenesis.

16 So we're dealing with a living cell that is
17 able to sense inflammation, respond to
18 inflammation, and through multiple secretory
19 factors switch off the inflammatory process that is
20 at the core of damaging tissue in GVHD, and that
21 causes death. So yes, we do understand the
22 mechanism of action very well, and it's a question

1 of how best to measure those assays in vitro to
2 ensure that we've got a safe and effective and
3 reproducible product for use in this very bad
4 disease.

5 DR. GARCIA: Thank you. No further
6 questions.

7 DR. HOFFMAN: Okay. Thank you.

8 We will now take a 10-minute break. Panel
9 members, please remember that there --

10 MS. STORTON: Sorry. Can I just follow up
11 on the question from Dr. Cheng? Because I have the
12 details here.

13 In the 001 study, there were 40 batches of
14 product used, manufactured from three separate
15 donors, and in Protocol 280, there were 227 batches
16 made from 9 separate donors. Thank you.

17 DR. HOFFMAN: Okay. Thank you.

18 DR. CHENG: Thank you.

19 DR. HOFFMAN: We'll now take a 10-minute
20 break. Panel members, please remember that there
21 should be no chatting or discussion of the meeting
22 topic with anyone during the break. We'll resume

1 at 10:30 a.m. with the open public hearing. Thank
2 you.

3 (Whereupon, at 10:31 a.m., a recess was
4 taken.)

5 **Open Public Hearing**

6 DR. HOFFMAN: Both the Food and Drug
7 Administration and the public believe in a
8 transparent process for information gathering and
9 decision making. To ensure such transparency at
10 the open public hearing session of the advisory
11 committee meeting, FDA believes that it is
12 important to understand the context of an
13 individual's presentation.

14 For this reason, FDA encourages you, the
15 open public hearing speaker, at the beginning of
16 your written or oral statement to advise the
17 committee of any financial relationship that you
18 may have with the sponsor, its product, and if
19 known, its direct competitors. For example, this
20 financial information may include the sponsor's
21 payment of your travel, lodging, or other expenses
22 in connection with your participation in this

1 meeting.

2 Likewise, FDA encourages you at the
3 beginning of your statement to advise the committee
4 if you do not have any such financial
5 relationships. If you choose not to address this
6 issue of financial relationships at the beginning
7 of your statement, it will not preclude you from
8 speaking.

9 The FDA and this committee place great
10 importance in the open public hearing process. The
11 insights and comments provided can help the agency
12 and this committee in their consideration of the
13 issues before them.

14 That said, in many instances and for many
15 topics, there will be a variety of opinions. One
16 of our goals today is for this open public hearing
17 to be conducted in a fair and open way, where every
18 participant is listened to carefully and treated
19 with dignity, courtesy, and respect. Therefore,
20 please speak only when recognized by the
21 chairperson. Thank you for your cooperation.

22 Speaker number 1, your audio is connected

1 now. Will speaker number 1 begin and introduce
2 yourself? Please state your name and any
3 organization you are representing for the record.

4 DR. CAPLAN: This is Arnold Caplan. I'm a
5 professor at Case Western Reserve University, and I
6 have no financial relationship with Mesoblast, and
7 I'd like to thank the FDA for this opportunity to
8 make a comment.

9 In the late 1980s, I named a special class
10 of cells isolated into cell culture from bone
11 marrow. I called them mesenchymal stem cells,
12 MSCs. Importantly, we could show that these cells
13 in culture could be made to form bone or cartilage
14 or fat, as Steve Bauer actually has already
15 commented. These cells, therefore in culture,
16 appear to be multipotent.

17 In the context of today's proceedings, in
18 the mid-1990s, we were the first to infuse
19 autologous cell culture expanded MSCs into cancer
20 patients who were undergoing bone marrow
21 transplantation procedures. Because of these cell
22 culture observations of multipotency, some people

1 have incorrectly referred to MSCs as stem cells,
2 and I have begged people to stop using the stem
3 cell nomenclature because we believe that this is a
4 capacity that these cells do not exhibit naturally
5 in the body, nor when they're introduced after cell
6 culture expansion.

7 We now know that all MSCs come from in situ
8 to habitats, which are around and just outside
9 blood vessels, and therefore are referred to as
10 perivascular cells. When such perivascular cells
11 are detached from injured or inflamed or broken
12 blood vessels, they then form activated MSCs.

13 These MSCs function, first, to sense their
14 unique and distinctive surrounding micro
15 environment. Second, they respond to these micro
16 environmental signals by secreting a spectrum of
17 emergency molecules that are immunomodulatory
18 intropic. These molecules are naturally secreted
19 to tune down the naturally over-aggressive immune
20 system so it does not interrogate or destroy the
21 injured tissue. And in the case of GVHD, it can
22 modify the over-aggressive immune response current

1 directed against the hosts.

2 Third, the secretory MSCs, which I've
3 renamed in 2010, medicinal signaling cells, MSCs,
4 can arise and be isolated from any disrupted
5 vascularized tissue in the body. Their natural
6 function is to initiate site-specific cell
7 progeneration, meaning that they activate the
8 innate regenerative capabilities of the injured
9 tissue in which they're embedded.

10 Last, by adding exogenously culture-expanded
11 MSCs to diseased or injured patients either in the
12 autologous or allogeneic study, we can medicinally
13 supplement the normal and inadequate titers of host
14 MSCs, indeed, endogenously added MSCs, home to
15 broken or inflamed blood vessels where they set up
16 shop and respond to that specific local
17 environment.

18 This response is the basis for all MSC
19 cell-based therapy. I believe that these
20 exogenously added cells function as they normally
21 do by providing medicinal molecules and signals at
22 sites of injury.

1 The website clinicaltrials.gov has over 1100
2 different clinical trials using MSCs. These MSCs,
3 when added back to patients, set up a local curtain
4 of molecules that are secreted by the MSCs, again,
5 either autologously or allogeneically, and this
6 curtain provides a barrier so that the host immune
7 system doesn't immediately see the donor MSCs.
8 Thus, MSCs are immunoevasive initially, and they're
9 not immunoprivileged.

10 I urge you, the committee, to allow the use
11 of MSCs for therapeutic purposes, and I urge you to
12 judge them as an aspect of cell-based therapy, not
13 as a single purified drug. These cells are alive.
14 They do what they do when they're isolated and
15 expanded from marrow or other tissues and are
16 implanted back into diseased individuals.

17 These perivascular medicinal cells are
18 unique therapeutic entities because they adjust
19 their responses to the micro environment in which
20 they have land. Probably on the order of 50,000
21 people have been infused with MSCs, and they have
22 been documented in various clinical trials to be

1 safe. I urge you to positively consider the
2 evidence-based information provided by Mesoblast
3 this afternoon of MSCs' medicinal capabilities for
4 pediatric patients with graft-versus-host disease.
5 If a BLA is granted, it is a watershed moment for
6 MSC technology and for the whole concept of
7 cell-based therapy. I look forward to your
8 deliberations. Thank you.

9 DR. HOFFMAN: Thank you.

10 Speaker number 2, your audio is connected
11 now. Will speaker number 2 begin and introduce
12 yourself? Please state your name and any
13 organization you're representing for the record.

14 MR. KOOSHESH: Hello. My name is Kameron
15 Kooshesh. I do not have any financial relationship
16 with Mesoblast or any of its competitors. Thank you
17 for allowing me to speak today. It means the world
18 to me.

19 I am a survivor of acute lymphoblastic
20 leukemia and graft-versus-host disease, and I
21 received remestemcel for the treatment of
22 steroid-refractory graft-versus-host. At age 9, I

1 was diagnosed with ALL and then underwent two and a
2 half years of chemotherapy. For most of this time,
3 I wasn't able to go to school and to see my
4 friends, and to live a normal life. However, on my
5 long awaited last day of chemotherapy and final
6 evaluation with the bone marrow aspiration, I was
7 told that I had relapsed and that I would have to
8 start all over again.

9 Statistically, the survivorship odds are
10 considerably worse after relapse. My best chance,
11 and maybe only chance, for a cure was a bone marrow
12 transplantation. I was told that I was very
13 fortunate to have a perfect 10 out of 10 bone
14 marrow transplant match. By that point, I had been
15 in and out of hospitals for so long, it was
16 starting to feel as if I would always have to live
17 with cancer.

18 My bone marrow transplant went well and I
19 was able to leave the hospital after a 30-day stay.
20 Finally, after so long, I felt like I was on the
21 road to recovery. My doctors had told me that
22 graft-versus-host disease could be a serious

1 complication, and the road to recovery may yet
2 still be lengthy, but I thought, what could
3 possibly be worse than what I just went through?
4 That was graft-versus-host.

5 Graft-versus-host disease started with what
6 I thought was one of the worst sunburns of my life.
7 I was awake all night itching, and what followed
8 was unbearable abdominal pain and diarrhea. I was
9 spending a lot of time in the bathroom with
10 uncontrollable pain. I was in so much pain that I
11 could not walk around our neighborhood block. It
12 caused me to be in and out of the hospital
13 constantly, as I was not well controlled on
14 steroids.

15 This was the gastrointestinal graft-versus-
16 host disease that I had heard so much about. Days
17 turned into weeks, weeks became months, and I still
18 teetered on the edge of an upset every day. I ate
19 a controlled diet approved with my doctors to
20 ensure that there was nothing that could upset my
21 graft-versus-host disease. Worst of all for me,
22 this meant no ice cream.

1 This is when I was told that graft-versus-
2 host disease was starting to damage my liver in
3 spite of the steroids that I was taking, and that
4 meant that the progression of my graft-versus-host
5 disease was starting to take a very serious turn.
6 I'd heard the whispers about a few of my friends
7 that had received bone marrow transplants and also
8 were developing liver graft-versus-host, and I knew
9 that they did not make it. After all I'd been
10 through, I thought to myself was it really possible
11 that it would come to this?

12 My doctor said that there was a possible
13 solution, a drug called remestemcel. Fortunately,
14 I was able to receive a course of the drug for
15 compassionate use, and within a matter of weeks, my
16 rashes receded, my abdominal pain abated, and my
17 liver function returned to normal. After a while,
18 I was able to go kayaking with my dad and hiking
19 with my mom, and I was even able to have ice cream.

20 To this day, I have not suffered further
21 complications of graft-versus-host disease or any
22 side effects of remestemcel. Remestemcel provided

1 me the opportunity to be a kid again and a second
2 chance at life that I would likely not have had
3 otherwise. Looking back years later from the other
4 side, I believe that my experience with remestemcel
5 and the inflection points that it created in my
6 life encouraged me to pursue medicine as a career.

7 As a current Harvard medical student, I have
8 been inspired by the difference remestemcel made in
9 my life to study cellular therapies as the new
10 revolution in personalized medicine. It continues
11 to give me hope. Thank you, again, to the
12 committee for letting me speak today. This means
13 the world to me.

14 DR. HOFFMAN: Thank you.

15 Speaker number 3, your audio is connected
16 now. Will speaker number 3 begin and introduce
17 yourself? Please state your name and any
18 organization you're representing for the record.

19 DR. GALIPEAU: This is Jacques Galipeau.
20 I'm going to ask if you could just move my slide
21 forward because I don't have any control -- sorry.
22 I take that back. I'm a professor of medicine at

1 University of Wisconsin-Madison, where I serve as
2 the associate dean for therapeutics development at
3 the School of Medicine in Public Health, and I'm
4 also the director of the Program for Advanced
5 Therapy at the school. I do not have any conflict
6 of interest, professional or financial, with
7 Mesoblast or any of its competitors, and the views
8 here expressed are all my own.

9 I'm internationally a recognized expert in
10 the MSC space having sponsored three phase 1
11 clinical trials, as well as published a number of
12 papers. I have recently published an invited
13 editorial commenting on the clinical trials
14 conducted by Mesoblast that are being discussed
15 today as noted on this slide.

16 The approach we use to think about
17 functionality and potency of MSCs is a comparative
18 biology approach. Secreted factors from MSCs,
19 captured in the box with the red factors here,
20 identify their competencies that are shared between
21 mouse and human MSCs in vitro. These have been
22 shown to block T cells and monocytes in vitro, but

1 importantly these selected factors shown here have
2 been further shown in mice to be central in vivo by
3 using gene-targeted knockout donor MSCs.

4 I'm highlighting the monocytes and
5 M2 macrophages because of their central importance
6 in the host response, because pharmacological
7 depletion of endogenous macrophages, clodronate
8 [indiscernible], abolishes MSC functionality
9 in vivo. Though these factors are necessary, none
10 of them are sufficient. For example, IL-6 knockout
11 MSCs, which retain CCL2 competency, also lose
12 functionality, which speak to the aggregate or
13 matrix function of MSCs.

14 I'd like to draw your eye to the right. Not
15 only are host macrophages important, but also host
16 IL-10 competency, in particular, as derived from
17 host macrophages are important. Subject matter
18 that's of importance here is the in vivo fate of
19 IV-administered MSCs.

20 Labeling of human MSCs injected IV in
21 mice -- you'll see the blue boxes on the
22 left -- will aggregate in the lung and will

1 disappear promptly within 24 to 72 hours. Dead
2 MSCs also aggregate the lung but will redistribute
3 to liver because they get preferentially
4 phagocytosed by MSCs, which leads to their IL-10
5 polarization.

6 These pieces of information inform two
7 functionalities. On your left are the cell
8 function, fitness-dependent functionality as you've
9 heard of today, but on the right is also a cell,
10 autonomous functionality, where MSCs can get
11 phagocytosed, which triggers an efferocytotic
12 response, where macrophages become IL-10 competent
13 in vivo.

14 The single most important quality attribute
15 one can think of for MSCs would be viability. Dead
16 MSCs do not antagonize live MSCs, but they're also
17 significantly less potent when they significantly
18 are void of potency. So MSC viability at infusion
19 also was found in clinical trials done by academic
20 centers to correlate with outcomes.

21 Mesoblast has done a series of pragmatic
22 studies in pediatric steroid-resistant graft versus

1 host, and they found imperatively that children,
2 especially with severe disease, respond better.
3 And I'd like to emphasize to this committee that
4 this reflects results erupting also by European
5 academic collaborative groups that had similar
6 outcomes in pediatric GVHD.

7 I'd like to point out that placebo
8 controlled is likely unfeasible. There was a large
9 study in Europe, the RETHRIM study, that had to be
10 stopped because they could not enroll patients to
11 the placebo arm due to subject-parent resistance.

12 I would conclude the main quality attributes
13 in the disease are viability, first and foremost,
14 and you would need at least one, and preferably
15 many, functional attributes that are informed by
16 comparative biology to determine a likely MoA in
17 human subjects. Post-derived predictive biomarkers
18 of response are something that need to be looked
19 at.

20 In conclusion, I'm bringing these closing
21 remarks which restate some of my points, but I
22 would like to state that, in my opinion, the

1 benefit-risk ratio of MSCs favors a clinical
2 utility for pediatrics steroid-resistant
3 graft-versus-host. Thank you very much for your
4 attention.

5 DR. HOFFMAN: Okay. Thank you.

6 The morning open public hearing portion of
7 this meeting has now concluded and we will no
8 longer take comments from the audience. The
9 committee will now turn its attention to address
10 the task at hand, the careful consideration of the
11 data before the committee, as well as the public
12 comments.

13 We'll now proceed with the questions to the
14 committee and panel discussions. I'd like to
15 remind public observers that while this meeting is
16 open for public observation, public attendees may
17 not participate except at the specific request of
18 the panel. I'll ask a member of the FDA to read
19 question number 1.

20 **Questions to the Committee and Discussion**

21 DR. BAUER: Steve Bauer here. This is
22 question number 1 for discussion. Product quality

1 attributes measured for remestemcel-L are intended
2 to ensure that key qualities of the drug product
3 are maintained consistently from lot to lot.

4 Please discuss the adequacy of the potency assay
5 established by the applicant for remestemcel-L.

6 Thank you.

7 DR. HOFFMAN: First, if there are no
8 questions or comments concerning the wording of the
9 question, we'll now open the question to
10 discussion.

11 (No response.)

12 DR. HOFFMAN: Please indicate your interest
13 in speaking by raising your hand.

14 (No response.)

15 DR. HOFFMAN: Do any of our guest members of
16 the committee have any comments about this
17 question? Dr. Robey?

18 DR. ROBEY: In going back to Dr. Bauer's
19 slide about the no clear relationship between TNFR1
20 levels and proposed mechanism of action, do you
21 have any thoughts about how you can address this
22 issue or if there are additional factors that could

1 be used to bolster the potential mechanism of
2 action in vivo?

3 DR. BAUER: Is that a question for me, Steve
4 Bauer?

5 DR. HOFFMAN: Yes, I believe so.

6 DR. ROBEY: No. I'm sorry. That's a
7 question for Mesoblast. In other words, I think
8 this is a major question that Dr. Bauer has raised
9 about the fact that there is no correlation. It's
10 an in vitro assay, and we're concerned about what's
11 happening in vivo. So what are your
12 forward-looking thoughts about how you will address
13 this issue or can you address this issue?

14 MS. STORTON: Yes. Geraldine Storton here.

15 Dr. Itescu, I'll get you to speak to that
16 question, and if possible, we would like to put up
17 some material to support the argument.

18 DR. ITESCU: Certainly. Thank you very
19 much.

20 First of all, if we could have slide MA-2
21 up, please? Thank you.

22 Shown on this slide is the relationship

1 between TNFR1 on the X-axis and production of
2 phosphorylated NF-kappaB on the left, M-CSF in
3 middle, and CCL2 on the right by remestemcel lots
4 that have had TNFR1 specifically knocked down with
5 siRNA. You can see that in the level of TNFR1 that
6 spans precisely the level expressed by clinical
7 grade product. We can see a direct correlation
8 between the production of each of these factors.

9 So all of them over time could be
10 established as additional assays of measurement of
11 potency, and what this demonstrates is the umbrella
12 nature of the TNFR1 sensor that results in
13 intracellular activation of the master regulator of
14 these factors NF-kappaB and the downstream
15 secretion of these factors. This is really
16 important.

17 If we could have slide MA-5, please? MA-5,
18 which we have shown previously, we are able to
19 demonstrate that there is a clear correlation
20 between a second potency assay, IL-2 receptor
21 inhibition in vitro and the reduction over a 28-day
22 period in activated CD4 T cells as defined by

1 expression of IL-2 receptor in HLA VF, a direct
2 significant correlation. That therefore allows us
3 to validate this as a potency assay.

4 If we could move on to slide MA-6, the next
5 slide shows the in vivo biomarkers that are
6 associated with outcomes. In the left two panels,
7 you see the proportion of activated CD4 T cells or
8 CD8 T cells significantly decline particularly in
9 the first 28 days during the treatment with
10 remestemcel, but they significantly decline over
11 the 180-day period of follow-up. This is in now
12 the pivotal phase 3 trial, demonstrating
13 bioactivity in vivo in patients relating to the
14 potency of the product.

15 In addition, on the two panels to the right,
16 we measure soluble ST2 and the composite of the
17 magic biomarkers for which incorporate ST2. These
18 are validated biomarkers that reflect the severity
19 of epithelial gut damage, and the higher the level,
20 the greater the severity of the GVHD disease and
21 the greater the likelihood of death.

22 What you see, again, in both of these panels

1 is a significant reduction within the first 28 days
2 of therapy, but continued reduction over 180 days
3 of follow-up in the cohort of patients in the
4 phase 3 trial treated with remestemcel, a
5 significant reduction in these biomarkers, which
6 reflects healing of the gut and ultimately
7 reduction in risk of mortality. Again, these are
8 the sort of biomarkers that we will be following in
9 the real world in patients who receive our therapy.

10 If we could go to slide MA-10, please? When
11 we looked at our phase 3 trial patients, we
12 evaluated outcomes based on severity score and,
13 again, the NBS biomarker score developed by the
14 MAGIC Consortium, the international consortium,
15 which has demonstrated that a score of greater than
16 0.29 is a validated biomarker for severity and
17 mortality in GVHD.

18 It turns out that 18 out of 29 of our
19 patients, approximately two-thirds, who were
20 measured for this were at a baseline level greater
21 than 0.29, which is associated with higher
22 mortality. When you compare three separate disease

1 cohorts on the left of steroid-refractory disease
2 patients, published in 2018, who have an MBS score
3 above 0.29, the day 28th overall responses of the
4 order of 18 to 32 percent. In contrast, in our
5 phase 3 trial, patients with this degree of
6 severity, MBS scored on 0.29, had a 61 percent day
7 28 response, demonstrating that we can predict
8 based on biomarker severity outcomes.

9 Next slide, please. That correlates with a
10 significant improvement in survival. These
11 same -- MA-11, please -- three cohorts, published
12 cohorts, demonstrate on the left that patients with
13 MBS biomarker score greater than 0.29, the
14 validated marker of severity, results in a survival
15 of between 20 to 40 percent at 6 months, extremely
16 poor survival.

17 In contrast, if you look at the Kaplan-Meier
18 on the right, in our phase 3 Trial 001, what you
19 see is that the patients with highest risk or
20 severity, which is two-thirds of our patients, have
21 a survival level that's approximately 60 percent at
22 6 months, and brings them in line with patients at

1 low risk for mortality, a very different outcome
2 than what we've expected with best available
3 standard of care.

4 These are the sort of outcomes that we will
5 be continuing to monitor in the real world,
6 correlating survival and responder rates with
7 severity scores at baseline and with various
8 biomarkers. Thank you.

9 DR. HOFFMAN: Dr. Robey, does that help with
10 your question?

11 DR. ROBEY: Yes.

12 DR. HOFFMAN: Okay.

13 DR. ROBEY: Thank you. Sorry. I'm having a
14 problem with my new mute here.

15 DR. HOFFMAN: Okay. No worries.

16 Can I get a sense from the members of our
17 committee -- I mean, this is not a voting question
18 here, of course -- whether we are comfortable with
19 the potency assay that the applicant has proposed,
20 the key part of this discussion question, without
21 reviewing everything again? I realize it's
22 complicated.

1 Dr. Morrison, do you want to comment?

2 DR. MORRISON: Yes. The points that
3 Dr. Bauer made are well taken. The Mesoblast
4 argument that the mechanism of action is likely
5 complex is also well taken. I think they're right
6 that this involves effects on multiple cell types
7 and multiple cell cytokines. It's really tough
8 because most of the data related to mechanism are
9 based on experiments performed in culture. It's
10 just a lot harder to do these experiments in vivo,
11 but we do have much less data on what these cells
12 are actually doing in vivo.

13 We've also had a couple of clinical trials
14 that didn't meet prespecified endpoints and reason
15 to believe that there's heterogeneity in the
16 product. So with such a complex mechanism of
17 action, I think there are real concerns about
18 knowing how to measure potency and to predict
19 activity.

20 DR. HOFFMAN: I think --

21 DR. MORRISON: If I --

22 DR. HOFFMAN: Please, go ahead.

1 DR. MORRISON: Sorry. May I just ask a
2 question of Dr. Itescu?

3 Do you know how long the cells actually
4 persist in vivo after they're injected, and what
5 impact does that have on how you think about
6 mechanism of action?

7 DR. ITESCU: Sure. Thank you very much.

8 What we do know is that the cells do not
9 engraft. They're allogenic, not autologous, so
10 they do not engraft. They do not persist long
11 term. From animal studies, we certainly know that
12 they last days to sometimes weeks, and then they're
13 certainly gone. So they're short-lived. They're
14 surely short-lived.

15 So therefore, how do we account for
16 long-term durable effects? Well, it's precisely by
17 their interaction with long-lived cells,
18 importantly macrophages and regulatory T cells.
19 What these cells do is they hand over and they
20 educate long-lived tissue resident macrophages to
21 become immunomodulatory and not to be
22 proinflammatory, and that's why we talk about the

1 M1 to M2 macrophage polarization, for example.

2 How they do that precisely remains an area
3 of further research, but they clearly are able to
4 do that, and they're able to hand over an
5 immunomodulatory effect through a variety of
6 factors, including CCL2 that we've demonstrated and
7 that has been shown by others, including TGF beta
8 that are important in regulatory T-cell
9 stimulation.

10 But ultimately, it's other cell types that
11 are critical in inducing an immunotolerant state
12 that takes over and are responsible for the
13 durability of the effects. I think that's the way
14 to think about this. Their mechanism by which they
15 do that is multifactorial, but their ability to do
16 that is triggered by their receptors, which sense
17 the proinflammatory state of the M1 macrophage that
18 drives a lot of this process. Their ability to
19 sense TNF alpha production by the M1-producing
20 macrophages is critical initiating the handover
21 process.

22 DR. MORRISON: Thank you.

1 DR. HOFFMAN: Dr. Garcia, do you have a
2 comment?

3 DR. GARCIA: Yes, Dr. Hoffman.

4 Jorge Garcia. Just perhaps for the
5 committee members to think and perhaps discuss
6 among ourselves, I think the data that we have may
7 be perfect, at least in my view and how I see it.
8 I'm not a hematologist and I don't do GVH, but I
9 think the bigger question that I have is, it sounds
10 like this is the best that we're going to be able
11 to get with the data that has been presented.

12 I understand the concerns from the FDA and I
13 understand the applicant position in context. I
14 think the question for us as a group and perhaps
15 for my committee colleagues would be do we feel
16 that there is an ideal clinical trial or at least a
17 basic or in vitro -- clearly, in vivo, as alluded
18 to before by Dr. Morrison, it's going to be very
19 challenging for us to prove that.

20 But the question is, is there such a thing
21 as an ideal study, whether it's in vivo, in vitro,
22 or what have you, that will actually overcome the

1 concerns that have been raised today? Because if
2 there is such a study, then I think that we can
3 discuss that, but if there's no viable study
4 because of the complexity of the product -- and
5 obviously with the heterogeneity, specifically with
6 the manufacturing controls, whether it's the
7 [indiscernible] or the process, then I think even
8 if another company or the applicant does another
9 trial or another study, I got a feeling that we're
10 going to be in the same position where we are
11 today.

12 So I'm just trying to actually see if you
13 have any other thoughts as to how we can overcome
14 the concerns that have been raised today.

15 DR. HOFFMAN: Well, I think that's actually,
16 I think, a good summary of where we are, or some of
17 us are, in our thinking. Maybe we should actually
18 put up the second discussion question because these
19 certainly are two related ones, if I could suggest
20 that, because that's basically the second question.

21 Would somebody from the FDA read that,
22 please?

1 DR. BAUER: Yes. Thanks, Dr. Hoffman.

2 Steve Bauer again. This is question 2 for
3 discussion. In addition to discussion of potency,
4 please propose and discuss other possible product
5 quality attributes or characteristics that could be
6 controlled to better assure consistent quality of
7 remestemcel-L with regard to safety or
8 effectiveness of the product. Thank you.

9 DR. HOFFMAN: If there's no discussion about
10 the wording of the question, I think Dr. Garcia
11 introduced this appropriately, and we welcome some
12 discussion about it among are committee members
13 here.

14 DR. GARCIA: Dr. Hoffman, Jorge again. If I
15 may comment?

16 DR. HOFFMAN: Yes, please, please.

17 DR. GARCIA: In the real world, we would
18 like to actually assure that if indeed this agent
19 gets approved, how we're going to control the
20 quality of the product, obviously, after it's
21 commercialized. I don't know if the company can
22 comment.

1 Is there any plan or any strategic plan for
2 the company to actually do -- in addition to what
3 has been described as the release test in the
4 phenotype, the potency and activity, is there any
5 other plan in place for the future that could
6 actually minimize or at least relieve that concern
7 as to the heterogeneity? Perhaps the product that
8 was tested is not consistent with the product that
9 you're going to release commercially.

10 MS. STORTON: Geraldine Storton here. I'll
11 make a comment, and then I'll pass over to Dr.
12 Itescu.

13 As we mentioned in our presentation, we have
14 set out acceptance criteria at this point of our
15 discussions with the FDA -- obviously, the BLA is
16 still under review -- in order to ensure that the
17 any commercial product will be reflective of the
18 same level of attributes as the product that was
19 used in the GVHD001 study. So that's the first
20 step that we've taken.

21 I'll ask Dr. Itescu to talk to any future
22 plans we may have for the product that may provide

1 opportunity to evaluate potentially some other
2 attributes that may be helpful.

3 DR. ITESCU: Sure. Thank you.

4 We of course continue to refine and optimize
5 and learn; that's without doubt. For example, we
6 will evaluate our donors in a way that we now
7 understand what a high-quality donor cell bank
8 needs to look like and the attributes that we would
9 be looking for from every donor product to be
10 consistent and to be reproducible.

11 Already we have a much higher level of
12 consistency and reproducibility across a number of
13 quality attributes. That is the reason that this
14 trial has been successful. The reason that this
15 trial is successful is precisely because we've
16 learned and optimized manufacturing.

17 The attributes that we've shown you today
18 look at the two ends of the spectrum, both of which
19 reflect matrix production of multiple factors of
20 the cells, at one end, the ability to ensure that
21 the cell is built with a machinery that is able to
22 sense the micro environment well. TNF receptor is

1 one; interferon gamma receptor.

2 There are other receptors, IL-17 receptors,
3 IL-1 receptors. They're all relevant to the
4 ability of the cell to sense the inflammatory micro
5 environment. We believe the TNFR1 is probably the
6 most important because TNF is implicated so
7 centrally in the diseases that we're targeting of
8 inflammation, and GVHD is a major disease that is
9 driven by TNF alpha. But ensuring the health of
10 the final product is a major focus for us.

11 You've heard how important viability is. We
12 ensure that this cell is very viable at the end, a
13 high level of viability at the 95 percent level,
14 and we will continue to learn from the science.
15 Genomics, proteomics, and matrix approach to the
16 health of the product and the reproducibility of
17 the product, both at the donor cell bank level and
18 at the final release stage, is critical. However,
19 the two attributes that we have in place already
20 have demonstrated, through over more than 400
21 patients worth of clinical data, how best to
22 approach the relationship between manufactured cell

1 therapy and clinical outcomes.

2 I think this is going to take more patient
3 exposures and ongoing relationship analyses between
4 optimization of manufacturing and clinical
5 outcomes, and that's what we're going to do.

6 DR. HOFFMAN: Dr. Robey, do you have a
7 comment?

8 DR. ROBEY: Yes, going back to one of the
9 comments that Sally Temple made this morning about
10 taking retention vials and looking at the quality
11 attributes of those vials in comparison to clinical
12 response. Nowadays, RNA seq and even single cells,
13 transcriptomics is getting so much cheaper.

14 Are you considering doing that? Are you
15 going to be looking at responders' and
16 non-responders' lost durability in certain factors,
17 that kind of an approach; and also, as a
18 certificate of analysis to have a transcriptomic
19 profile or a transcriptome [indiscernible] profile
20 that you can attach to that product and track how
21 effective that product was?

22 MS. STORTON: Dr. Itescu, would you like to

1 respond?

2 DR. ITESCU: Yes. Thank you. I think
3 characteristics of products are critical.
4 Characteristics of the recipient are just as
5 critical. To determine respond and non-responder
6 outcomes is going to require, again, large data
7 sets. We can look at things like baseline severity
8 scores, baseline biomarkers.

9 I showed you earlier that the sort of
10 responses we're getting with this product give us
11 substantially improved outcomes in the most severe
12 patients based on biomarker criteria. That would
13 allow us, for example, to do further evaluation by
14 stratifying the most severe patients against other
15 therapeutics and be able to demonstrate these types
16 of relationships.

17 In terms of genomic characteristics of the
18 recipient, yes, they need to be evaluated in
19 outpatient settings. And in terms of tracking the
20 product itself by genomic analysis, I think those
21 are the sort of studies that we'd want to do
22 longitudinally over time.

1 DR. ROBEY: Thank you.

2 DR. HOFFMAN: Thank you. Dr. Morrison?

3 DR. MORRISON: Yes, a couple of questions
4 for Dr. Itescu.

5 There's been an explosion in the last few
6 years of basic science studies done in mouse models
7 that have shown a lot of unanticipated
8 heterogeneity among mesenchymal progenitors around
9 different kinds of blood vessels in the bone
10 marrow, functional heterogeneity in vivo, as well
11 as a lot of new markers that hadn't been taken into
12 account when the field was based mainly on
13 characterization of cells that grew out in culture.

14 Do you want to say anything about whether
15 those studies have influenced the way that you
16 think about heterogeneity of the product that
17 you're growing out?

18 DR. ITESCU: Yes. I think that's critical.
19 In fact, we use that science precisely in what we
20 do as a company. For example, we are very much
21 aware of the STRO-1 antigen being critical to
22 identify the earliest progenitor of this cell, and

1 in fact the chief scientific officer, Professor
2 Paul Simmons, identified this antigen originally as
3 being critical to the earliest precursor of this
4 lineage. CD271 and a number of other markers have
5 been identified as being on the surface of the
6 earliest progenitors of the mesenchymal lineage.

7 So we use those types of markers to identify
8 at a very pure level when we isolate and extract
9 these cells and start the whole process because we
10 do agree that by starting with relatively
11 homogeneous populations. If selection for cells
12 that express these markers gives us greater
13 homogeneity, then we have the ability to end up
14 with cells that are very well characterized by
15 lineage and ultimately by function; because we're
16 talking about the earlier progenitors, and we
17 maintain the earlier progenitor phenotypes through
18 the culture process, et cetera.

19 So yes, that is a major focus of the company
20 in terms of optimizing products right through the
21 manufacturing process.

22 DR. MORRISON: I'm also thinking about the

1 more recent studies, though, where people have
2 started doing extensive fate mapping in vivo of
3 different subpopulations of mesenchymal cells in
4 the bone marrow, where it's not exactly clear yet
5 how the markers -- the markers probably change to a
6 certain extent when you put these cells in culture,
7 so it's not exactly clear how the recently
8 characterized populations compare to populations
9 that have been characterized primarily in culture
10 in earlier studies.

11 But it has become clear that there really is
12 a lot of heterogeneity within the bone marrow,
13 cells that at least have different properties
14 in vivo and that could potentially be similar when
15 grown out in culture but might ultimately have
16 different impacts once they're put into a patient.

17 DR. ITESCU: Look, I think the point you
18 make is excellent, and it cuts across cell therapy
19 more broadly. This is not something that is
20 limited to the mesenchymal lineage. Neural cells
21 and other cell types share this type of issue
22 between single-cell specificity versus -- and we're

1 talking about clonal single-cell specificity versus
2 cultured progeny that contains some degree of
3 in-process heterogeneity, yes.

4 I think this is the nature of the cell
5 therapy field as we're evolving and as we're
6 building out the ability to develop products that
7 can do good in terms of clinical outcomes. I think
8 it's an evolution, and we are committed as a
9 company to continuously optimizing and improving
10 and raising the bar to maintain scientific
11 excellence linked with clinical excellence.

12 I think we have already brought to the
13 table, currently, a high-level product that is
14 reproducible, that is consistent, that we
15 understand, at least in part, its mechanism of
16 action, and that translates into the ability to
17 generate clinical outcomes that are clearly
18 beneficial to patients in a way that other
19 approaches do not exist. We're talking about
20 patients who are the most refractory with a severe
21 risk of death that we are changing the outcomes
22 for.

1 I think we will continue to optimize. And I
2 agree with you. I think that there needs to be
3 ongoing scientific and rigorous development to
4 continue to optimize product potency, but today we
5 have a safe product. We have a product that has no
6 serious adverse events and a clear safety profile
7 with a very potent clinical outcome in a patient
8 population that has no alternatives.

9 DR. MORRISON: One last question. You
10 showed us data indicating that the best correlation
11 in terms of predicting potency was with TNF
12 receptor. You also, I think, made the correct
13 point that the mechanism of action is likely
14 multifactorial complicated, involving multiple
15 cytokines.

16 In the analyses where you arrived on
17 TNF receptor, did you try doing multifactorial
18 correlations to see if you could get better
19 predictive value from incorporating some
20 combination of multiple factors?

21 DR. ITESCU: We looked at the factors that
22 had already been incorporated as part of release

1 criteria across more than 400 patients that the
2 product had been used in through clinical trials.
3 Beyond TNF receptor viability, inhibition of T-cell
4 proliferation, gender, age, and disease severity,
5 we're not yet in these trials. We hadn't been
6 measuring, I suppose, other quality attributes or
7 other factors.

8 Moving forward, of course we will, but these
9 were what were available to us. One would have
10 expected in these kind of multivariable regression
11 analyses that the strongest predictors of outcome,
12 in particular, survival, would be disease severity
13 or would be potentially age. In fact, we were
14 really, really surprised that the predictor of
15 survival, at least using these parameters, the
16 strongest was the level of TNFR1 expression, the
17 degree of expression.

18 The reason that we were able to detect that
19 was precisely because we had such high variability
20 from the older process that was used 10 years ago
21 in two trials that did not meet their primary
22 endpoint versus the optimized process that is being

1 developed and manufactured today.

2 That kind of large variability within a
3 single key parameter allows us to then to determine
4 its relationship to outcome. Its strength came out
5 through the regression analyses, and the fact that
6 it was more related to outcome than traditional
7 GVHD severity grade -- grade 3/4 CD,
8 et cetera -- tells us how important this quality
9 attribute is on this product. But over time, we
10 will evaluate additional CQAs.

11 DR. MORRISON; Thank you.

12 DR. HOFFMAN: Dr. Halabi?

13 DR. HALABI: Yes. Susan Halabi. Thank you,
14 Dr. Hoffman.

15 I'm also still struggling on the whole issue
16 of variability in vivo versus in vitro. In one of
17 your slides, I believe MA-2, you showed
18 correlation, a proportion of variability range from
19 0.72 to 0.8, but then in the in vitro, I believe
20 IL-2R alpha, you looked at that correlation with
21 the CD3, et cetera. But that correlation, as
22 measured by the proportion of variability, was

1 really small, was only 0.38. I'm wondering if you
2 also looked at other correlations similar to what
3 you've done in MA-2 for in vitro versus in vivo.

4 That was one of the questions. I think my
5 other question you've already addressed, based on
6 what Dr. Morrison asked in terms of other analyses
7 that takes into account other factors.

8 DR. ITESCU: Thank you very much.

9 If we could have MA-2 slide up again,
10 please?

11 What's important about this slide is it
12 shows strong correlations, as you've noted, between
13 the absolute level of TNFR1 on the X-axis and three
14 different intracellular characteristics of the
15 cell. What's important between these TNFR1 levels
16 on the X-axis is that they encompass the absolute
17 level that is seen in our clinical trials, so they
18 relate very precisely to the levels of TNFR1 that
19 we talk about in our correlations with survival
20 across the three trials to date.

21 The fact that by knocking down TNFR1 to
22 levels that encompass what's been in the clinic

1 gives us a very good sense of the ability of the
2 cell to respond when it has a low level of TNFR1
3 and when it has a 50 percent higher level of TNFR1
4 with respect to factors that are likely to be
5 relevant in vivo and we know are biologically
6 critical, such as CCL2, that is very important in
7 macrophage polarization to M2.

8 By doing these in vitro assays and then
9 taking the levels of TNFR1 that here you can see
10 relates to intracellular bioactivity of the cell,
11 and then showing that these very levels of TNFR1
12 then correlate with survival benefits in patients I
13 think links the surface attribute of the cell with
14 its bioactivity with long-term survival of the
15 patient, and that's the way we will continue to
16 optimize our product.

17 When you mention the other correlation
18 between the proportion of CD4 activated T cells
19 in vivo with the ability to suppress activation of
20 T cells in vitro, you are correct. The correlation
21 was less tight. And that's why we are using the
22 ability of the cells to suppress T-cell activation

1 and proliferation in vitro as really a qualitative
2 bioassay, because it does not correlate quite as
3 well with in vivo reduction of activated T cells.

4 This is really the way we're going to
5 continue to optimize and learn about which
6 characteristics are best for quantification in
7 relation to in vivo outcomes versus which are
8 relevant to ensuring that the product has a
9 biologic activity that is reproducible but is not
10 necessarily able to measure a quantitative in vivo
11 outcome quite as precisely.

12 This is the slide that shows that, yes, we
13 are able to demonstrate that in vitro inhibition of
14 T-cell activation has a correlation with reduction
15 of activated T cells in vivo, but that correlation,
16 you are correct, is not as strong as the
17 correlations seen between TNFR1 and the production
18 of factors by the remestemcel factors that are
19 relevant to immunomodulation.

20 DR. HALABI: Thank you. The follow-up
21 question also regarding slide MA-10, with that, I
22 know the sample size was small, but in one of your

1 graphs -- I believe the one to the extreme right
2 where you had an MBS score -- I think you were
3 looking at MBS score with survival.

4 DR. ITESCU: Yes.

5 DR. HALABI: Well, not this slide. You had
6 four Kaplan-Meier curves. It wasn't this one.

7 DR. ITESCU: MA-11, next one.

8 DR. HALABI: Right. If you look at the last
9 Kaplan-Meier -- yes, that's exactly right -- my
10 understanding is this is what you're likely going
11 to see in patients, so the Kaplan-Meier curve on
12 the right.

13 DR. ITESCU: That's right.

14 DR. HALABI: If you look at the difference,
15 even though you did see, based on cohorts A and
16 validation cohorts 1 and 2, there is a huge gap
17 between the area in terms of high and low, but in
18 terms of what you're expecting to see in the
19 clinic, it looks like really a high MBS does not
20 reflect the benefit here.

21 DR. ITESCU: Let me explain. No, I think
22 you misinterpreted the slide. Let me explain it.

1 In the three Kaplan-Meiers on the left, they
2 represent the outcomes of steroid-refractory
3 population of patients treated with best available
4 therapy today, and what you see is that those
5 patients with a high MBS score above 0.29, they are
6 in blue, those patients with the best available
7 therapy today have a survival of no better than
8 20 percent to 40 percent through 12 months. That's
9 what the blue line shows. In contrast, today, if
10 you have a low biomarker score, you have an
11 excellent survival.

12 So this is a validated biomarker score by
13 the Levine Group that is now well accepted in the
14 GVHD community. It's validated based on these
15 three cohorts as being able to predict patients who
16 otherwise are going to have a very high mortality
17 to 12 months.

18 If you look at the Kaplan-Meier on the
19 right, which is the results of our phase 3 trial,
20 where we've also looked at the same biomarker MBS
21 greater than point 0.29 or less than 0.29 at
22 baseline, now we see in blue those patients that

1 have high MBS scores greater than 0.29 no longer
2 have a poor survival. Those patients now have a
3 survival at day 180 at 6 months, approximately
4 60 percent, which is not significantly lower than
5 patients with low MBS score at baseline.

6 So we've shifted the survival curve of the
7 high-risk patient from what would have been
8 expected to be a 20 to 40 percent survival to a
9 60 percent survival at 6 months. That's the point.

10 DR. HALABI: Okay. Thank you; although the
11 sample size is really small. You have only
12 29 patients, and then the follow-up, it seems you
13 needed a longer follow-up.

14 I assume this is ongoing; correct?

15 DR. ITESCU: That's correct.

16 DR. HALABI: Okay. Thank you.

17 DR. HOFFMAN: Dr. Singec?

18 DR. SINGEC: Yes. Hi there. I have a
19 question regarding TNF alpha receptor expression.
20 Has it changed as you culture the cells, the early
21 passage verses late passage?

22 MS. STORTON: I will start the response to

1 that, and then I'll ask Dr. Itescu to comment. We
2 test the levels of TNFR1 at the donor cell bank
3 stage and at the drug product stage, and we see
4 similar levels at passage 2 and then again at
5 passage 5.

6 Dr. Itescu, would you like to add anything
7 to that comment?

8 (No response.)

9 MS. STORTON: Dr. Itescu, are you there?

10 (No response.)

11 MS. STORTON: I think we've lost him.

12 DR. SINGEC: Can I ask a follow-up question?

13 DR. HOFFMAN: Yes.

14 DR. SINGEC: I think it's still rather
15 risky. Functional heterogeneity has been brought
16 up several times. Also considering powerful
17 technologies like single-cell analysis, you could
18 really get an idea of heterogeneity at the
19 single-cell level and potentially have taken
20 advantage of that and prospectively isolating the
21 cell type that could be most beneficial in this
22 context.

1 So I'm still wondering if and how the
2 approach could be tested so that you basically
3 don't simply rely on cells attaching differentially
4 to a plastic surface. If I understand correctly,
5 this is the current method of basically filtering
6 out the cells initially after the bone marrow
7 aspiration and plating cells on plastic, and those
8 that seem to attach are then being further
9 propagated.

10 So overall, it could be very useful to have
11 really a comparison of what you have initially and
12 what happens over the course of isolating the
13 cells. Again, the use of animal serum will also
14 introduce confounders potentially; so basically
15 having some better handle on prospectively
16 isolating cells could be of value here so that you
17 could really pinpoint better the cell product that
18 you eventually want to develop.

19 Any comments on that?

20 DR. ITESCU: Yes. May I add to this,
21 Geraldine?

22 MS. STORTON: Yes.

1 DR. ITESCU: I think, look, now that we
2 understand how important the cell surface receptors
3 are for the integrity of the cell and its ability
4 to respond to the micro environment in vivo, we now
5 have levels that we will use through the entire
6 manufacturing process at the level of the donor
7 cell bank, at the level of each passage, at the
8 level of harvesting, and final freeze/thaw, for
9 example.

10 So we are able to now protect the integrity,
11 ensure that the surface receptors are intact, are
12 functional, and are able to signal internally and
13 result in the release of these important factors.
14 Certainly, I think the entire manufacturing process
15 will be designed around ensuring that levels of
16 TNFR1, amongst other receptors, are maintained at
17 optimal levels for cellular function, and we're
18 building outputs that will allow us to continue to
19 ensure that is a reproducible process.

20 DR. HOFFMAN: Thank you.

21 Dr. Garcia, do you have your hand up or
22 that was from before?

1 DR. GARCIA: I apologize.

2 DR. HOFFMAN: No worries.

3 I think if we've learned nothing else, the
4 complexity of this subject is enormous, and I think
5 we've had a very thorough discussion from experts,
6 not including myself, who know more about this
7 technology than I do. I think of one of the
8 comments that Dr. Garcia made earlier, which is
9 that this is the state of the art at the moment,
10 and obviously we have what we have, and obviously
11 improvements and modifications and other changes
12 are being made to perfect this. I think this has
13 been helpful for us to have a sense of the
14 complexity of this subject matter.

15 Before we adjourn the morning session, are
16 there any last comments from the FDA?

17 DR. BAUER: Yes. This is Steve Bauer. I
18 wanted to express my appreciation for the comments
19 and questions the committees discussed so far and
20 the applicant's responses. I think, as Dr. Sally
21 Temple first brought up, this issue of continually
22 addressing the complexity that you just mentioned,

1 Dr. Hoffman, and that we all acknowledge is
2 important and a very iterative process. I think
3 Dr. Itescu has mentioned that several times, and
4 we've brought it up as well, and I think it's
5 important to keep that in mind going forward.

6 Our committees asked the applicant many
7 questions, but I do want to ask one last time if
8 any members or panelists have any specific
9 proposals for specific analyses or ways to improve
10 the state of the art and to continue a short
11 consistent quality of remestemcel-L going forward.

12 DR. HOFFMAN: Dr. Hinrichs, do you have a
13 comment?

14 DR. HINRICHS: Yes. I think part of why
15 there's not a giant wave of answers to this
16 question is that with a complex and somewhat
17 unclear mechanism of action, it's really difficult
18 to think about how you would want to see the
19 potency determined and what attributes and what
20 characteristics you would want to see tested. For
21 me personally, that is a bit of an obstacle to
22 thinking clearly about exactly what I would want to

1 know about the product.

2 DR. HOFFMAN: Dr. Robey?

3 (No response.)

4 DR. HOFFMAN: Did you have your hand up?

5 I'm sorry, Dr. Robey

6 (No response.)

7 DR. HOFFMAN: Perhaps not. Okay.

8 I just want to be sure I don't miss anybody
9 before I conclude our morning session.

10 DR. BAUER: May I ask if any of our FDA --

11 DR. ROBEY: I --

12 DR. BAUER: -- oh, go ahead. Sorry.

13 DR. ROBEY: Sorry. This is Pam Robey. I
14 lost connection there momentarily. We've talked
15 about the need for better analyses, and I just want
16 to say very specifically that I think that each lot
17 of cells should have a transcriptomic profile
18 associated with it, and that it would come in
19 extremely handy for future evaluations and also
20 address the issue of lot-to-lot variability. So I
21 think specifically that is a recommendation, from
22 me anyway.

1 DR. HOFFMAN: Okay.

2 Dr. Hinrichs, your hand is up or is that
3 left over?

4 (No response.)

5 **Adjournment**

6 DR. HOFFMAN: Left over. Okay.

7 I think this can conclude the morning
8 session. We'll now break for lunch. We'll
9 reconvene at 1:00. Maybe I could suggest that we
10 maybe try to come on even 5 or 10 minutes before
11 1:00 if we can because I suspect there'll be a lot
12 of discussion this afternoon as well, so that we
13 can start at least sharp at 1:00 for the afternoon
14 session of today's meeting.

15 Panel members, please remember that there
16 should be no discussion of the meeting topics
17 during lunch or with other panel members. Thank you
18 very much.

19 (Whereupon, at 11:41 a.m., the morning
20 session was adjourned.)

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