FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUG ADVISORY COMMITTEE (ODAC)

Thursday, August 13, 2020

1:02 p.m. to 5:24 p.m.

Afternoon Session

Virtual Meeting

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

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

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(1:02 p.m.)

Call to Order

Introduction of Committee

DR. HOFFMAN: Good afternoon, and welcome. I'd like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Kristin Jarrell. Email address is kristen.jarrell@fda.hhs.gov, and her phone number is 301-796-0137.

My name is Philipp Hoffman, and I will be chairing today's meeting. I will now call the afternoon session of today's Oncologic Drugs Advisory Committee to order. Dr. Joyce Yu is the acting designated federal officer for today's meeting, and we'll begin with introduction of this afternoon's meeting roster.

DR. YU: Good afternoon. My name is Joyce Yu. When I call your name, please introduce yourself by stating your name and affiliation. My name is Joyce Yu, and I'm the acting designated federal officer for today's meeting of the

Oncologic Drugs Advisory Committee.

Dr. Hoffman?

DR. HOFFMAN: My name is Philipp Hoffman. I'm a medical oncologist at the University of Chicago.

DR. YU: Thank you.

Dr. Garcia?

DR. GARCIA: Jorge Garcia, chief medical oncology, University Hospital, Seidman Cancer Center, Case Western Reserve University in Cleveland, Ohio.

DR. YU: Thank you.

Dr. Halabi?

DR. HALABI: Good afternoon. I'm Susan Halabi. I'm a biostatistician at Duke University, Durham, North Carolina.

DR. YU: Thank you.

Dr. Hinrichs?

DR. HINRICHS: Christian Hinrichs, senior investigator, National Cancer Institute, Bethesda, Maryland.

DR. YU: Thanks.

Dr. Sung?

DR. SUNG: Anthony Sung, hematopoetic stem cell transplant physician at Duke University.

DR. YU: Thank you.

Dr. Cheng?

DR. CHENG: Good afternoon. Jon Cheng, medical oncologist. I'm the industry rep, and I'm with Merck.

DR. YU: Thank you. Dr. Bunin?

DR. BUNIN: Hi. Nancy Bunin, a blood and marrow transplant physician, Division of Oncology at the Children's Hospital of Philadelphia.

DR. YU: Thank you.

Dr. Finestone?

(No response.)

DR. YU: I believe Dr. Finestone has dropped her phone. We'll get back to her.

Dr. Kamani?

DR. KAMANI: Hi. Good afternoon. This is Naynesh Kamani. I'm a pediatric immunologist and BMT physician at Children's National Hospital in Washington, D.C.

DR. YU: Thank you.

Ms. Pearl?

MS. PEARL: Good afternoon. My name is Diane Pearl. I am the parent of two young adult Fanconi anemia patients and post-bone marrow transplant, from Park City, Utah.

DR. YU: Thank you.

Dr. Walters?

DR. WALTERS: Mark Walters. I'm a pediatric hematologist/oncologist in the blood marrow transplant program at University of California San Francisco in Children's Hospital, Oakland.

DR. YU: Thank you.

If Dr. Finestone can hear me, could you please go ahead and introduce yourself and your affiliation?

DR. FINESTONE: Yes, my apologies. Sandra Finestone, consumer representative.

DR. YU: Thank you so much.

We'll now introduce our primary FDA participants for this afternoon session.

Dr. Pazdur?

DR. PAZDUR: Richard Pazdur, director of the Oncology Center of Excellence.

DR. YU: Thanks.

Dr. Bryan?

DR. BRYAN: Wilson Bryan, director of the Office of Tissues and Advanced Therapies, in the Center for Biologics, Evaluation, and Research.

DR. YU: Dr. Theoret?

DR. THEORET: Hi. Marc Theoret, deputy director, Oncology Center of Excellence.

DR. YU: Thanks.

Dr. Puri?

DR. PURI: Hi. This is Raj Puri. Good afternoon. I'm the director of the Division of Cellular and Gene Therapies in the Office of Tissues and Advanced Therapies in CBER, Center for Biologics, Evaluation, and Research.

DR. YU: Thanks.

Dr. George?

Good afternoon. Bindu George. I'm the chief of the Clinical Hematology Branch in the Office of Tissues and Advanced therapies in CBER.

Thank you.

DR. YU: Thanks.

Dr. Przepiorka?

DR. PRZEPIORKA: Donna Przepiorka, CDER, Division of Hematologic Malignancies I. Thank you.

DR. YU: Thanks.

Dr. Baird?

DR. BAIRD: Hi. Kristin Baird. I'm a medical officer in the Clinical Hematology Branch in the Office of Tissues and Advanced Therapies. Thank you.

DR. YU: Thanks.

Dr. Lin?

DR. LIN: This is Stan Lin. Good afternoon. I'm with the CBER OBE, Office of Biostatistics. I'm a statistical reviewer. Thank you.

DR. YU: Thank you.

Dr. Xu?

DR. XU: Hi. Good afternoon. This is Zhenzhen Xu. I'm the statistical team lead at the Division of Biostatistics at FDA.

DR. YU: Thank you so much. That concludes

our afternoon session introductions. Thanks.

DR. HOFFMAN: For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

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

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

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the

media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks. Thank you.

Dr. Joyce Yu will read the conflict of interest statement for the meeting.

Conflict of Interest Statement

DR. YU: Thank you.

The Food and Drug Administration, FDA, is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal and conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting

and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These

interests may include investments, consulting, expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves biologics license application 125706 for remestemcel-L, ex vivo culture-expanded adult human mesenchymal stromal cells suspension for intravenous infusion, submitted by Mesoblast, Incorporated. The proposed indication for use for this product is for the treatment of steroid-refractory acute graft-versus-host disease in pediatric patients. The afternoon session will discuss results from clinical trials included in BLA 125706.

This is a particular matters meeting during which specific matters related to Mesoblast's BLA will be discussed. Based on the agenda for today's afternoon meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all

standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue. With respect to FDA's invited industry representative, we would like to disclose that Dr. Jonathan Cheng is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Cheng's role at this meeting is to represent industry in general and not any particular company. Dr. Cheng is employed by Merck & Company.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. HOFFMAN: We will now proceed with the FDA opening remarks from Dr. Bindu George.

FDA Opening Remarks - Bindu George

DR. GEORGE: Thank you, Dr. Hoffman.

Good afternoon. My name is Bindu George, and I'm an adult hematologist and oncologist, and I'm the chief of the clinical hematology branch in the Office of Tissues and Advanced Therapies, or OTAT, in CBER.

I would, on behalf of the FDA, like to welcome and thank the members of the advisory committee for participating in this afternoon session, which will focus on the clinical aspects of the BLA for remestemcel-L for the treatment of pediatric patients with steroid-refractory acute GVHD.

The FDA generally agrees with the applicant's conclusion regarding the safety of remestemcel-L. Our concerns and our presentation this afternoon focuses on the product's efficacy. As discussed this morning, the mechanism of action of remestemcel-L is unclear, and it has been

difficult to identify product characteristics that correlate with efficacy outcomes in GVHD.

In this setting where the scientific basis of activities are uncertain, we rely heavily on the clinical trial results to provide persuasive evidence of efficacy. The efficacy data for remestemcel-L come primarily from MSB-GVHD001, a single-arm study in pediatric patients with steroid-refractory acute GVHD. The primary efficacy endpoint was day 28 overall response rate.

The results from the study were statistically significant, however, due to the limitations of the study design, we have concerns regarding the interpretability and persuasiveness of those results. Our concerns regarding the effectiveness of remestemcel-L include consideration of its overall clinical development program. Remestemcel-L has been evaluated in trials and other immune-mediated diseases such as Crohn's disease and type 1 diabetes without demonstrating a treatment effect.

The clinical development program in acute

GVHD includes 2 randomized-controlled trials, Study 265, a randomized-controlled trial in patients with newly diagnosed acute GVHD, and Study 280, a randomized-controlled trial in steroid-refractory acute GVHD. Both trials enrolled pediatric and adult patients and had statistically negative results. A post hoc subgroup analyses of these randomized studies led to the hypothesis of the potential for remestemcel-L to treat pediatric steroid-refractory acute GVHD. MSB-GVHD001 was therefore designed as a study solely in pediatric patients.

The FDA believes that the pathogenesis of newly diagnosed and steroid-refractory acute GVHD are the same in pediatric and adult patients and asks this committee to consider the extent to which the results of Studies 265 and 280 are relevant to the proposed pediatric indication for remestemcel-L.

Dr. Kristin Baird's presentation today will focus on a few issues. First, we are concerned about the limitations of the single-arm study,

particularly the challenges with minimizing bias. We're concerned about the potential for bias due to differences between the study group and the control group in baseline prognostic factors, concomitant medications, and outcome assessments in that some of the assessments that contribute to staging of GVHD may not be resistant to bias. Differences in naming or all of these factors could bias the studies' efficacy results.

Furthermore, the efficacy data from study MSB-GVHD001 also raised concerns of bias or confounding that warranted a sensitivity analyses with exclusion of some subjects. These subjects either experienced an improvement in the severity of acute GVHD prior to initiation of treatment with remestemcel-L or received concomitant medications during the 28-day period to assess overall response rate.

Second, we are concerned about the difficulty in selecting an appropriate external control to support a valid null hypothesis for this study, particularly considering a landscape of

available therapies with a broad range of day-28 overall response rates.

In the setting of uncertainty about the appropriate control, it can be difficult to have confidence in the study results. Our request to this advisory committee is to consider these issues and the clinical development program when assessing the treatment of remestemcel-L.

Despite our substantial concern regarding the efficacy of remestemcel-L, the FDA is also concerned about missing the opportunity to make a new therapy available to patients with a life-threatening disease and a substantial unmet need. We look forward to the deliberations of this committee and to the comments in the open public hearing.

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

DR. HOFFMAN: Thank you.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To

ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

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

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with presentations from Mesoblast, Incorporated, immediately followed by the FDA presentation.

Applicant Presentation - Geraldine Storton

MS. STORTON: Good afternoon, Mr. Chairman, members of the advisory committee, and the FDA. I'm Geraldine Storton, head of regulatory affairs and quality management at Mesoblast. We're pleased to be here today to discuss remestemcel-L for the treatment of steroid-refractory acute graft-versus-host disease in pediatric patients. Mesoblast is committed to the development of cellular medicines, particularly for children with this devastating and often fatal orphan disease.

Acute graft-versus-host disease is a serious and fatal complication of allogeneic hematopoietic stem cell transplantation. It occurs when the immune cells from the donor attacks the recipient, triggering an immunological response.

The pathophysiology of acute GVHD is complex and is characterized by three phases: host tissue damage by bone marrow transplant conditioning; immune cell activation and cytokine storm; and inflammation and end-organ damage primarily involving the skin, gut, and liver.

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

Children who do not respond to first-line corticosteroids, considered steroid refractory, had the highest risk of treatment failure and as high as 70 to 90 percent mortality. Currently, there are no available therapies considered standard of care, and children under 12 have no approved treatment for this frequently fatal disease.

Remestemcel-L is a novel, off-the-shelf cellular therapy that comprises culture expanded mesenchymal stromal cells. Mesenchymal stromal cells have a unique immunological profile that

underpin their rationale as an allogeneic treatment for acute GVHD.

In our presentation today, we will refer to the active simply as remestemcel. Since mesenchymal stromal cells are hypoimmunogenic, cells from a single donor can be used in recipients with that tissue matching or the need for immunosuppressive agents. Remestemcel has a multimodal mechanism of action that modulates the patient's immune response, allowing the body to adjust and recover.

This slide demonstrates two major characteristics of remestemcel's mechanism of action. Firstly, the cells use surface receptors such as tumor necrosis factor receptor type 1 to sense the presence of high levels of inflammatory cytokines such as TNF alpha, produced by inflammatory macrophages and T cells within the micro environment.

TNF signaling through TNFR1 activates cytoplasmic NF-kappaB, which moves into the nucleus and is the master regulator of multiple

anti-inflammatory factors, which ultimately result in polarization of inflammatory M1 macrophages to anti-inflammatory M2 macrophages, switching off TNF alpha production and inducing production of the anti-inflammatory cytokine IL-10.

The end result of multiple anti-inflammatory factors, produced either in response to signaling through TNFR1 or other surface cytokine receptors, is inhibition of CD4 T-cell activation.

Let me briefly take you through our development program in steroid-refractory acute GVHD that led to the Pivotal Study 001 and the extension Study 002 using the optimized remestemcel manufacturing process with enhanced potency. This study demonstrates the substantial evidence of efficacy in our target patient population.

The program began with Protocol 280, a randomized-controlled trial in adults and children receiving standard of care plus remestemcel or placebo. EAP 275 was initiated in 2007 to provide an avenue for physicians to continue to treat pediatric patients with remestemcel given a salvage

therapy.

In parallel, quality manufacturing improvements were made throughout development to optimize and streamline the overall process. This included enhancements made in the manufacturing process that resulted in an increase in the TNFR1 levels on the surface of remestemcel and an increase in the ability to inhibit IL-2R alpha, a marker of T-cell proliferation.

Analyses have demonstrated an association between the increase in these potency attributes and improved patient survival. Protocol 280 and part of EAP 275 used a less potent product. Approximately one-quarter of EAP 275 and all of Pivotal Study 001 used product made with the optimized process.

In 2014, Mesoblast met with the agency to determine if an adequately designed and conducted single-arm trial could be sufficient to support a marketing application. Based on discussions and input from the FDA, and our learnings from earlier studies, Mesoblast designed Study 001 to

investigate remestemcel as first-line therapy in pediatric patients with steroid-refractory acute GVHD. FDA granted the application orphan drug designation and fast-track status.

With that background, let me take you through the agenda. Next, Dr. Joanne Kurtzberg will present the significant unmet medical need for pediatric patients with acute GVHD, followed by Dr. Fred Grossman, who will present our clinical efficacy and safety results.

Finally, Dr. Kurtzberg will return to provide her clinical perspective and conclude the presentation. We also have an additional expert with us today to answer any questions. All external speakers have been compensated for their time.

I will now turn the presentation to Dr. Kurtzberg.

Applicant Presentation - Joanne Kurtzberg

DR. KURTZBERG: Good morning. My name is Joanne Kurtzberg, and I'm a professor of pediatrics and pathology at the Duke University School of

Medicine. I'm also the director of the Marcus Center for Cellular Cures, the Pediatric Blood and Marrow Transplant Program, and the Carolinas Cord Blood Bank. I was a lead investigator on the remestemcel pivotal and EAP trial.

We're here today because there's a significant unmet need for steroid-refractory GVHD therapies in children, and from my clinical experience, I can say that remestemcel fills that need for my patients.

Acute graft-versus-host disease is a progressive and fatal complication of allogeneic, hematopoietic stem cell transplantation. In the United States, approximately 1300 allogeneic transplants are performed annually in children with refractory hematologic malignancies or life-threatening genetic diseases. Despite transient prophylaxis, 25 to 80 percent of these children will develop acute GVHD.

The first line of treatment for acute GVHD is corticosteroids, usually IV Solu-Medrol, but unfortunately only 50 percent of patients will

respond to this intervention. The other 50 percent have steroid-refractory GVHD, and as many as 70 to 90 percent of these children will die.

Acute GVHD primarily affects the skin, GI tract, and the liver, causing significant symptoms that may lead to death. When I see a patient with GVHD, they often have a sunburn-like or measle-like rash, sometimes covering their entire body like you can see in this picture. If the GI tract is involved, children can have severe abdominal cramps and large volumes of diarrhea. If it involves the liver, rising bilirubin causes jaundice.

It's particularly difficult to treat children whose GI tract is involved because they have large volumes of watery, often bloody diarrhea that requires aggressive IV infusions to maintain adequate fluid and electrolyte balance. Most children also have anorexia, nausea and vomiting and cannot maintain their nutrition with oral or enteral feeding. Thus, many of these children become dependent on total parenteral nutrition and require multiple platelet and red blood cell

transfusions every week. They remain hospitalized, and 70 to 90 percent of these children all ultimately die.

The typical course of a child with acute steroid-refractory GVHD is shown on this slide. Three to six weeks after transplant, often concomitant with or shortly after neutrophil engraftment, the child develops rash that is itchy or burns the skin and sometimes fever. Treatment with steroids is indicated and initiated, but the rash doesn't improve. Days to a few weeks later, the child develops severe diarrhea with anorexia and vomiting.

Second-, third-, and fourth-line off-label agents like daclizumab; basiliximab; Remicade or infliximab; ATG; Imuran; alemtuzumab; additional steroids; and others are added without response. The child develops failure to thrive, renal insufficiency, very poor immune reconstitution, if any, leading to uncontrolled opportunistic infections and death from multi-system organ failure.

I agree with the FDA's assessment of the therapies we currently use and that none are considered standard of care. First, there are no approved drugs for treatment of steroid-refractory acute GVHD in children less than 12 years of age.

Off-label immunosuppressants are often used, but they only have category 2 or lower-level data that are not sufficient to allow the National Comprehensive Cancer Network or Blood and Marrow Transplant Clinical Trials Network to recommend use of one over the other. These off-label options often have mixed efficacy and high toxicity. Many have high renal toxicity and all cause further immunosuppression, leading to life-threatening and sometimes fatal infection.

Currently, ruxolitinib is the only FDA-approved treatment available for pediatric patients with acute steroid-refractory GVHD, however, it is not approved for children under 12 years of age due to safety concerns. Additionally, there are limitations with the use of ruxolitinib in this population.

First, the drug is given orally, which is difficult in children who have poor compliance with oral therapy. In addition, most of these children have severe diarrhea or vomiting. The diarrhea causes shortened GI transit times and poor absorption. Thus, oral drugs generally are not used in children with GI GVHD.

In addition, ruxolitinib causes thrombocytopenia, which already exists and can be difficult to manage in these patients. Thus, this may not be adequate for children with steroid-refractory acute GVHD. As the FDA explained in their briefing book, since the lowest available strength of ruxolitinib precluded safe treatment in infants and children, the indication was limited to patients 12 years of age and older.

In summary, pediatric patients with steroid-refractory acute GVHD urgently need a safe and effective treatment to reduce mortality. These children already have been treated for their primary disease and are immunosuppressed and highly vulnerable after a stem cell transplant, so it's

important to offer therapies that are well tolerated with a low morbidity risk.

The limited treatments currently in use usually are ineffective and cause significant toxicity, and further compromise immune reconstitution. For children under 12 years of age who do not respond to steroids, there are no available FDA-approved therapies to effectively treat this potentially fatal complication.

Remestemcel-L has the potential to meet this urgent unmet need and significantly reduce the high morbidity and mortality in these children. I've been using remestemcel for more than a decade through the clinical trials and expanded access program. After seeing results from EAP 275, a randomized placebo-controlled pivotal trial would not have been possible.

My colleagues and I would not enroll children with severe refractory disease where there was a risk of receiving placebo. The expanded access data showed an extremely favorable safety profile and high response in survival rates with

remestemcel, and I wanted that option to be available for all of my patients in the pivotal trial.

Thank you. I'll now turn the presentation to Dr. Grossman.

Applicant Presentation - Fred Grossman

DR. GROSSMAN: Thank you.

I'm Fred Grossman, chief medical officer at Mesoblast. I'll be presenting the clinical trial data that demonstrates a significant and clinically meaningful benefits of remestemcel in critically ill pediatric patients with steroid-refractory acute GVHD.

During the development history of remestemcel, we have performed 4 distinct clinical programs, culminating in Pivotal Study 001. You've been asked to discuss many questions, but what it comes down to is whether our pivotal single-arm study in children provide substantial evidence of efficacy in the context of 2 randomized controlled studies that did not meet their primary endpoint primarily in adults.

So our presentation in response to FDA's questions will focus on addressing the totality of evidence supporting the efficacy of remestemcel in treating children with steroid-refractory acute GVHD with Pivotal Study 001 providing substantial evidence of efficacy.

We agree with the FDA conclusions that results in Study 001 was statistically significant, the response was durable, and the results were consistent across subpopulations and secondary endpoints. We also agree with the FDA that there were no safety signals of concern identified in the studies of remestemcel, and that there were no remarkable differences between remestemcel and placebo.

Let me share our learnings from the two randomized controlled trials that did not meet their primary endpoints. Protocols 265 and 280 enrolled primarily adult patients. Importantly, patients in 265 were treatment naive, which is not the population in our proposed indication. Additionally, the primary endpoints in both studies

were different than Study 001, which used the currently adopted day 28 overall response that is highly correlated with survival. So I will focus on the relevant studies for our indication in steroid-refractory acute GVHD starting with Protocol 280.

Protocol 280 was a randomized placebo-controlled study in adults and children with steroid-refractory acute GVHD, including grades B through D. Of the 260 patients enrolled, 28 were children. Patients received remestemcel or placebo in addition to institutional standards second-line treatment.

The primary efficacy endpoint was durable complete response. Overall, 34.7 percent of patients in the remestemcel group had a DCR compared to 29.9 percent of patients in the placebo group. Thus, the results of this endpoint were not statistically significant.

In May of 2009, scientific leaders discussed acute GVHD clinical trial endpoints at the NIH-FDA public Workshop. They concluded that day 28

overall response was a valid efficacy outcome for trials of acute GVHD treatment. Additionally, several studies have demonstrated that day 28 overall response is highly correlated with long-term survival, therefore, we conducted an analysis of Protocol 280 results using the now accepted day 28 overall response endpoint.

The analysis of day 28 overall response showed us that remestemcel outperformed placebo in patients with severe disease, which represented over 75 percent of the study population, and when we looked at the prespecified analysis of the pediatric population using day 28 overall response, we saw a signal of efficacy. While the sample size is small, the analysis provided a signal of potential efficacy in survival with remestemcel in children with severe steroid-refractory acute GVHD.

Based on these findings, Expanded Access Protocol 275 continued to enroll pediatric patients. Expanded Access Protocol 275 represents a real-world population with the most severe patients who fail to respond to multiple lines of

additional therapy.

Two hundred forty-one pediatric patients with grades B through D, steroid-refractory acute GVHD were enrolled with 80 percent of the patients having severity grades of C and D. Additional prophylactic and second-line treatments for acute GVHD were administered before and during remestemcel treatment, resulting in a heavily pretreated and very refractory population.

Despite the severity of these refractory children, 65 percent achieved an overall response at day 28, and when looking at the most severe children with steroid-refractory acute GVHD, there is an overall response at day 28 of 63 percent in grade C and D. Importantly, overall survival at day 100 was 66 percent.

The response at day 28 was significantly associated with day 100 survival. The survival rate in responders was 82 percent compared to 38 percent in non-responders. These clinically meaningful results and learnings from Study 280 informed the design of Pivotal Study 001 in

children with steroid-refractory acute GVHD.

Based on advice from the FDA, Trial 001 eliminated potential confounding from all other agents by excluding additional treatments other than steroids during the first 28 days. Additionally, there was agreement on the inclusion/exclusion criteria, disease severity and study endpoints.

Moving to Pivotal Study 001 and 002, as noted earlier, we agree with the FDA conclusions of Study 001, that they were statistically significant, the measured response was durable, and that the results were consistent across subpopulations and secondary efficacy endpoints.

FDA guidance consider single-arm trials to support a marketing approval in instances where there are no available therapies that would be considered standard of care and where the effect of response is presumed to be attributable to the investigational product. We've already established that there are no available therapies that would be considered standard of care. Next, we'll show that

the efficacy response is attributable to remestemcel compared to an appropriate comparative control rate, and that the clinical effect is consistent and durable.

I'll begin by describing the appropriate external controls that justify and validate the null hypothesis used for the 001 pivotal trial. As the FDA briefing book states, "Appropriate external controls can be a group of patients treated at an earlier time or during the same time period, but in another setting."

We used the International Conference on Harmonisation guidance to identify the appropriate external controls using similar baseline characteristics between the controls and the study patients. It was also essential that the standard of care used in the control cohort included freedom for the physician to choose alternative therapies to align with Study 001's design.

Here we see six potential control cohorts in this patient population. The top three are most relevant because patients were treated first line

after steroids. These studies use the same primary endpoint as the Pivotal Study 001 and allowed use of best available therapy. The three cohorts on the bottom tested single experimental agents and had varying endpoints.

All three external controls justify and validate the 45 percent null hypothesis used in Study 001. Rashidi and colleagues included 61 children with steroid-refractory acute GVHD, grades 1 to 4. The overall response observed at day 28 was 34 percent. Protocol 280 was an earlier remestemcel trial that included a pediatric subgroup of 14 patients with steroid-refractory acute GVHD, grade B through D, treated with available therapies, and the overall response at day 28 was 36 percent.

Finally, the Mount Sinai Acute GVHD International Consortium, or MAGIC database, is a contemporaneous data set that was developed to study acute GVHD. The MAGIC control cohort included 30 children with steroid-refractory acute GVHD that were matched to Study 001's eligibility

criteria. Patients had grades B through D disease, excluding grade B skin only. The day 28 overall response was 43 percent.

All three of these external cohorts aligned with the patient population in Study 001 and are appropriate controls that justify the null hypothesis of 45 percent used in Study 0001.

Let's look at the study in more detail. Study 001 was a phase 3, single-arm, open-label trial intended to show significant increase in day 28 overall response attributable to remestemcel as initial second-line therapy following steroids.

Fifty-five children between 2 months and 17 years of age with acute GVHD, grades B through D, enrolled in the study. Patients with grade D skin only were excluded. The null hypothesis would be rejected if the day 28 overall response, 95 percent lower confidence interval excluded 45 percent.

Eligible patients received remestemcel twice per week for 4 consecutive weeks and were assessed for response at day 28. At that point, patients who had a complete response or no response stopped

receiving remestemcel but continued assessments. Those with a partial or mixed response continued treatment once a week for 4 additional weeks with follow-up assessments at day 56 and day 100.

Day 100 marked the end of Study 001 and the beginning of Study 002 for patients who continued into the extension through 180 days. Importantly, remestemcel was not administered during the follow-up period.

The primary endpoint was overall response rate defined as complete or partial response at day 28. Response category was evaluated based on improvement in symptoms of rash, GI symptoms of diarrhea, and bilirubin. The key secondary endpoint was overall survival at day 100. Study 002 was primarily a safety study looking at adverse events and survival through day 180 as well as duration of response.

Moving to disposition, of the 55 patients who enrolled in Study 001, 54 were treated with remestemcel; 40 patients or 74 percent completed the study alive; 32 of the 40 eligible patients

from Study 001 enrolled in Study 002, and 97 percent completed to day 180. We were able to obtain vital status through day 180 for all but 2 of the 54 patients treated in Study 001. Our analyses are based on the 54 patients who were treated with remestemcel.

Turing to demographics, Study 001 treated patients across a broad age range, from 7 months to 17 years. The median age was 7 years and the majority of patients were male and white. The study included patients with representative transplant types, the most common being bone marrow, followed by peripheral blood stem cells, and then cord blood. Seventy-six percent had an unrelated donor, which we know is the key driver of GVHD.

Severity was based on the IBMTR classification system and 89 percent included grades C and D. With respect to organ involvement, lower GI and multi-organ made up 74 percent and the 14 skin-only patients included severity stages 3 and 4.

Now, let's look at the results. Study 001 met the primary endpoint with 70 percent response at day 28 in treated patients, excluding the null hypothesis of 45 percent. The FDA performed to sensitivity analyses, excluding patients who received concomitant medications or who improved prior to treatment initiation.

In sensitivity set 1, these patients were removed from the analysis and the day 28 overall response was 75.6 percent. In sensitivity set 2, these same patients were analyzed as treatment failures, resulting in an overall response of 61.8 percent. However, we do know that 4 of these patients were actually responders. What's important here is that regardless of the analysis, the lower 95 percent confidence interval excluded the 45 percent null hypothesis.

Efficacy, particularly in severe disease, was consistent across disease severity, including in those with the most severe grade C and D and where the overall response was 73 percent. This is where other therapies have very limited efficacy.

In particular, those with grade D, who typically have a high mortality, had an overall response of 76 percent.

As the FDA points out, duration of response is an important consideration to assess the clinical meaningfulness of response outcome in a single-arm trial. We acknowledge there are differences in how this can be calculated, but we agree with the FDA that remestemcel provided a durable response when looking at our calculations or any of the calculations used by the FDA.

When looking across the three trials, you see that results were consistently high in children. Day 28 overall response with remestemcel ranged from 64 to 69 percent when used with or without standard of care and as salvage therapy. Summarized, the data demonstrate that the effect of the clinical response is attributable to remestemcel.

The primary endpoint of day 28 overall response in Study 001 was statistically significant and all sensitivity analyses conducted by Mesoblast

and the FDA excluded the null hypothesis. The appropriate external controls were used to justify and validate the null hypothesis used in the pivotal study. We agree with the FDA that the measured response was durable and the results were consistent across three separate pediatric cohorts.

Next, let's look at survival. Survival outcomes across studies were consistently high for children treated with remestemcel. The MAGIC cohort in the pediatric control arm of Protocol 280 had similar survival rates at day 100 and day 180. Highlighted here, you can see that remestemcel treated children had high rates of survival across studies. In Pivotal Study 001, survival was 74 percent at day 100 and 69 percent at day 180.

I mentioned earlier that day 28 overall response is predictive of survival, so as expected, the day 28 overall responders in the pivotal study had a high survival rate of 87 percent at day 100 and 79 percent at day 180. This compared to non-responders with only 44 percent survival at day 100 and 44 percent at day 180. This has

important clinical implications because the increase in day 28 responders seen with remestemcel, compared with the appropriate external controls, is likely to result in a higher number of children who survived.

Turning now to safety, the safety of remestemcel has been thoroughly investigated in more than 1100 patients across all programs. Across all studies, including those for steroid-refractory acute GVHD, the safety profile was similar to placebo.

In pediatric patients from Protocol 280, there were no meaningful differences when comparing remestemcel on top of standard of care versus standard of care alone. Similarly, when looking just at pediatric patients across all studies, there were no meaningful differences between the control group from 280 and remestemcel treated patients.

In summary, there were no safety differences between remestemcel and placebo. We agree with the FDA that no safety signal of concerns were

identified in the remestemcel studies.

The FDA is asking how to interpret the positive results from Study 001 in the context of other remestemcel studies. Now let's review the relationship between manufacturing enhancements in the GVHD studies.

While 265, like Protocol 280 and three-quarters of Expanded Access Protocol 275, occurred before the manufacturing enhancements, we will focus the subsequent analysis of manufacturing enhancements and clinical outcome to studies of just steroid-refractory acute GVHD, which includes 280, 275, and 001. Let me walk you through the data demonstrating how the overall survival results across studies correlated with the potency of the product.

An assessment of the measured potency attributes for product used in the three steroid-refractory acute GVHD trials showed that patients treated with remestemcel in trials after 2009 received product with higher critical quality attributes as a result of the optimized

manufacturing process.

This table shows that mean TNFR1 and percent inhibition of IL-2 receptor expression were increased with product made using the optimized process, resulting in improved day 28 overall response and day 100 survival with the best outcomes in Pivotal Study 001, where all patients received optimized product.

Using log rank statistics, this Kaplan-Meier plot shows significantly improved survival in patients who received only product made with the optimized process versus those who received only product made with the original process across all three trials in steroid-refractory acute GVHD.

In this slide, we show that within one pediatric study, EAP 275, children who received a single donor lot product made with the optimized process had significantly better survival than those who received product made with the original process. This demonstrates the relationship between the optimization of critical attributes on a single product lot in survival benefit.

You can see on the right that children in the pivotal phase 3 Study 001, where only product made with the optimized process was used, had an almost identical survival outcome at day 100, 74 percent, which demonstrates the survival benefit associated with the optimized manufacturing process.

In conclusion, Pivotal Study 001 provided substantial evidence of efficacy in children with steroid-refractory acute GVHD. The study successfully met its primary endpoint with a clinically meaningful overall response rate of 70 percent that excluded this 45 percent null hypothesis, which was justified and validated using the appropriate external controls. The 95 percent lower confidence interval in every sensitivity analysis excluded the null hypothesis. Study 001 demonstrated that remestemcel provides meaningful clinical benefit in children with steroid-refractory acute GVHD.

I'd like to come back to the criteria in FDA's guidance for a single-arm trial to support

approval. We've shown you today that remestemcel meets these criteria. We've heard from Dr. Kurtzberg that there are no available therapies that would be considered standard of care in children, and we've also shown that the effect of day 28 overall response is attributable to remestemcel.

The totality of data demonstrate substantial evidence of efficacy and supports approval of remestemcel for children suffering with steroid-refractory acute GVHD, who urgently need a treatment to increase survival. In addition, Mesoblast is committed to expanding the indicated patient population of remestemcel beyond children to include adult patients with severe steroid-refractory acute GVHD post-approval using product manufactured with the optimized process.

Two weeks ago, we held an advisory board meeting with global experts in adult GVHD to discuss potential trial designs to provide robust and clinically meaningful and useful data. Planning is underway for a randomized-controlled

trial of remestemcel versus standard of care that is designed to demonstrate improved overall response and survival. We will focus on adults with a continued high unmet need despite approved therapies or who have not responded to existing therapies.

Now I'd like to invite Dr. Kurtzberg to provide her clinical perspective on the benefit-risk of using remestemcel to treat children with steroid-refractory acute GVHD.

Applicant Presentation - Joanne Kurtzberg

DR. KURTZBERG: Thank you, Dr. Grossman.

I'd like to conclude by bringing this back to the patients. Children with steroid-refractory acute GVHD have dismal survival of 2 years. In a report published this year by MacMillan and colleagues, 370 children with acute GVHD were treated with prednisone.

As you can see, response at day 28, shown by the green line, was strongly correlated with overall survival. Steroid responders at day 28 had approximately 68 percent survival of 2 years,

whereas those who failed to respond to steroids had roughly 35 percent survival.

This red line represents the patients we're discussing today. This is the unmet need we're addressing. Today we've seen that remestemcel can change the trajectory for these children. In Studies 001 and 002, survival at day 180 was 69 percent. We need this treatment to be available as soon as possible to reduce the number of deaths in these children.

The efficacy and safety data reported remestemcel supports a positive risk-benefit ratio and aligns with my personal experience. These children, less than 12 years of age, have no approved treatments for steroid-refractory acute GVHD. For years, we have tried multiple, unapproved treatments that carry the risk for high toxicity.

After treating more than 30 patients with remestemcel as an investigator and as part of the expanded access program, I've seen the benefits shown in the sponsor's presentation firsthand. I

also know all too well the morbidity and mortality in children treated with other options, giving me confidence that Study 001's results, compared to historical controls, are accurate.

I need to have remestemcel available to ultimately reduce the number of children dying from this disease. The safety profile and mode of administration allow me to use remestemcel without concerns of adverse events, including in patients who can't tolerate an oral medication.

In my opinion, as both a treating physician and an academic researcher, the data clearly support benefit, particularly in improving survival in children with steroid-refractory acute GVHD, and I sincerely hope that this treatment is approved.

DR. HOFFMAN: Thank you, Dr. Kurtzberg.

We'll be happy to answer your questions during the question and answer period.

Dr. Baird?

FDA Presentation - Kristin Baird

DR. BAIRD: Hi. Good afternoon. My name is Kristin Baird, and I'm a pediatric oncologist and a

medical officer for the Office of Tissues and Advanced Therapies in CBER, and I will be presenting the FDA's session on clinical evidence. I'd like to thank the committee members for their participation today, and I look forward to the discussion that will follow my presentation. This slide shows the FDA review team for BLA 125706, and a word of thanks to all of the contributors listed here.

The proposed indication for remestemcel is the treatment of steroid-refractory acute graft-versus-host disease in pediatric patients. One single-arm trial, Study MSB-GVHD001, which I will refer to as Study 001, serves as the basis of efficacy for this application. Please note the FDA's analysis used data pooled from Study 001 and the companion safety follow-up Study 002. The results of these analyses are reported together under Study 001 for the remainder of this talk.

As the applicant has already presented their results to the committee this afternoon, I will focus our presentation on the issues encountered in

our review of this application. First, I will discuss issue number 1, the trial design of Study 001. I will review the regulatory background as it relates to the choice of controls. Next, I'll review Study 001, the trial design, and the issues identified in our review. Finally, I'll discuss the issues with the justification of the null for day 28 overall response rate or ORR.

Next, I will discuss the second issue, evidence of effectiveness for remestemcel. I will start with a review of the regulatory background on single trials to support licensing. I will discuss the FDA analysis of Study 001 results, and then we'll review the FDA analysis of the supporting evidence provided by the applicant.

Please note, FDA did not discover differences from what the applicant has shown in their safety review, and therefore product safety will not be included in our discussion. In addition, as described in the 2018 FDA guidance document for clinical trial endpoints, time-to-event measures such as overall survival are

difficult to interpret in single-arm trials, and Study 001 was not designed to detect differences in survival. And therefore, survival endpoints will not be discussed further by FDA.

First, I will present the trial design issues encountered with Study 001. As previously described by Mesoblast, the design elements of Study 001 include the following: single-arm trial design; enrollment of pediatric patients up to the age of 17 years; steroid-refractory grades B through D acute GVHD, excluding skin-only grade B: the treatment plan as previously described by the applicant; the primary efficacy endpoint of day 28 ORR and the durability of the response; and success defined as day 28 ORR of greater than 45 percent.

In our presentation, we will address the design elements in Study 001 that are potentially problematic, including the reliance on a single-arm trial design and how the null hypothesis was determined. To obtain marketing approval, the FDA requires that sponsors provide substantial evidence of efficacy and safety of their products based on

the conduct of adequate and well-controlled studies.

There is no requirement to demonstrate superiority over other treatments, although randomized superiority trials with a placebo or active control design generally provide the strongest evidence of effectiveness.

There are circumstances under which trials not using a placebo control, superiority design, or randomization may be acceptable. However, as we will describe in this presentation, due to limitations in historic control data for the pediatric acute GVHD patient population, the utility of a non-randomized design in this patient population may be limited.

Generally speaking, the limitations of a single-arm trial are as follows: a lack of randomization can lead to differences in patient characteristics or concomitant treatments in the trial population compared to the external control population, which may lead to differences in outcomes that are unrelated to the investigational

treatment; and a lack of blinding may introduce bias in concomitant treatment or endpoint assessments.

For these reasons, external control designs are usually reserved for specific circumstances, which is trials of diseases with high and predictable mortality or progressive morbidity. However, it is often possible, even in these cases, to use alternative randomized concurrently-controlled designs.

The use of single-arm trials can be effective if the following criteria are met: the natural history of the disease is well defined; the external control population is very similar or exchangeable to the study population. Externally-controlled trials are most likely to be applicable when the study endpoint can be objectively measured and therefore resistant to bias.

Concomitant treatments that may affect the primary endpoint do not differ between external controls in the study population, and success is

based on compelling evidence of a change in the established progression of the disease.

I will highlight the second bullet point here, which refers to the external control population, which is a significant issue in the review of this licensing application.

The International Conference on Harmonisation E10 guidance describes the expectations when choosing an external control for a clinical trial. The E10 guidance states that it is always difficult, and in many cases impossible, to establish comparability of the treatment and control groups, and thus to fulfill the major purpose of a control group.

The groups can be dissimilar with respect to a wide range of factors other than the use of the study treatment that could affect outcome. This includes demographic characteristics; diagnostic criteria; stage or severity of the disease; concomitant treatments; and observational conditions such as methods of assessing outcome.

Such dissimilarities can include important

but unrecognized prognostic factors that have not been measured. As such, externally-controlled trials can be subject to bias and may overestimate efficacy of test therapies. Tests of statistical significance carried out in such studies may be less reliable than in randomized trials.

The prespecified statistical analysis plan from Study 001 proposed a primary efficacy endpoint of day 28 ORR within the full analysis of that population. Ideally, the null rate would be based on the expected day 28 ORR in patients who are untreated or treated with a standard-of-care comparator with a target treatment effect based on a clinically meaningful improvement from the null rate.

However, the ideal approach was not employed by the applicant. Instead, for Study 001, the null hypothesis was determined as follows. At day 28, ORR was anticipated to be 65 percent based on the rate observed in Protocol 275 and for the remestemcel treated pediatric subgroup of Protocol 280. This is problematic because the null

was determined not by comparable external controls, but rather by data generated from previous studies with the same product in different patient populations than that to be studied in 001, and that these patients were treated with additional salvage therapy for steroid-refractory acute GVHD.

For assessment of efficacy, the applicant chose an effect size of 20 percent to be clinically meaningful based on their discussion with clinical experts on GVHD. Therefore, the null hypothesis using 45 percent ORR was calculated as a rate that was 20 points lower than the anticipated 65 percent overall response rate.

FDA acknowledges there's a lack of data available for pediatric patients with steroid-refractory acute GVHD who are untreated, and the only existing data is those who have received additional salvage or second-line therapy. However, additional justification for the null determination was requested.

Although FDA agreed that an effect size of 20 percent might be clinically meaningful,

additional justification for the null rate of 45 percent was requested. To this end, the applicant provided the following. In the standard of care plus placebo arm of Protocol 280, the ORR was 74 percent for patients with standard risk steroid-refractory acute GVHD and 37 percent for those with high risk.

Assuming accrual of standard-risk to high-risk patients at a 3 to 1 ratio in Study 001, the risk-adjusted null rate would be 46 percent for a study of 60 patients. Major limitations of this data was that it was derived from a study of mostly adult patients and additional salvage therapy for acute GVHD was administered on the trial.

Additionally, in data provided to FDA from Study 265, which was the study for newly diagnosed acute GVHD patients, it was observed that in the steroid plus placebo arm, there were 33 patients identified as not responding to steroids by day 7 who would, thus, meet the definition for steroid-refractory acute GVHD and who continued the study on placebo. Of these 33 patients, 14, or

42 percent, achieved a CR or PR at the day 35 assessment, or 28 days later, with no additional therapy. Major limitations of this analysis is that it was a subgroup analysis and also performed in adult patients.

Further establishing the appropriateness of the 45 percent as the null, the applicant provided two post hoc analyses of ORR in several groups, first with patients in the control arm and the pediatrics subgroup of Protocol 280, and the analysis of pediatric patients with steroid-refractory acute GVHD identified in the MAGIC database.

In the standard of care plus placebo arm of Protocol 280, the day 28 ORR was 36 percent for the 14 patients accrued to that arm. So the utility of this comparator is limited by the small numbers, additional salvage therapies administered on the study, the fact that this was a subgroup analysis, and that patients were not stratified by age at enrollment.

In the MAGIC database, the applicant

identified 30 pediatric patients transplanted between 2005 and 2019 who received salvage therapy for grades B through D steroid-refractory acute GVHD. For these 30 pediatric patients, the day 28 ORR after first salvage therapy was 43 percent, which is slightly higher than that for the 95 adult patients with similar disease features, which had an ORR of 35 percent.

The main limitation of this analysis is that it was performed post hoc and does not inform the determination of the null, but rather this analysis may inform the understanding of the background rate. Additionally, although there were similar features to the enrollment criteria for Study 001, this group was not controlled for comparison to Study 001 by additional factors, calling into question the exchangeability of this population to the study population as an external control.

Therefore, additional literature support for the generation of the null hypothesis and to explore the background rates in the treatment of pediatric steroid-refractory acute GVHD was sought

by FDA. No additional information was uncovered to help the determination of the null hypothesis due to the lack of placebo-controlled trials in this patient population.

To try and find an additional perspective to the historic control rates, FDA found several small, uncontrolled studies. First was a retrospective analysis of day 28 ORR for salvage or second-line therapy for steroid-refractory acute GVHD from all first allogeneic stem cell transplant recipients at the University of Minnesota between 1990 to 2016.

They found that day 28 ORR was 34 percent for the 61 pediatric patients evaluated. Notably, in this study, the pediatric subgroup had the lowest day 28 ORR, 34 percent for patients less than 18 years of age, when compared to the older cohorts. Although there were relatively large numbers in the study, there's a question of whether these patients are exchangeable with the study population of 001.

Next, three additional pediatric-only

studies for steroid-refractory acute GVHD treatment provided additional context. A prospective study evaluating the use of etanercept in 25 children with grade 2 through 4 steroid-refractory acute GVHD, using the modified flux for criteria, observed an ORR of 68 percent. However, the ORR was measured at day 7. In addition, the study was stopped prematurely when the null hypothesis of 40 percent was excluded.

The retrospective analysis from the Pediatric Blood and Marrow Transplant Consortium evaluated the efficacy and safety of infliximab in 22 children with steroid-refractory acute GVHD. The ORR, which was defined as the maximum response within 56 days of starting treatment, was 82 percent.

Finally, a single-center prospective study of alemtuzumab as a second-line agent for grades 2 through 4 steroid-refractory acute GVHD, where steroid refractoriness was defined as patients who did not improve within 5 days but worsened within 48 hours after corticosteroids, found an ORR of

67 percent at 4 weeks. All three studies are limited by small numbers, varied endpoints, and very definitions of steroid refractoriness.

Therefore, there is significant difficulty in establishing the null rate for the proposed population for identifying an appropriate historic control group. Overall, the ORRs are highly variable. There's the potential for publication bias and there are wide confidence intervals with small numbers of patients.

There's limited ability to ensure population exchangeability because of differences in baseline disease characteristics, baseline prognostic factors, both known and unknown, concomitant drug use, and supportive care measures that could influence efficacy outcomes. And finally, there's a limited ability to ensure that the reported endpoint is the same due to differences in endpoint definitions and measurements.

In summary, Study 001 was a single-arm trial designed to determine if the day 28 ORR exceeded 45 percent for pediatric patients with

steroid-refractory acute GVHD treated with remestemcel. Although the null rate and hypothesis were prespecified in the statistical analysis plan, there are some limitations with regard to how the 45 percent was chosen.

It is uncertain as to whether the data cited for use of historic controls are applicable for either establishing the null hypothesis or as an appropriate control group for the purposes of quantitating a treatment effect in a single-arm trial of a new therapy for steroid-refractory acute GVHD in pediatric patients. FDA would be interested in the committee's discussion of the strengths and weaknesses of the trial study design given the limitations described here today.

Next, we will look at the totality of evidence provided in the licensing application to evaluate the level of evidence of effectiveness provided. FDA frequently requires more than one trial to establish efficacy.

In the effectiveness guidance, it states that the reliance on a single trial to establish

effectiveness will generally be limited to situations in which the trial has demonstrated a clinically meaningful effect on a potentially serious outcome and confirmation of the results in a second trial would be practically or ethically impossible.

With that context, we will review the efficacy outcomes of Study 001, which is a single-arm trial and the sole trial to provide data supporting the licensing application.

FDA confirmed Mesoblast's findings of 16 patients with CR and 22 patients with a PR at the day 28 assessment, giving an ORR of 69.1 percent with a 95 percent confidence interval of 55.2 to 80.9. Therefore, under the assumption of a 45 percent ORR for the null hypothesis, the study met its primary objective.

FDA conducted three additional analyses of day 28 ORR, one in the treated population and two sensitivity analyses. The two sensitivity analyses excluded 9 subjects who had confounders for determination of the day 28 ORR, and it's referred

to as the sensitivity set.

These analyses excluded one patient who withdrew consent prior to treatment; subjects who received concomitant immunosuppressive medications, that although not started for acute GVHD treatment or medications, that could potentially impact the day 28 primary endpoint analysis; and 4 subjects who did have active acute GVHD but with symptoms that improved by one grade in the interval between the determination of steroid refractoriness and the baseline acute GVHD evaluation. One subject was excluded for both reasons, therefore the total number excluded in the sensitivity analyses was 10 subjects.

In the first sensitivity analysis, sensitivity set 1, these subjects were removed from the analysis and the day 28 ORR was 75.6 percent. In the second sensitivity analysis, these subjects were analyzed as treatment failures, resulting in an ORR of 61.8 percent.

None of these analyses changed the highly significant departure from the null hypothesis of

an ORR of 45 percent. However, despite the positive outcomes of this trial, the clinical meaningfulness is still unclear in the setting of the uncertainties and limitations in setting the null for this population.

Duration of response is an important indicator of clinical benefit of acute GVHD treatment. FDA and Mesoblast definitions differ with regard to whether progression is called on the basis of one assessment, on the basis of two consecutive assessments, and whether progression is called in comparison to the day 28 response or in comparison to the nadir response at day 28 or later. Please refer to table 3 in the FDA briefing document for the complete definitions and additional differences in the definitions utilized by the applicant and FDA.

Using the FDA definition of duration of response, the duration of response is calculated at 54 days, which is shorter than that calculated by the applicant, and this should be taken into consideration when looking at the totality of

evidence.

The applicant has previously described their product development program, and this table highlights the acute GVHD trials that included the pediatric patients that helped to inform the FDA analysis of effectiveness.

In the first column is Study 001, which is contrasted to Protocol 280, which was the randomized placebo-controlled trial that evaluated the efficacy of remestemcel, and investigators choice of additional salvage or second-line therapy versus salvage therapy plus placebo in 260 patients with grades B through D, steroid-refractory acute GVHD.

The third protocol, Protocol 275, was the expanded access protocol, which specifically enrolled pediatric patients with steroid-refractory GVHD and also allowed investigator choice of additional salvage or second-line therapy.

Of note, there are significant differences between Study 001, 275, and 280. The most prominent differences is that Protocols 275 and 280

permitted the addition of other salvage acute GVHD therapies at study entry at the discretion of the treating physician. This is in contrast to Study 001 where no additional salvage immunosuppressive agents were allowed.

Additionally, both Studies 280 and 275 allowed the more mild, grade B, skin-only acute GVHD. Finally, the primary endpoint of Study 280 was a CR of 28 days duration or greater. As such, there are substantial differences between the supporting pediatric trials in Study 001 in study population and treatment plan.

When looking at the day 28 ORR in only the pediatric population across these studies, we find relative consistency in the ORR, although it is difficult to make any firm conclusions from this comparison, as Studies 280 and 275 both allowed additional salvage therapy for the treatment of acute GVHD, and the numbers are small in Study 280 and the confidence intervals are wide.

This table highlights the randomized placebo-controlled acute GVHD trials that also

helps inform the FDA analysis of effectiveness. Protocol 265 evaluated the efficacy of remestemcel in combination with systemic corticosteroid therapy in 192 adult patients with newly diagnosed grade B through D acute GVHD versus steroid plus placebo. The study population treatment regimen and primary endpoint in Protocol 265 all differ from that of Study 001.

As previously mentioned, Protocol 280 evaluated the efficacy of remestemcel plus investigator's choice of additional salvage therapy in 260 mostly adult patients with grades B through D, steroid-refractory acute GVHD versus placebo, plus investigator choice of additional salvage therapy. As such, there are substantial differences between the two prior randomized placebo-controlled trials in Study 001 in study population, study endpoints, and the treatment plan.

The primary endpoint of Studies 265 and 280 was a complete response that lasted 28 days duration or greater. Post hoc analyses of 265 and

280 were performed to evaluate the ORR at day 28. It is difficult to make cross-study comparisons due to the different patient populations and the allowance for a salvage acute GVHD therapy on Study 280.

Most importantly, however, is the fact that no treatment effect was observed in either of the two prior randomized placebo-controlled trials. The ORR in the remestemcel treated arms ranges from 54 to 70 percent with wide confidence intervals. And in data not shown here, no conclusions in the subgroup analyses according to disease severity can be made due to lack of statistical significance and high variability among the studies and wide confidence intervals.

Therefore, the question is whether Studies 265, 275, and 280 provide any additional supportive evidence or, alternatively, do these trials provide evidence against the effectiveness of remestemcel in the treatment of pediatric steroid-refractory acute GVHD? In comparison to Study 001, they have substantial differences in the

primary endpoint evaluations, patient populations, trial design, and study conduct.

In summary, the primary endpoint results of Study 001 were statistically significant, the measured response was durable, and the study results were consistent across subpopulations' secondary efficacy endpoints.

However, the results of Protocols 265 and 280, the two randomized trials, did not provide evidence of a treatment effect for remestemcel in acute GVHD even when we analyzed using the efficacy endpoint of day 28 ORR. In fact, treatment effect has not been identified in any of the previous clinical trials conducted in various disease entities, including type 1 diabetes mellitus, Crohn's disease, myocardial infarction, or severe chronic obstructive pulmonary disease.

FDA requests that the committee please discuss whether the results of Studies 265 and 280 are relevant to the effectiveness of remestemcel for the treatment of pediatric steroid-refractory acute GVHD, and FDA may require an additional

clinical trial to support the effectiveness of remestemcel in pediatric steroid-refractory acute GVHD. If so, what are your recommendations regarding the design of such a trial?

Finally, the committee will be asked later this afternoon to consider the following voting question. Do the available data support the efficacy of remestemcel in pediatric patients with steroid-refractory acute GVHD?

Thank you. That is the end of my presentation, and I will now turn the discussion back to the chair, Dr. Hoffman.

Clarifying Questions to Presenters

DR. HOFFMAN: Thank you very much.

We will now take clarifying questions to the presenters. Please use your hand-raised icon to indicate that you have a question. Please remember to put your hand down after you have asked your question. Please remember to state your name for the record before you speak, and please direct your question to a specific presenter if you can.

It would be helpful to acknowledge the end

of your question with a thank you and end of any follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Dr. Sung?

DR. SUNG: Sorry. I had trouble turning off the mute. Can you guys hear me now?

DR. HOFFMAN: Yes.

DR. SUNG: Anthony Sung, Duke University. This question is for Dr. Baird. On your slide where you were discussing the single-trial requirements for approval, you mentioned demonstrating a clinically meaningful effect and also that confirmation of the results in the second trial would be practically or ethically impossible.

At the same time, I was wondering if you could talk about the FDA approval ruxolitinib, which was approved for steroid-refractory acute GVHD on the basis of a single-arm trial; although, as you know, the REACH1 investigators went on to subsequently conduct a randomized clinical trial, REACH2. I was wondering if there would be lessons

from that setting that could be drawn to this situation.

DR. PRZEPIORKA: Hi. This is Donna Przepiorka. I will take that question.

Thank you, Dr. Sung. We do acknowledge that ruxolitinib was reviewed and approved on the basis of a single-arm trial, and that was for a drug which had additional approvals and a much longer track record of success. We will be looking at every drug individually on the basis of the effectiveness of that drug, in the demonstration of evidence of effectiveness in the clinical trials of the individual drug. We would not be extrapolating any evidence or lack of evidence from approvals of other drugs. Thank you.

DR. SUNG: Sorry. Just to follow up on that, I understand, though, it was a different drug with a different background, but it does strike me as a similar situation in that it was a single-arm trial, and the day 28 overall response rate in that single-arm trial I believe was fairly comparable to the day 28 overall response rate reported here.

Likewise, the control rate that they used was similar to the control rate -- or the historical control rate they used there was similar to the historical controls here. It just seems to me that there should be some consistency in how these studies are analyzed.

DR. PRZEPIORKA: Yes. Thank you very much for your comments. We would not be able -- this BLA is obviously still under review, so we're not at the present time going to be discussing any comparisons of this review versus any other review. But we would certainly be open to hearing from the committee what their Viewpoint is on design of trials and whether or not the design of the trial for remestemcel would be appropriate to test for evidence of efficacy in the pediatric population. Thank you.

DR. HOFFMAN: Thank you.

Dr. Finestone?

DR. FINESTONE: Yes. Can you hear me?

DR. HOFFMAN: Yes.

DR. FINESTONE: I apologize up front for the

naivete of my question, but it's to the manufacturer. In Study 001, it has shown that the subjects are 2 months to 17 years. I was wondering if there is any difference in the respond rates by age.

DR. GROSSMAN: I thank you for that question. We did look at age very specifically.

Can I have slide EF-6 shown, please? As you can see, we looked at those that are over 12 years of age, in adolescents and those younger than 12, and we do not see a difference in the 28-day overall response, 69 percent younger than 12 and 73 percent older than 12.

I also want to address, if I might, the questions that came up before concerning ruxolitinib. I just want to point out something that I think is important, and that is we see a consistent efficacy result in severity of C and D. In that REACH1 study that was alluded to, efficacy in grades C and D was 41 percent. Given the relationship between 28-day overall response and survival that's been established, there is a

considerable difference in what we see in our 28-day overall response.

I wonder if Dr. Kurtzberg can address the high mortality rate in the issue with treating these children.

DR. KURTZBERG: I think it's incredibly impressive that the grade C and D disease patients, who were two-thirds of the patients on the 001 study, had a 69 percent response rate. That is something you typically do not see. It's definitely not seen with any of the currently available off-label agents, and to me, it just emphasizes that this cell product really works.

I don't think you would have noise just in that population. Their clinical course is pretty well described and, really, there's been no therapy in the past 10 years that has changed it. I think what we're seeing with remestemcel is dramatic. Thank you.

DR. HOFFMAN: Thank you. I had --

DR. FINESTONE: I had --

DR. HOFFMAN: -- I'm sorry.

DR. FINESTONE: I did have another question if you don't mind.

DR. HOFFMAN: Sure.

DR. FINESTONE: Could I ask if there has been any identifier between the responders and non-responders? Have you been able to come up with any identification there at all?

DR. GROSSMAN: Yes, we have, and that's based on the biomarker data. In particular, I would like to have Dr. Levine first describe the MAGIC biomarker. And then right after that, I'd like Dr. Itescu to describe our data in the pivotal trial using that biomarker.

Dr. Levine?

DR. LEVINE: Thank you. The MAGIC biomarkers are proteins that are released by the GI damage that's caused by GVHD. We can consider the MAGIC biomarkers' score equivalent of a liquid biopsy, the extensiveness of the GVHD.

DR. GROSSMAN: Dr. Itescu, can you please describe the biomarker data from 001 using the MAGIC biomarker?

DR. ITESCU: If we could have slide MA-7, please? When we looked at the cohort as a whole and measured the MAGIC biomarkers, ST2 is a component, and then the composite on the right, what you see is that starting within the first 28 days of treatment, patients reduce their baseline biomarkers, and then continue to reduce their MBS biomarkers through at least 180 days of follow-up. This indicates the overall healing process of the inflamed gut.

If we could go to slide MA-10, please? When you look at patients by MBS biomarker severity grade, what has been previously published in the three bars to the left is that for those patients who have a baseline severity score above 0.29, the validated score of severity and predictor of death, what you see is that only about 18 to 32 percent of patients would be expected, using best available therapy, to achieve day 28 overall response. In contrast, two-thirds of the patients in our 001 trial had a severity score above 0.29 at baseline, and yet what we see is that 61 percent achieved day

28 overall response, quite substantially higher than each of the three validated cohorts to the left.

Next slide, please, MA-11. We then looked at survival in these cohorts. What is important on the left-hand, three Kaplan-Meiers, those three cohorts, the validation cohorts for the biomarker itself, you see separation between MBS at baseline less than 0.29, which is a higher curve, and MBS greater than 0.29, which is a lower curve in each of the three cohorts.

What you see is that this validated biomarker severity score actually is predictive of very poor survival, so at least 12 months at follow-up, such that at 6 months, day 180, survival of patients with a biomarker MBS score above 0.29 is of the order of 20 to 40 percent.

In contrast, if you look at the Kaplan-Meier on the right, which is data from our phase 3 trial, 001, you see that in fact those patients with a baseline MBS score above 0.29 in blue have a survival at day 180 at 6 months that approximates

60 percent, and it's statistically no different than those patients at low risk, with a lower MBS score at baseline.

This indicates that this treatment has resulted in substantial improvement in survival in those patients at high risk for mortality that would otherwise had been expected to have died.

DR. HOFFMAN: Okay. I had a question for Dr. Grossman. Pardon me if I'm mixing up the terms, but with this 002, or basically the continuation, were the patients receiving the drug during that time or that was observation?

I guess, basically, my question is, the patients that responded to this, at some point you stopped giving it. Does the process simply stop being inflammatory, and things settle down, and the patient then recovers and doesn't require further therapy of the GVHD? Is that what we're -- it's not the field I work in.

DR. GROSSMAN: No, that's absolutely correct. The treatment is a 4-week treatment, 2 infusions per week. Once patients completed 001

and went into 002, they did not receive any other remestemcel treatment. This aligns very closely to the mechanism of action. We have both short-term and long-term effects of these cells, and I'd like to ask Dr. Itescu to discuss the conversion of M1 to M2 macrophages and why we see long-term efficacy and survivability after those 8 infusions.

Dr. Itescu?

DR. ITESCU: Thank you. Yes, this is central and core to the mechanism of action of the cells. The cells are activated using the surface receptors by proinflammatory cytokines, notably TNF alpha.

So through TNF receptor type 1, they're activated when they encounter high levels of TNF, activating cells internally to secrete a number of paracrine factors that modulate multiple arms of the immune system, and particularly cells that are long-lived and that are immunomodulatory, particularly M1 macrophages, which actually produce the inciting inflammatory cytokines, and then modulated to become into macrophages that are

anti-inflammatory and produce high levels of interleukin 10.

That is a primary mechanism by which our cells are able to turn off as damaging inflammatory response. In addition, they activate regulatory T cells, which are also long-lived. Both regulatory T cells and M2 macrophages produce high levels of interleukin 10 and other factors that are immunomodulatory and provide durable and long-term immunomodulation.

It's well established that if you can come to grips with your allogeneic graft within a 6-month period, you can induce long-term tolerance. And here we believe that this is what remestemcel cell does even though the cells are not themselves long-lived.

DR. GROSSMAN: I'd like to add it's also been established that there's that close relationship between 29-day overall response and survival, and we've seen that in 001, and we've also seen that in 275.

DR. HOFFMAN: Dr. Walters?

DR. WALTERS: Yes, thank you. This is Mark Walters. This is for the Mesoblast team. The chief medical officer can direct this to whoever is appropriate.

I was curious. Could you explain or speculate the biological differences of steroid-refractory GVHD in adults and children, or for that matter, steroid-refractory acute GVHD versus newly diagnosed GVHD in terms of the responses you've observed with remestemcel-L?

In particular, what biological properties of the remestemcel-L, with respect to the new manufacturing methodology and heightening potency, is observed or that is purported, and how that addresses these biological differences that might explain the disparity in responses to the therapy. Thank you.

DR. GROSSMAN: Yes. I will ask Dr. Itescu to address this, but I'd like to -- I think you're getting at something very fundamental and very important here.

The way these cells work is they respond to

the inflammatory environment. That's why in steroid-refractory acute GVHD, we're seeing the responses that we're seeing, and these are children who are clearly in a hyper-inflamed state. That's also why in 265 we saw equivalent response, both in the 80s by the way, between those that are on steroids and those on remestemcel because this is a much less severe population.

Now with respect to TNFR1 and the biologic relationship, I'll ask. Dr. Itescu to speak to that relationship.

DR. ITESCU: Sure. Thank you. Could we have slide MA-2, please? I think it's really important to understand the process changes that were performed in 2009. The most important during the streamlining process was a maximal time limit on trypsinization during cell culture.

Trypsinization, if you wait for too long, it results in shearing off of a whole range of surface receptors and molecules, including TNFR1. It is clear that as trypsinization time is shortened, the integrity of the surface of the cell has been

maintained. In fact, as we showed you, 50 percent higher levels of TNF receptors are now routinely being seen on our final product.

How does that relate to the ability of a cell to sense inflammation? By having higher levels of TNFR1, it's able to be activated more efficiently by circulating TNF levels. And what you see here on this slide is that at ranges that span with the final product, you see a dose-dependent relationship between the level of TNFR1 on the surface and the intracellular activation, NF-kappaB, M-CSF, CCL2 or M-CP1.

Therefore, the master regulators or factors that ultimately impact on immunomodulation is dependent on the level of TNFR1, and we believe that we've got a far more potent product now by virtue of the manufacturing process.

DR. GROSSMAN: Thank you. And finally, the differences between adults and children, that's in the literature as well.

(Crosstalk.)

DR. ITESCU: The database suggests there is

no difference.

DR. WALTERS: I was just curious about what those differences were and if you could amplify that in terms of understanding the results of the two trials in adults and children.

DR. GROSSMAN: Yes. I think what we believe is given the older original manufacturing process, that we had a less potent product, which may have accounted for what was seen in those earlier trials. But having said that, in the post hoc analysis of grade, we did see responses versus placebo in the higher grades, and in children, we did see a response in that population as well. But we believe the reason for not meeting the primary had to do with it was a 10-year old study, and it used an older process.

DR. WALTERS: Thanks. No further questions.

DR. HOFFMAN: Dr. Kamani?

DR. KAMANI: Yes. Thanks. This question is for the Mesoblast team, Dr. Grossman. You provided, I believe, post hoc data that shows that the optimization of the manufacturing process

resulted in higher levels of TNF receptor 1, and that perhaps you're intimating that this may have resulted in higher potency of your more recently used products.

Can you amplify on that, and can you tell us whether there are differences in TNF receptor 1 expression in products from different donors and how that will be incorporated into the potency qualification of the final drug product? Thank you.

DR. GROSSMAN: Yes.

DR. HOFFMAN: Wait -- I'm sorry. One second. Let me just interject here. While it's a reasonable question, it's much of what we spent the morning discussing, so I'd like to keep that piece of it brief even though I realize Dr. Kamani wasn't present this morning. I don't want to redo the whole morning.

DR. GROSSMAN: Yes, I appreciate that. Just to keep it brief, what this slide shows, Dr. Kamani, is if you look across the studies, you see that TNFR1 potency increases to the current

322 peak gram per milliliter. And you can see the difference and the improvements in day 28 ORR, as well as day 100 overall survival as the TNFR1 concentration increases.

DR. HOFFMAN: Dr. Kamani, are you ok then?

DR. KAMANI: I guess -- that's ok. I have no more questions.

DR. HOFFMAN: Dr. Halabi?

DR. HALABI: Yes. Susan Halabi. I would appreciate the sponsor today answering the following questions. The first one, there was an analysis conducted where you adjusted for the MBS in predicting your outcome. I did notice that across the three or four different cohorts, the prevalence of patients with high MBS was different.

DR. GROSSMAN: Okay. Is that your question?

DR. HALABI: This is one of them. I also wanted to know the distribution of patients across the different cohorts, not only in the pivotal trial. In terms of distribution, I'm not only talking about age but other characteristics, especially in children. I don't believe I've seen

this data. The last question is I noticed the majority of responses in GVHD001 were partial responses, and I don't know what to make out of it.

Basically, these are my three questions for now. I think the other questions were answered by other people.

DR. GROSSMAN: Sure. I'd like to refer that question to Dr. Levine from MAGIC.

DR. LEVINE: I'm not sure I quite understood the question. This is regarding the proportion of patients with a high biomarker score across the three different studies?

DR. HALABI: Yes. I mean, obviously the numbers are very small. I believe in the 001 study, you had 18, I believe, 29 [indiscernible]. Obviously, you cannot do any [indiscernible] --

DR. LEVINE: I'm sorry. Are you asking for a comparison to the MAGIC data that's been published, the proportion in the MAGIC in our study that we published in 2018, or are you asking in the other remestemcel trials?

DR. HALABI: Yes, in the remestemcel trials.

Again, I do recognize the numbers are very small, but I'm just curious if you have done an analysis.

DR. GROSSMAN: Dr. Levine, I think what we want to get at here is -- what's being asked is that the numbers are small, but maybe you can speak to the validity of the MAGIC biomarker score and what you saw in the data that we presented.

DR. LEVINE: Sure. If you could bring the slide back up that had the 4 Kaplan-Meier curves, what that slide demonstrates, I think, is kind of a really key finding. A high biomarker score, the biomarker score, it measures the extent of disease, and it has a very strong predictive value for non-realized mortality, which in patients with steroid-refractory GVHD is almost always due to the GVHD itself.

What we're seeing here is in three separate cohorts, including validation cohort 2 -- which is exclusively patients who were transplanted in just the year 2016, so it's very contemporaneous -- a high biomarker score correlates with these blue curves, correlates with an exceptionally low

probability of survival.

Although the numbers are small, it's still 18 patients with a high biomarker score in these children from Study 001, who have survival that is exceptionally good. Their survival appears to be very similar to patients with a low biomarker score, or for that matter, patients who have steroid-responsive GVHD.

I don't know about the proportion of patients with a high biomarker score in the other studies, but certainly I think this data speaks very compellingly to the effectiveness of the treatment in terms of reversing the severity of the damage. That was also demonstrated in a figure that was shown earlier, that showed the steady decline in the biomarker score following treatments with the remestemcel. That would be my response.

DR. GROSSMAN: Thank you.

I'd like to make a comment about the clinical response in survivability, and I'd like to bring this to Dr. Kurtzberg to give her comment as well. We see across our studies, whether it's the

cohort from 280 of pediatrics or the most difficult patients in 275 or 001, a consistency in 28-day overall response and survival. Really, what we're talking about here is survival, and the MAGIC biomarkers are sort of comporting biologically to that.

But getting back to the patient's themselves, Dr. Kurtzberg, can you speak to the survivability currently and what it means to have this kind of difference that was just described by Dr. Levine?

DR. KURTZBERG: Sure. The most severe patients who are a grade C and D or have the high MBS in the MAGIC study are patients who are going to have survivals generally below 20 percent by year. These are patients who have a very dismal course, where they get treated with multiple different agents and don't respond, and ultimately develop multiple opportunistic infections because their immune system has been destroyed or severely damaged, and then multi-system organ failure.

The difference with remestemcel is that it

essentially converts these patients to look like the steroid responders, if you go back to the MacMillan studies that I showed one slide on at the end of my talk, or the low-risk MAGIC patients, or even steroid responders, if you go back to the ones that have acute GVHD. So you're essentially converting a population of patients who are likely to die after a dismal medical course to survivors who are healthy and go on to recover from the transplant and live productive lives. So it's a dramatic difference.

Yes, this shows you that slide that I showed at the end of the clinical talk, of the red line, which steroid non-responders are the group of patients that have been treated with remestemcel and whom now, on the right, have a 69 percent, 180-day survival, which correlates with overall survival because this disease is acute and early. And if you convert it, as Dr. Itescu mentioned, then you change the outcome. And it's a permanent change; it's not a 54-day response. It's a multiple-year response without recurrence of

disease. So thank you.

DR. HALABI: Thank you. Though, I do have a concern because for this Kaplan-Meier curve, you have about 25 patients with missing data, if I understand this correctly, and I'm wondering why their MBS score was missing. It's almost about 46 percent of the patients in the 001 study.

DR. GROSSMAN: Not all of them had the biomarkers completed. Jack Hayes, maybe you can speak specifically, quickly, and how many didn't.

MR. HAYES: Jack Hayes, biometrics, Mesoblast. The biomarker study in GVHD001 was a substudy. Not all the patients consented to have the samples taken. Approximately 30 patients had data, and the 29 that are shown in this analysis had the data required to do this analysis. But the subgroup of patients that participated in this study are represented at the overall patient population in the study.

DR. GROSSMAN: The strength of the biomarkers and the consistency that we see -- of course, we're going to continue to do this,

especially in the adult study that's planned. So we'll continue to accumulate more data, but the directionality of the biomarkers that we're getting is very important, and we're going to continue to study that as well.

DR. HALABI: Okay. Regarding the other questions, do you have data on the patient characteristics, specifically children across the same cohort? I don't believe I've seen that.

DR. GROSSMAN: Yes, we do have characteristics in Study 001 across the children.

Can I have ES-61 shown, please? This is breaking down by age, gender, and race, and you can see that across the demographic characteristics, we see consistency of response by age rate differences as well as males respond a little bit more than females. There are only 19 patients in the female cohort, and by race.

DR. HALABI: It would have been useful if we would have access to the 95 percent confidence interval, but I guess this was not calculated across these groups.

DR. GROSSMAN: Not across these groups.

DR. HALABI: Okay. Thank you.

DR. HOFFMAN: Dr. Cheng?

DR. CHENG: Thanks, Dr. Hoffman.

Jon Cheng, industry rep. I had a question, actually, for Dr. Kurtzberg. I think I heard you say that a randomized phase 3 trial could not be done in this patient population, that you or your colleagues probably would not be willing to randomize patients.

I was wondering if maybe you could expand on that because although there are no standard therapies approved, there are therapies that seem to have a response to the 28 day. So I wasn't sure why there is a loss of clinical equipoise. I wasn't sure if it's the mortality or is it the response and type of responses, because the best available therapy does have some activity even though they're not approved.

Can you please expand on that?

DR. GROSSMAN: Dr. Kurtzberg?

DR. KURTZBERG: Sure. Myself and my

colleagues would not be interested in participating in a randomized trial of remestemcel in this patient population because they're already quite sick, and everyone is aware of the rapid downhill course they can take. And taking the risk that they would receive a placebo over a month really takes a risk that they will ultimately die when they didn't have to.

Remestemcel is very well tolerated. It has basically a 70 percent response rate, and it is a better therapy to use than the currently available either not approved for children over 12 or one agent that is approved for children over 12.

The reasons for that are many. One, remestemcel doesn't have overlapping toxicities with other agents that are required to be used to maintain a child post-transplant. So children are on multiple agents that are being given for infections with prophylaxis and other causes that are nephrotoxic and also sometimes immunosuppressive. The beauty of remestemcel is you can add it into the mix without causing other

overlapping toxicities.

I noted that that FDA presenter talked about alemtuzumab, or Campath, as an agent that has a 28-day response rate, which was higher than I'm familiar with but accepting that. You need to realize that alemtuzumab causes viral reactivation because of its long-standing immunosuppression. It delays B- and T-cell recovery, sometimes for 6 to 12 months, and it's typically associated with the occurrence of multiple opportunistic infections. So it is a totally not benign therapy.

In contrast, remestemcel really has a very favorable safety profile, given intravenously, which in my view as a pediatrician is an advantage because you know it gets in, and you don't have to worry about delivery in young kids or children with GI disease. It's got a better response rate of anything available that's approved for GVHD and/or use off label for GVHD. Thank you.

DR. GROSSMAN: I'd like to also add something about alemtuzumab about that study. It's a study by Khandelwal, and it was quoted as having

67 percent 28-day overall response. It actually was not 67 percent. Alemtuzumab was used as an experimental agent, and at 28 days the response was 47 percent. If one did not respond to alemtuzumab, then they were given a third-line or fourth-line treatment, and it's only when they went down multiple lines of treatment that they started to get differences.

In fact, the alemtuzumab study comports very closely with the top three in terms of the expectation of steroid-refractory acute GVHD, standard-of-care type treatments, 34 percent, 36 percent, 43 percent, and 47 percent, and that aligns with our 45 percent null hypothesis.

DR. CHENG: Thank you.

DR. HOFFMAN: Dr. Klinker, were you just going to address that answer or shall I come back to you with a different question?

DR. KLINKER: Yes. This is Matt Klinker. It was not directly related to that last question, so if you could just come back to me before we end the question and answer session, that would be

great.

DR. HOFFMAN: Dr. Sung, did you have a question?

DR. SUNG: I did. Regarding the duration of response and survivability, could both the sponsors as well as the FDA discuss further what happened to these patients after they responded? Were they able to successfully stop steroids?

I noted in the FDA briefing document that they talked about flares in GVHD, which often can occur if steroids are titrated, and the discussion just alluded to oftentimes we'll need to add a third or fourth agent. So while survival may be excellent in these patients, how many of them, when they tried to taper their steroids, they flared up and they had to go on a third or a fourth agent, which potentially could be responsible for the improved survival?

DR. GROSSMAN: Yes. We in fact had significant durability. Let me first address steroids. We had a steroid taper that was recommended and followed. If someone had an

overall response for 3 to 5 days following a minimum of 2 doses of remestemcel at any time, they could reduce by 10 percent per week, not exceeding 25 percent per week the steroids. Nearly half of those patients successfully tapered off steroids by 180 days. So many of them, if not most, were able to taper off of their steroid by day 180.

With respect to flare, if someone within post the 4-week treatment who was a CR, who then went back to maybe a PR, they were given another 4 weeks of treatment. And of those patients -- can I have slide EF-10, please? So 16 patients, as you see here, achieved complete response at day 28. Six of them post-day 28 received flare therapy, and of those six who received flare, which was the addition of remestemcel, three went back to complete response, two were partial response, and one had a mixed response at day 100.

Generally speaking, we also see durability of response. Can I have the slide of durability, please? There was a slide that just disappeared. Can I have the slide on durability, please? Thank

you. Can we show this slide? Thank you.

At day 28, 70 percent, or 38 out of the 54 patients, were overall responders, and we know that that's correlated to survival. At day 100, 89 percent, or 34 of the 38 patients, remains in OR. In terms of survival durability, 40 of the patients who went into the second half -- who went into 002, 40 patients, or 74 percent of the 54, were alive at day 100, and 37 of the 40, or 93 percent, were alive. So we're seeing sustainability and durability of the response.

In terms of the analyses that were done by us, by the FDA who did two analyses, the one that was noted was obviously the most conservative, and that analysis that had 54 days median was -- if there was any change, so if bilirubin went up by 0.1 for example, that would have met that criteria.

So even in the most conservative analysis, we see a 54-day median. In those that take clinical responses into consideration, the one at the bottom that the FDA completed, we're seeing 111 days. So I think we're in agreement with the

FDA that we're seeing durability of response to remestemcel.

DR. SUNG: If I have heard you correctly, it sounded like of the 38 patients who responded, you said only half of them were able to stop their steroids. So the other half it sounds like either needed to continue steroids or receive additional therapies.

DR. GROSSMAN: Did not receive additional therapy. Only 4 patients -- let me clarify that. In terms of the steroids, virtually half of them were off steroid; the others remained. There were only 2 patients who had an increase in steroid and there were only 4 patients who had an additional medication to day 180.

DR. SUNG: Do you know what happened beyond day 180? Again, I'm just wondering how well does this actually work, if this may be a short duration and then eventually they need to go on to another agent, or if you're not able to get them off steroids, what happens to them, because no one wants to be on steroids.

DR. GROSSMAN: Yes. I'd like to ask. Dr. Kurtzberg to discuss her experiences, especially even beyond 180 days and the steroid changes.

Dr. Kurtzberg?

DR. KURTZBERG: Yes. Thank you. So I've treated over 30 patients with remestemcel for acute steroid-refractory GVHD, and most of the patients I've treated, except those on Study 001, were also refractory to multiple other agents.

The patients that I treated, in general, responded to remestemcel, were able to wean steroids, and did not require the addition of other therapies. If they were responders, they had durable responses and are long-term survivors unless they relapsed from their underlying disease as a cause of transplant failure.

I think that it's really important to note that when you treat a child with GVHD and you're tapering steroids, you do it slowly because you gain more, in my opinion and my experience, by going slow and being able to maintain the gains of

reduction in dose, then rapidly gaining and then having to go back up.

So even for the children in the 001 study who may not have weaned off steroids completely by day 100, they continued to wean and were able to come off steroids in the subsequent months. And none of these children that I treated required the addition of other anti-GVHD drugs, they did not relapse, and they sustained a durable response in a very good performance status.

So I can speak to the durability of this therapy, and I can also say that it results in more of a durable response than most of the other drugs that we try. Thank you.

DR. HOFFMAN: Dr. Klinker?

DR. KLINKER: Thanks for the opportunity to bring up one other issue that we talked about earlier. I'm the primary CMC reviewer, and there was some discussion earlier in this Q&A session about the potency assay and about control of the product. We discussed this in the morning, but I just wanted to clarify and reiterate FDA's position

on the utility of that potency assay.

The applicant has discussed the manufacturing changes made before the 001 study was conducted, that those manufacturing changes have made a product that's more potent and have used that TNFR1 assay to justify that claim.

I wanted to clarify that, based on the analyses that were in the briefing document, the associations that they showed from that pool analysis of those three studies is difficult to interpret because of the different study populations and the concomitant medications, and the fact that the significance of this connection between potency and clinical effectiveness was not observed when they looked at just the 001 study.

I wanted to also point out that while the TNFR1 levels are increased using the modern manufacturing process, the clinical effect, at least in the pediatric population, the applicant is saying that that is consistent. I wanted to just clarify that. There are still some questions about whether that potency assay is really getting to and

effectively measuring something that is associated with the clinical effectiveness.

DR. GROSSMAN: Dr. Itescu, can you address some of those issues, please?

(No response.)

DR. GROSSMAN: Dr. Itescu, are you on mute?

DR. ITESCU: Yes. I'm sorry. I was on mute.

Look, the single best way to evaluate the value of a potency marker on a product's ability to impact on clinical outcomes is to do it in large numbers of patients and have a substantial variability in that market in order to be able to detect relationships to survival, and we've done that across three trials over a 10-year period with outcomes relating to survival, where substantial improvements and changes were made in defined periods.

What we see is when you look at old process versus new process -- and if we could bring up MA-29, please, slide MA-29. What you see across trials is that that those patients who received the

optimized process have had a substantial improvement in survival, on that same slide, with those who received the original process. That's highly significant, and you can only see that when you have a lot of patients.

To account for the cross-study differences, look at the panel on the right, which takes just one single study, EAP 275, in only patients who got a single product lot, so you can specifically relate the lot TNFR1 level with outcomes. Again, what you're seeing here within one clinical trial is a significant relationship between the older product and the newer optimized product in survival.

This is a correlation. It relates to the potency that we have in place, and we certainly, in terms of the phase 3 trial itself that we just completed, are using a product that has a 50 percent higher level than the original product, and its survival is identical almost to what you're seeing there in the blue line, where the center [indiscernible] was using a different trial.

The lack of variability is the strength of the manufacturing process. The 50 percent higher level of TNFR1 expression is a strength of the manufacturing process. So the only way to show a relationship is when you have a high degree of variability, and we have worked hard to have a process that has a very low variability and a high level of expression in the product that can be used and manufactured with locked-in, repeated donors in the current manufacturing process.

DR. GROSSMAN: I'd like to add one other thing, and that is, again, to come back clinically. We learned a lot over the last decade from these trials starting with 265. That's not an area of unmet need for us because steroids work reasonably well as remestemcel did in the milder patient.

In 280, we learned that there was a signal in pediatrics. We learned that severity did mean something. And then as we moved into 275 and the product improved, we learned that severe patients, the most difficult patients, responded, and this is, of course, on top of several therapies. From

that we learned that it's pediatrics where the unmet need was probably the greatest. There was no treatment younger than 12 where patients die, and that's why we designed, with the FDA, 001 to remove the confounding of additional treatments in the first 28 days.

Dr. Kurtzberg, you may want to comment on that as well. I think it's brilliant.

DR. KURTZBERG: I think it's really important to visualize what a patient is like with severe, acute steroid-refractory GVHD. There are children who have rashes that itch and burn, who can't sleep, and who are extremely irritable. Their children end up vomiting and bloody diarrhea, and can't maintain electrolytes, and have to be on continuous IV fluids in port.

There are children whose nutrition suffers. And don't forget that in growing children, even a few weeks of poor nutrition can have long-term consequences. So they're fed with TPN, which is only partially successful, particularly in light of having to maintain electrolyte balance, and they

are unhappy, uncomfortable, suffering, in pain, and unable to do normal activities of a day or even play in the hospital play group.

It's not an option to not continue to try to help them and continue to try to treat their disease and alleviate their symptoms. So although the standard notion of a randomized placebo-controlled design sounds good on paper, when you have an acutely ill suffering child in front of you, it's not ok. And when you have a therapy you know has a 70 percent chance of helping them, you want to use that therapy, and that's the situation we're in now. Thank you.

DR. HOFFMAN: Alright. Thank you. We're going to take a 10-minute break now. Panel members, please remember that there should be no discussion of the meeting topic with anyone during the break, and we will resume at 3:35 with the open public hearing. Thank you.

(Whereupon, at 3:26 p.m., a recess was taken.)

DR. HOFFMAN: I think we're back on the

record. Before we do the open public hearing portion, was there one last question that you had, Dr. Sung?

DR. SUNG: Yes, I did. This is Anthony Sung, and this question is for Dr. Levine.

Going back to the MAGIC biomarker paper, your Blood 2018 paper where I believe the test and validation cohorts for the Kaplan-Meier curves are derived, I noted that the median age was 51, 49, and 48. While those cohorts did include children, I wonder what is the MAGIC marker profiles in children, as that may be a more appropriate comparison to the GVHD001 study data than the entire MAGIC cohort.

DR. LEVINE: Sure. It's identical. That data was presented in an abstract form. We've tested the biomarkers in 194 children at the start of GVHD, and we also have validated the biomarker scores, the response biomarker in children, as well as the predictive prior in asymptomatic children. That data has been presented in abstract form. It will also be presented at EBMT, and the paper will

soon be submitted.

DR. SUNG: Thank you.

Open Public Hearing

DR. HOFFMAN: Okay. We're going to begin the open public hearing session.

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

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

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

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

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

Speaker number 1, your audio is connected now. Will speaker number 1 begin and introduce

yourself? Please state your name and any organization you're representing for the record.

MS. BRADLEY: Good afternoon. My name is Allyson Bradley, and I do not have any financial ties to anyone involved in this hearing. First, I would like to thank you for allowing me to speak today. This is very near and dear to my heart. If it were different times, I would have purchased the plane ticket and come to see you in person.

Our son Aiden was diagnosed with leukemia June 28, 2018, right before the starting of his senior year in high school. For six months, the doctors tried regular chemotherapy protocol, but to no avail. We then scheduled his bone marrow transplant for February 22, 2019. His donor is from Germany, and she is a 12 out of 12 match along with the same blood type. The transplant went well, and he was released from UCSF on April 4th.

The doctors had talked to us about hoping Aiden would get a little GVHD. They said it would be a positive thing but no more than a little. On April 15th, he started throwing up and having

diarrhea, which became increasingly worse over the next few days. We had a regular checkup and infusion appointment on Thursday, April 18th. The doctors took one look at him and admitted him immediately to the BMT oncology floor.

By Friday evening, they were sure he had severe GVHD and it had attacked his gut. There was no lining left to hold anything inside of him. He was on a TPN IV for three weeks with nothing else to eat and only ice chips to suck on.

Dr. Kharbanda went into action on Saturday. She told us UCSF had been part of a trial with the mesenchymal cells and they were our best hope.

By Thursday, April 25th, Aiden received his first round of cells. She moved mountains. Dr. Kharbanda got the FDA, Mesoblast, and the board of UCSF all to agree and approve the allocation of the mesenchymal cells. In the meantime, the doctors were trying regular protocol, which included high doses of steroids, which have horrible side effects. The side effect Aiden developed was avascular necrosis in his knees,

which is a chronic ailment that he will have to deal with for the rest of his life. It was the mesenchymal cells that slowed and eventually helped Aiden's gut heal with no adverse effect.

He went from being the starting wide receiver on his football team at 170 pounds to an 111-pound young man on May 16th. Without amazing doctors like Dr. Kharbanda, Aiden may not have survived or survived a horrible, long-term existing issue. Not every child will be lucky enough to have a Dr. Kharbanda in their life, but they should be lucky enough to receive cells when they need them. We were blessed to be in the right place at the right time. We are, and will always be, grateful to Dr. Kharbanda, her team, Mesoblast, and UCSF for moving these mountains.

Aiden's T cells are fully functioning and he is now cancer-free. Thank you very much for your time and your consideration today.

DR. HOFFMAN: Thank you.

Speaker number 2, your audio is connected now. Will speaker number 2 begin and introduce

yourself? Please state your name and any organization you're representing for the record.

MS. BAZAN: Hello. My name is Mercedes. I have no financial ties to anybody or any organization either. Again, good afternoon. I want to thank the FDA for giving me the time to share my family's experience dealing with GVHD.

I'm the mother of Liam and Audrey. Liam, my youngest, was diagnosed with the hemophagocytic lymphohistiocytosis with CNS involvement back in 2011 when he was a few weeks old. That diagnosis eventually led us to the bone marrow transplant when Liam was only 6 months old. We spent several months at the oncology, hematology, and bone marrow transplant unit at Morgan Stanley Children's Hospital at New York Presbyterian.

Unfortunately, there was a straight line of complications before, during, and after Liam's transplant. He didn't get completely well before he got sick again following chemotherapy and conditioning from the bone marrow transplant. He received his bone marrow transplant in September

2011. After transplant and after engraftment, he developed GVHD grade 2 and 3 in his skin, liver, and mostly in the GI tract.

Within four months of his transplant, Liam was already receiving high doses of steroids along with other immunosuppresant medications. His steroids were at such a high dose that they started to affect other parts of his body, and doctors said that there was no room to increase the dose without becoming dangerously harmful to his body.

I didn't have many options because there were no other options. So the medical team decided or suggested to try the mesenchymal cells and the treatment remestemcel, a different type of stem cell. I was very fearful of the consequences or side effects, but, again, I had no other choices for my son. Later I realized it really helped, and it was a great decision.

Liam's treatment consisted of 2 cycles of that therapy, and by the second cycle, I realized that there was a significant improvement and not just in blood work; I could see it physically in

him. I was able to see on my own that he got better emotionally and physically. I noticed he was in less pain and in better spirits.

I cannot tell you how important this is for a parent. I have seen him go through so much stuff during the time of treatment, with pain, and seizures, and vomiting, being in a coma, life support, among other things before, pre- and post-transplant. We were able to wean him off immunosuppresant medication when he was around 3 and a half years old, and then he is considered in remission. The only side effect of his treatment, he has sensorineural hearing loss.

Liam is a now 9-year-old little boy who, really, you cannot tell anything happened to him where he has gone through so much. He went through chemotherapy, bone marrow transplant, probably around 20 surgeries, and he looks really healthy and really handsome. Liam, this really makes [indiscernible], but I really wish my happy-ending story to many families.

I want to share my story because this kind

of treatment and after transplant was very helpful for my family. It worked well on my child, and it's good to have approved options along with the data to support it so that parents can make informed choices about their children's treatment. Thank you very much, everyone, and stay safe in this difficult time.

DR. HOFFMAN: Thank you.

Speaker number 3, your audio is connected now. Speaker number 3, please begin and introduce yourself, and state your name and any organization you're representing for the record.

MR. HARRISON: Hi. My name is Ivan Harrison. I'm just confirming I do not have any financial relationships. I would first like to thank the FDA advisory committee for giving me this opportunity to speak. I wanted to speak today to share the story of my family. I particularly wanted to share the story of my oldest daughter who is currently 17 years old.

At her young age of 17, my daughter is already a four-time cancer survivor. When my

daughter was only 2 years old in October 2005, she was first diagnosed with acute lymphoblastic leukemia. She started her chemotherapy treatments. We live in Chicago, and she started them nearby our home. But unfortunately, two years later in November 2007, my daughter relapsed prior to completing her chemotherapy treatment regimen. Since she relapsed prior to completing her full treatment, her oncologist at the time recommended that she have a bone marrow transplant.

We chose to do the bone marrow transplant at Children's Hospital of Wisconsin. It's a far distance, but when we did the research, that seemed to be the best place to do it in our area, so we did that. She had the bone marrow transplant in March of 2008 at the age of 4. It was a 9 out of 10 match, an unrelated donor. Unfortunately, a year later, in March of 2009, her doctors found some abnormal cells, monosomy 7 cells. My daughter was diagnosed with myelodysplastic syndrome, which is kind of an early sign of relapse. So as a result, her oncologist felt that she was going to

require a second bone marrow transplant.

For the second bone marrow transplant, they did try to reach out to the previous donor, but the donor was not available, so we did have to identify an alternative donor. For her second bone marrow transplant, which she had in May of 2009 at the age of 5, it was a 5 out of 6 unrelated umbilical cord blood donor.

After my daughter had the second bone marrow transplant, she developed really, really severe graft-versus-host disease. Her skin was literally peeling. Her intestines were hemorrhaging quite a bit. At the time, she was in the hospital, so she was wearing pull-ups. We were changing her pull-ups frequently, at least hourly, and the pull-ups would all be saturated with blood.

We were very scared, as were her doctors. Needless to say, my daughter ended up in the ICU. The doctors tried everything that they could, whatever they could, to try to address the internal bleeding and the GVHD, however, nothing seemed to work. Nothing that they tried was working.

Finally, one of the doctors talked to us about the possibility of trying what they explained to us was mesenchymal cells. It was an experimental treatment that was not yet FDA approved, but they explained to us that it could be used in her case under compassionate use since there were no other options available to her. We were scared with even hearing this, that this was an experimental treatment, not knowing anything about it, but we didn't feel that we had any other choice. So we went ahead and agreed for her to try the mesenchymal cells.

She had the treatment, and to our surprise, and we were extremely excited about this, she responded very well, very positively. Her bleeding stopped, and my daughter was able to get out of the ICU, and she was almost even at her baseline, just in time for her 6th birthday in June 2009.

Since she's had the second bone marrow transplant and the mesenchymal cells in May of 2009, she has remained in remission from leukemia. Unfortunately, she did develop a tumor on her

kidney in 2017 and was diagnosed with kidney cancer. So she did have to have a partial nephrectomy to remove the tumor, but as of today she is now and continues to be in remission from all cancers.

It is my sincere hope that given the stories of children like my daughter, that this extremely important treatment will be approved and made more readily available. We saw firsthand how effective it was 11 years ago. My daughter has continued to grow and thrive 11 years later, and I'm convinced that we have the mesenchymal cells to thank for that. And we're also very appreciative and grateful for all the staff at Children's Hospital of Wisconsin, particularly. Dr. Margolis and Dr. Talano, who talked to us and gave us this option that basically saved my daughter's life.

So in closing, I just like to thank the committee again for allowing me to speak and to share my daughter's story. Thank you.

DR. HOFFMAN: Thank you.

Speaker number 4, your audio is connected

now. Will speaker number 4 begin and introduce yourself? Please state your name and any organization you're representing for the record.

MS. COWDEN: Good afternoon. I sincerely appreciate the opportunity to speak with you today. My name is Meredith Cowden, and before I begin, I would like to state that I do not have any financial disclosures to make. I believe that I'm presented with a rare opportunity to speak as a patient with you today. I have GVHD, and as such, I would like to provide you with information regarding my experience throughout the treatment process and offer insight.

To start. I was 19 years old when I was diagnosed with AML, so not quite pediatric but also not quite adult. I started out on the pediatric unit for my initial treatment of chemotherapy without radiation, and then moved to the adult unit for my bone marrow transplant, which took place on September 12, 2001. My oldest sister was a perfect match, and I did very well directly following the transplant, and I was able to go home on

September 27th in time for my birthday on October 3rd, which was my goal, so I was very happy about that.

But it was at this time when I started to develop a burning rash on my feet and hands, which spread to my torso and back. I also struggled with loss of appetite, nausea, and vomiting. I was diagnosed with acute GVHD on October 15, 2001. On October 16th of 2001, I started taking prednisone, and I haven't stopped taking it since then. Between 2001 and today, I have developed several medical conditions, either secondary to the use of steroids or GVHD. I've been on varying doses of prednisone along with several other immunosuppressive medications.

To give a brief overview of my medical journey, I quickly developed a avascular necrosis and osteoporosis due to the high doses of steroids. I went into ovarian failure and had early onset menopause at the age of 21. In 2003, I developed ocular GVHD. In 2004, I developed vaginal GVHD. In 2005, I developed hypercalcemia and

polymyositis, and due to the increase in prednisone, I also developed diabetes.

The hypercalcemia and polymyositis put me back in the hospital for treatments. Peripheral neuropathy was identified in 2006. It was at this time that I also had cataract surgery. In 2007, I was diagnosed with bronchiolitis obliterans. In 2008, I was lucky enough to be able to visit the NCI at their chronic graft-versus-host disease clinic, and I participated in a historical study of the disease. I managed to do well for quite some time following my visit to the NCI.

In 2012, I had a recurrence of GVHD manifesting as polymyositis. This also occurred in 2015 and most recently in February of this year. Last year, I was diagnosed with stage 3 chronic kidney disease due to the medications that I've taken for the last 19 years.

All of this is only speaking to the physical manifestations, not the mental or emotional impact, which is quite profound and requires just as much attention as the physical consequences and

comorbidities. In 2007, six years after my transplant due to my family's overall frustration and lack of our ability to find information surrounding GVHD and ways of coping with the symptoms, my family founded a nonprofit organization in my name to help provide education and further the treatment of GVHD. The foundation has held 10 symposia centered around research and treatment of GVHD, combining both medical professionals and patients to create a meaningful discussion. This October will be the 11th symposium.

While I deeply value what I've learned from my journey so far, I do wonder what my life would have been like if none of these things that I've talked about had happened. What if I didn't have all of these health conditions? I'm not old, but I'm tired, and I know that the impact of this will continue for the rest of my life. If it's possible to prevent all of this for someone else, which it seems to me that it may be, then I ask please help to do that.

I was young when I developed GVHD, but I was not as young as many who will develop it, and whoever they are, they deserve the opportunity to avoid all that can happen with GVHD. I know that I'm luckier than others in respect to the disease, and I hope that there will be others who are luckier still. It seems to me that this may provide that chance for someone. Thank you so much.

DR. HOFFMAN: Thank you.

Speaker number 5, your audio is connected now. Will speaker number 5 begin and introduce yourself? Please state your name and any organization you're representing for the record.

DR. WIEDL: Thank you for the opportunity to speak this afternoon. My name is Christina Wiedl, and I'm a pediatric transplant physician at VCU. I do not have any disclosures.

Steroid-refractory GVH is one of the most feared complications of stem cell transplant with a mortality rate of up to 80 percent. The suffering refractory GVH brings is hard for anyone to

imagine: weeks of severe bloody diarrhea and abdominal pain. Many patients are incontinent and can develop skin breakdown or can develop severe skin changes as if they had been severely burned. Liver dysfunction further complicates an already very difficult situation.

Unfortunately, dozens of treatment modalities have been tried for this scenario, but fewer reverse the disease process course and most increase immunosuppression, which further increases the risk of infection for these already very compromised patients. Many patients die from infectious complications after weeks of suffering. Mesenchymal stem cells offer the opportunity to treat the underlying disease process without adding significant immunosuppression.

I have seen the impact of the treatment firsthand. NW was a 10-year-old male with Warsaw breakage syndrome and ITK deficiency. These two conditions not only increase the risk of malignancy but also carry with them a higher risk of complications during the stem cell transplant

process. When he initially presented to our care, he was presenting with EBV driven lymphoma and unfortunately was found to have multiple infectious complications at the time of presentation, as well as interstitial lung disease.

He underwent a fully matched unrelated donor transplant in the spring of 2017 with ATG and methotrexate and tacrolimus for GVH prophylaxis. His early transplant course was complicated by rhino enterovirus infection, and he developed severe engraftment syndrome with high fevers, hypoxia, and capillary leak by day-plus 10 post-transplant.

Thankfully, he responded rapidly to a short course of steroids and was rapidly weaned off. But then, unfortunately, by day 17 post-transplant, he started to have increasing volume of diarrhea and was again started on high doses of steroids. He initially had a brief response, but by day 25, his LFTs started to rise and he developed a diffuse skin rash.

By day 28, his symptoms had markedly

worsened and he was having severe abdominal pain. He was started on a PCA. He had been NPO for over a week at that point, meaning he was not allowed to eat anything. He had had high-dose steroids and frequent transfusions. As you've heard from prior families talking, the bloody diarrhea is extremely severe, and you're oftentimes transfusing these patients multiple times a day, trying to keep up with their blood loss. He was on therapeutic tacrolimus, but, unfortunately, nothing was helping him.

This is the clinical scenario that every transplant physician dreads, a child with refractory early GVH, pre-existing immunodeficiencies, a prior history of infections, and it's a scenario when you have to have heartbreaking conversations with the family about the potential prognosis in the situation, and that every treatment you offer potentially carries an increased risk of death from complications from the treatment itself.

Given his refractory GVH, he was enrolled on

the Mesoblast study and started treatment by day-plus 33. He had a remarkable response with stool volumes that rapidly decreased from more than 30 cc's per kilogram per day with severe refractory abdominal pain down to less than 10 cc's per kilogram per day by day-plus 40. His skin rash and LFTs also improved, and he was back to the adorable smiling child that we had all grown to love. His methylprednisolone was gradually weaned and he continued to clinically improve. He was able to be weaned off his PCA and eventually his enteral feeds were also able to be increased.

He was discharged home and completed the continuation phase of the mesenchymal stem cell study. I am now happy to say that he has three years post-transplant off of all immunosuppression. He is back to school -- well, back to school before the pandemic that is -- and he spends his time with his two sisters and playing Avengers. Thank you for the opportunity to speak today.

Questions to the Committee and Discussion

DR. HOFFMAN: Thank you.

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

We'll now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

May I ask someone from the FDA to read the first discussion question, please?

DR. GEORGE: This is Bindu George. I'm happy to read the question. Are you able to hear me?

DR. HOFFMAN: Yes.

DR. GEORGE: Thank you.

The first discussion question is, limitations of the single-arm study design of

MSB-GVHD001 include, but are not necessarily limited to the following: a) limited ability to ensure that baseline prognostic factors, both known and unknown, were similar in MSB-GVHD001 and the applicant's control; b) limited ability to ensure that unknown and known potential confounding factors -- example, additional salvage therapies for treatment of acute GVHD -- that could influence efficacy outcomes was similar in MSB-GVHD001 and the historical control group; c) potential bias with selection of patient's subjective nature of the assessments to score aGVHD; d) the adequacy of the historical data to support a null hypothesis.

Please discuss the strengths and weaknesses of the design of Study MSB-GVHD001. Thank you.

DR. HOFFMAN: Okay. If there are no questions or comments concerning the wording of the question, we'll now open the question to discussion among the committee.

I want to apologize in advance. Dr. Kamani, I think I cut you short earlier, so I want to be sure you do have a chance to speak. Also,

Dr. Bunin we haven't heard from and certainly would like to hear your thoughts as well. So please let's discuss the strengths and weaknesses of this 001 study.

Dr. Bunin, you have your hand up. Good.

DR. BUNIN: I do. This is Nancy Bunin, Children's Hospital Philadelphia. Regarding the 001 study, I had an issue with eligibility regarding the definition of steroid-refractory GVHD as it relates to study entry, with one defined as progression within 3 days or no improvement within 7 days of consecutive treatment of 2 mg of kilo of methylpred.

Well, 3 days is not much time to see an effect from steroids, so I would be interested to know what percentage of patients were defined as progression with 3 days versus those who had I think the more accepted definition of steroid refractory, which is 7 days of therapy; and also, some concerns regarding enrollment and cherry-picking, which is going to occur with a study like this.

DR. HOFFMAN: Okay. I think we probably need to ask someone from the sponsor to answer your question; Dr. Grossman, probably.

DR. GROSSMAN: Yes. We can get that data to see what number enrolled in 3 days and what number enrolled to 7. So I'm going to ask the team to get that while the discussion is going on, and we'll come back.

DR. HOFFMAN: Okay.

DR. BUNIN: Okay. Thank you.

DR. HOFFMAN: Dr. Garcia?

DR. GARCIA: Thank you, Dr. Hoffman.

Jorge Garcia. Obviously, when you look here at our discussion from the morning session as to the MOA and the biology of this agent and you try to add that on top of the clinical data, I have to admit that -- I have to be simple when I think of this. This is a very simple, straightforward phase 2 trial. It's just very hard to be able to actually throw, really, big conclusions, especially with the phase 2 nature of the data and the sample size of this trial; 54 patients may be a large

anecdote at best.

I do see, however, that when you look at drug development of this compound, with Study 280 -- Protocol 280, rather -- we've been actually 15 years plus working with this agent. I do recognize and I appreciate the input from the applicant stating that perhaps the discrepancies noted between 2006 and 2009 relate to manufacturing improvement and so on, and I have to believe that may be the case with evolution in technology.

Having said that, I think there is a compelling argument that this is really an orphan disease state, if you will, and it is really an unmet clinical need. So looking at that and looking at 16 years, roughly, or 15 years of safety data, to me it's somewhat compelling that when you look at the safety, the lack of overlapping AEs, and what Dr. Kurtzberg mentioned in her clinical experience, it's quite telling to me.

Again, I don't know if we're going to be able to actually really get a better trial, to be honest with you, and maybe in addition of this

comment, perhaps if the FDA can clarify that there's such a thing as if this agent was to be approved for label, if there would be any postmarketing commitment that the FDA, the agency, would require from the company, from the sponsor.

It's hard for me to believe that with the existing data in the adult patient population, in the recent advisory board, they were counseled to do a large adult patient population trial when, in fact, in these days, the efficacy data noted in the pediatric population, I will be probably far more interested in expanding the clinical experience in the pediatric patient population.

Lastly, it is very telling that if you hear an expert in the field stating the fact that you wouldn't be able to randomize a patient, in the case of GVHD, to anything else outside an active agent, as imperfect as those active agents are, it would be very hard for us to -- at least in my mind, I'm trying to think as to what other trial I can require to be able to actually really assess better efficacy, if you will, in the context of the

current applications.

DR. HOFFMAN: Well, your point does get to the second question that we'll be talking about in a bit as well, in terms of a potential future trial.

Dr. Grossman, do you have a response to the question that was asked earlier by Dr. Bunin?

DR. GROSSMAN: Yes, I do. There were 35 patients who met the steroid-refractory criteria based on no improvement within 7 days, and there were 19 patients who met the criteria based on progression within 3 days.

I also want to address the comment about patients coming in, and I think the term "cherry-picking" was used. I'd like John Levine to address that, please.

DR. LEVINE: Sure. I think it's obvious that if there was any cherry-picking, it was towards patients with more severe disease. The majority of the patients had severe disease on clinical grounds grade C and D, and I think it was two-thirds of the patients that also had high

biomarkers, which is associated with exceptionally high mortality.

So if there's any cherry-picking, I would say that it was that the patients were weighted more heavily to severe disease than perhaps some other trials. Thank you.

DR. HOFFMAN: Okay. Dr. Walters?

DR. WALTERS: Yes, Dr. Hoffman. Thanks very much.

I don't have a lot of new comments. I think the strengths of this study is the apparent strong treatment effect, the 70 percent overall response rate. I found the biomarker data quite compelling. If that was in the briefing information, I must have missed it. But I found that today in the presentation quite compelling, that there's a biological effect that tracks with the clinical responses.

So those were the strengths. At the end of the day, however, I worry that we'll have yet another single-arm, phase 2 trial that shows quite promising results without really strong evidence of

how and when it's best to use this particular agent in our armamentarium for steroid-refractory acute graft-versus-host disease. I think the study design of REACH2 through the license and trial is the ideal type of trial that would give us more confidence in using a new therapy such as this one. That said, however, Dr. Kurtzberg's arguments are compelling as well. There are certainly patients who respond to this and have dramatic responses.

I'll just finish with I have this haunting memory of the BMT CTN 0802 study that started with randomized phase 2 studies, single agents with steroids to look at optimal response to newly diagnosed acute GVHD that John Levine knows better than I do. Out of the 4 agents that were compared, mycophenolate mofetil had the best response or the overall response rate of about, as I recall, two-thirds or 66 percent. But when that was tested in a randomized-controlled trial, there was no treatment effect, so it ended up being a negative trial published in Blood in 2014.

What I learned from that experience, in

GVHD, where the endpoint is largely subjective, although the way we score that is getting better and better, it is probably important to have randomized clinical trial design to be certain about the clinical effect. So from my point of view, those are the strengths and weaknesses of the evidence presented today. Thank you.

DR. HOFFMAN: Dr. Kamani?

DR. KAMANI: Yes. Sorry. Thank you, Dr. Hoffman.

I don't want to repeat what some of the other committee members have already said, but if we're looking for the gold standard, phase 3, randomized double-blind trial, this clearly does not meet that requirement. However, I think there is some validity to what Dr. Kurtzberg mentioned about whether a truly randomized double-blind trial or even a randomized trial could be conducted in this disease, so we may never know the answer to that question.

However, I think some of the strengths of the study is that the response rate of 70 percent,

which considering the types of patients that were enrolled onto this single-arm trial seems quite robust, knowing that, at least in my experience, when you have grade C and D acute graft-versus-host disease, the risk of failure with most of the available off-the-shelf agents is significant, often in the range of about 50 to 80 percent.

So I think the data, even though it's not from a randomized trial, is somewhat compelling, considering the types of patients that ended up receiving this product. Secondly, if our main concern is that the null hypothesis or the data to support the null hypothesis is flawed, it's hard for me to know why a null hypothesis of 40 percent was acceptable for another agent and may be problematic for this agent.

So not knowing the answer to that, I think in a disease that has severe morbidity and significant mortality, in a disease where there is a significant unmet need, and an agent that does not have the secondary effects of immunosuppressive drugs that are often used for these patients, I

think really serve as the strength of this trial and its results. I think those are my comments.

DR. HOFFMAN: Thank you.

Dr. Hinrichs?

Just a reminder, if you're finished with your question to lower your hand electronically.

Dr. Hinrichs?

DR. HINRICHS: I would comment on the question here, which is to discuss the strengths and weaknesses of the design. Of course, the weakness is that it's a single-arm study that relies on historical data. There's no way to get around that weakness.

Single-arm studies that rely on historical data are always inherently weak and they've historically been misleading. There are a huge number of examples in the field of oncology where single-arm studies with promising results do not bear out when you move to a randomized trial.

So in terms of what the weakness is, the weakness is the obvious one, that it's a single-arm study without any real controls. So in that

situation, what is it that I would require to be convinced that this drug is effective? One thing that I would look for would be a dramatic effect in the absence of any other intervention that might be causing that effect, and here that data's confounded by the treatments.

It's also confounded by the fact that it's not like a single-arm study of an agent for the treatment of cancer, where we might be looking at objective response rate where the expected objective response rate would be zero, but here with an agent, you see that there actually is a response rate, tumor shrinking, that it's doing something. Then you just decide, well, how much of a response rate does it take you to find that compelling that there's activity there. But here you're really talking about differences between levels of response with this versus historical levels of response, so that's much less clear and much less compelling for me.

The last point is that, especially in a single-arm trial, I would want a very hard

objective endpoint. We argue about how objective response rates in tumors may be flawed in that certain endpoints like progression-free survival or disease-free survival are not as hard as overall survival. Here when you're scoring GVHD progression, it may be even softer than those softer endpoints that we don't like. So I just present that for the committee's consideration. Thank you.

DR. HOFFMAN: Okay. Dr. Finestone?

DR. FINESTONE: Yes. I just wanted to speak from the consumer perspective. While I appreciate the FDA's apprehension and the other speakers' apprehension about a single-arm study, I just wanted to bring to the attention comments made by Dr. Kurtzberg and the other patient advocates that we've heard; that patients, and apparently both clinicians, are very reluctant to accrue to a clinical trial that has a placebo arm, and I think that should be taken into consideration with regard to this issue. Thank you.

DR. HOFFMAN: Okay. Dr. Bunin's hand is up,

too, but I want to ask a question myself, but it relates to our members of the committee who are practicing pediatric hematology.

In light of Dr. Kurtzberg's comments about her level of comfort in randomizing a child to potentially placebo rather than this, if there were a randomized trial, how would my colleagues on the committee feel about that? Would you have a similar feeling? And I don't want to put you on the spot. You don't have to answer if you don't wish to.

(No response.)

DR. HOFFMAN: Maybe I'll move to the Dr. Bunin whose hand was up.

DR. BUNIN: Well, I can answer that from my blood and marrow transplant perspective. I'm going to take just gut GVHD since I think most of the comments had to do with severe gut GVHD, which can be very difficult to treat and is often steroid refractory.

I am not convinced that this is better than infliximab, which is commonly used for gut GVHD and

we find to be very successful in treating gut GVHD. Nothing is a hundred percent, but I'm not convinced. So if a randomized trial were to be considered, I would confine it to gut GVHD and consider infliximab as the other arm. That's probably not a very interesting study to be done, but that's one way to look at a randomized trial. I think most of us would be reluctant to do, especially for gut GVHD, placebo versus another drug.

One of the very attractive things about this particular product is its lack of immunosuppression, however, compared to every other drug we use to treat graft-versus-host disease -- and I think that does need to be taken into account, and we may get into this in question 2 in terms of study design -- for me to really understand efficacy, I want to know how many patients were off steroids at a particular point.

If you have a response at day 30, that's great, but if you are still on steroids 6 months after transplant and you cannot be weaned, to me

that's not a success. So I really think in terms of study design, duration of steroids needs to be looked at very closely.

DR. HOFFMAN: Okay. We have a couple more comments. I think to some extent, we're also getting into the essence of question 2, which we'll move on to in a minute or two probably.

Dr. Halabi, I think you're next.

DR. HALABI: Yes. Thank you, Dr. Hoffman.

In order not to repeat what everyone has said. I think we all understand the limitation in terms of single-arm trials and the problem with historical control. The major concern is this is not a randomized trial, and it does not minimize bias in terms of known or unknown prognostic factors.

One thing that really struck me is the variability in CR 28 days ranged from 30 to 45 percent. So even though we have seen responses as high as 70 percent, the durability did not look really high. I would have personally preferred to look at a randomized trial, and I understand this

is not feasible, neither the clinicians nor the patients, so I think this is really an important point. But we all recognize this is an unmet medical need.

In terms of the weakness -- sorry, strength, I agree with what my peers have said, that clearly this drug has some activity and you have some responses. So at the end of the day, we may think of what the options are for the patients and the treating clinician, and we need to bear that in mind.

DR. HOFFMAN: Dr. Sung?

DR. SUNG: I would just add to Dr. Bunin's comment as my question earlier alluded to. I do think it's important to look at the ability to get patients off of steroids. The FDA was asking about future studies. I would advise considering that as an endpoint.

Now, there's some debate over whether or not if you can get someone down to 5 of prednisone or 10 of prednisone, would you still consider that a win? I think many of us physicians probably would

consider that a win, but I do think that's something to be considered in future trials, are you able to get patients off of steroids.

Now, if a patient flares while you're tapering to steroids, I don't necessarily think that's a loss unless the patient flares to the point where you have to go to a third or a fourth agent. But if they flare just because you titrated the steroids too quickly because they were having steroid psychosis or something else, I don't think that necessarily represents failure of the treating agent.

With regard to the question of a randomized trial, in addition to infliximab, I would point to the REACH2 study, which, again, going to the example of ruxolitinib, which first received FDA approval based on a single-arm study, but then, as many of you may know, in May of this year published a randomized, multicenter study comparing ruxolitinib to dealer's choice of, I believe, 9 commonly used second-line agents for steroid-refractory graft-versus-host disease.

So I don't think a randomized trial has to have a placebo in the sugar pill sense. You can still randomize them to other agents, and REACH2 showed that an RCT can be done.

Now, I'm an adult transplant physician; I'm not a pediatric transplant physician, so I defer to Dr. Kurtzberg. She knows that population much better than I do. But it does seem that Study 280 that was discussed here did randomize children to the interventional if I'm not mistaken. So it seems that at least some kids can be entered into RCTs for steroid-refractory acute GVHD.

DR. HOFFMAN: Let's go back to Dr. Walters, and then we'll move on to the second question.

DR. WALTERS: Thank you. Thank you, Dr. Hoffman. This is just in response to your question about whether or not it's feasible and ethical to conduct a randomized phase 3 trial in children with steroid-refractory acute GVHD.

For all the reasons that were just stated, because of the readily available other therapies showing potent overall response rates, I think it

is ethical, but I don't know that it's practical because of the superior toxicity background associated with remestemcel-L that we've heard about, and also because now there are enough investigators like Dr. Kurtzberg who have experience with it and have developed, obviously, strong belief systems around its efficacy that would also, I think, be a barrier to completing a large randomized clinical trial. So ethically, yes; feasible, perhaps not. Thank you.

DR. HOFFMAN: Okay. Dr. Grossman, did you have something you wanted to add?

DR. GROSSMAN: Yes. I wanted to just clear up a couple of things; first the issue of the confounding of other treatments. There was no treatment allowed for the first 28 days, and the 28-day OR is indeed a surrogate for survival. Second, in terms of steroid use, the responders -- I'd like to see slide EF-25 come up if you don't mind. I think I can clear up the steroid question as well.

Could we have EF-25, please? Alright. I'll

just tell you what it is, then. We did a responder analysis -- oh, here we go. Not yet. Okay. We did a responder analysis by 28-day overall response of the responders with respect to mean steroid dose, and as expected, at baseline for responders, the steroid dose was 2 milligrams per kilogram.

For those that are responders, day 28 responders, the mean steroid dose went down to 1.1, which would be expected. The non-responders had started with 2.1 milligrams per kilogram and didn't go down much. It stayed at 1.7 milligrams per kilogram. So I just wanted to make sure that was clear.

One last thing. In terms of the infliximab study, that actually was a failed study, and I'd like to ask John Levine to very quickly comment on that.

DR. LEVINE: Sorry, I was muted. There was a randomized phase 3 trial with adult patients for infliximab as primary GVHD treatment. In fact, the patients randomized to infliximab had worse responses than patients who just got treated with

steroids alone.

DR. HOFFMAN: Okay. I think we have covered as well as we're able to question number 1. In terms of the strengths and weaknesses, we've commented on the high response rate. We've heard some very compelling clinical information about how the patients do, and I think we've also wrestled with some of the inherent weaknesses in single-arm trials and the fact that the product itself underwent some changes over time that may have had an impact, therefore, on more recent data compared to older data.

Let's move on to the second discussion question.

Can I ask someone from the FDA please to read that? Maybe Dr. George?

DR. GEORGE: Yes, I'm available. I'm just waiting for the slide to be put up.

Thank you. The second discussion question comes in two parts. I'll stop after the first part and then go to the second part after the discussion of the first part.

As noted previously, primary endpoint results in Study MSB-GVHD001 were statistically significant. The measured response was durable with a median of 54 days. However, the results of Studies 265 and 280, the two randomized trials, did not provide evidence of the treatment effect for remestemcel-L in acute GVHD even when reanalyzed using the efficacy endpoint of day 28 ORR. In fact, a treatment effect has not being identified in any of the previous clinical trials conducted in various disease entities, including type 1 diabetes mellitus, Crohn's disease, myocardial infarction, or severe chronic obstructive pulmonary disease, and the mechanism of action of remestemcel in mitigating acute GVHD remains unclear.

Question A, please discuss whether the results of Studies 265 and 280 are relevant to the effectiveness of remestemcel-L for the treatment of pediatric steroid-refractory acute GVHD. In your discussion, please consider not only the similarities and the differences in the study populations, but also any other factors; example,

number of years between studies, pathophysiology of adult GVHD or steroid-refractory GVHD versus pediatric acute GVHD or steroid-refractory GVHD that you deem relevant. Thank you.

DR. HOFFMAN: Okay. If there's no discussion about the wording of the question, we can move to discussing this. I think we actually have discussed it to some degree in our comments in the last half hour, but I'm happy to hear additional comments about this.

(No response.)

DR. HOFFMAN: Do people think we've -- Dr. Sung?

DR. SUNG: I would just say that I would actually compliment the sponsor in that they had some failed clinical trials and they didn't give up. They refined their product, and they apparently came up with a better result. So to me, I consider that actually a strength and something they should be commended on for persisting, although one could argue that, well, could this just be chance? The first few trials didn't work.

If you do something often enough, maybe it'll work.

But at the same time I think that expanded access protocol, where they showed dramatically different survival rates between patients who were receiving the original product versus patients who received the new product, I found that very compelling to suggest that, yes, there actually is something going on with this newer product.

If I may, returning to Dr. Grossman's comment, if I heard correctly, at day 28, for patients who responded, they were on a median of a mg per kg per day of steroids. Maybe this is because I'm an adult physician and things are different in the pediatric world, but a mg per kg at day 28 is pretty high in my opinion. Again, that's with an adult perspective. I don't know if that was just because the protocol, as Dr. Kurtzberg mentioned, required a very slow taper or if that's just a difference between kids and adults.

DR. GROSSMAN: Yes, I can answer that. It was a slow taper. There was a guided slow taper,

and 50 percent were off of all steroids by 100, day 100.

DR. SUNG: Okay.

DR. HOFFMAN: I'm going to actually interrupt for a minute and ask Dr. George to read the second part of the question because I think they're related, and then I'll take the comments from the people that have raised their hand right after that.

DR. GEORGE: Sure. Thank you.

Question B, FDA may require an additional clinical trial to support the effectiveness of remestemcel-L in pediatrics steroid-refractory acute GVHD. If so, what are your recommendations regarding the design of such a trial? For example, please discuss the population, example, acute GVHD or steroid-refractory GVHD, adult and/or pediatric treatment assignment, randomized versus single-arm primary and secondary endpoints, example, day 28 ORR, day 100 survival, day 180 survival, et cetera; and any other aspects of the trial design.

DR. HOFFMAN: Dr. Kamani, you have a hand

up.

DR. KAMANI: Yes. I wanted to respond to the first question, which is whether the results of previous Studies 265 and 280 are relevant. I think they are relevant, however, I think that considering that this is a cell therapy product and considering that the sponsor has done some additional refinement of the manufacturing process, plus showed some surrogate data that suggests a more potent product, I think it's difficult to compare what may have been seen with those previous studies and what you're encountering with either the 001 trial or the more recent enrollment onto the expanded access protocol.

So I think one has to keep that in mind as we look to try and see if the data from previously controlled randomized clinical trials is relevant to the findings of this study. That was my major comment in response to this question.

DR. HOFFMAN: Thank you.

Dr. Hinrichs?

DR. HINRICHS: I'm struck by the randomized

trials and find them compellingly negative. Now, I realize that there have been changes in the manufacturing at this point, but I don't think that they're entirely irrelevant, and it goes again to the question of whether from this single-arm study we're convinced that this has efficacy. I do think that the two prior randomized trials convincingly show that the other product, at least in the population that was being studied, which is similar but not the same, clearly did not have meaningful activity.

So do we think that these tweaks to the manufacturing have suddenly made it highly effective and the change in patient population has suddenly made it highly effective? Thank you.

DR. HOFFMAN: Dr. Walters?

DR. WALTERS: Yes. This is mostly a reiteration of other comments and my own opinion, which is that, again, I haven't been convinced today that there's really a biological difference between steroid-refractory acute GVHD in adults and children, and I'm certainly not convinced, on the

basis of 14 patients in the arm of pediatric patients in Protocol 280 really providing compelling evidence that there is a response.

So like others, I was more convinced by the improvements in the potency of the product that evolved over time, in the drug product, and that it would be very interesting to see this tested, this optimized, refined drug product tested again in adults and perhaps also in children in a design like Protocol 280, and that might be something to ask the sponsor about if there are plans to do that, or if we could encourage them to do that. Thanks.

DR. HOFFMAN: Dr. Bunin?

DR. BUNIN: I agree with Dr. Walters in that the difference in product may be significant. I mean, we may be talking about really two completely different products, and I would strongly encourage a second trial, a well-done second trial, in adults and potentially pediatrics with the optimized product.

The other consideration I would have for a

future trial is to prospectively look at biomarkers. I think of this product as a bit of a black box. For example, we know how infliximab works, we know about rux, but this is, to me, a bit of a black box. I've looked at the little cartoons in TNF, and da-da-da, but to really more rigorously look at biomarkers to see if there is a response that correlates with this particular agent, I think that would be important. We may find a subgroup of patients that this will be great biologic and for others, don't bother.

DR. HOFFMAN: Dr. Grossman, did you want to comment on a future trial question?

DR. GROSSMAN: Yes, please. We fully plan, and it's in the works now, to do a trial in adults with severe steroid-refractory acute GVHD. We are going to use the MAGIC biomarker score to make sure that there are equal numbers of severe patients in both groups, both remestemcel and best available therapy, which obviously would be ruxolitinib. We do plan to measure 28-day overall response as well as durability possibly in a combined score. We

will be looking at survival. We've already had the discussions with some of the key investigators who are anxious to get this started.

So we fully plan, post-approval, to do such a study that covers the biomarkers that will be randomized in adults, in severe patients, and we're confident we can actually recruit in such a study based on the engagement of the transplant center investigators.

DR. HOFFMAN: Thank you.

Putting this together. I think we have a lot of comments about what a future trial should involve, and should it be both adults and children, and what it might be compared against, and so on. Although I'm not sure I would want to use the same term that Dr. Bunin used of a "black box," I do think that is confounding our thinking a bit because if we were, say, looking at the use of docetaxel, for example, in this patient population, we're dealing with a specific known compound of known chemical structure and a known dose, and we would really wrestle in that case with, well, why

was this a positive study and that one was a negative study?

But in this case, we really are dealing with a product that probably may differ slightly from lot to lot, whether that's meaningful or not. But from the time standpoint, from the earlier iterations of the product to later iterations, there have been biologic changes made, and it's hard to quantitate that.

I'm going to ask, Dr. Halabi, if you have a comment, and I think then we'll move on to the voting.

DR. HALABI: Thank you, Dr. Hoffman.

Susan Halabi. I agree with some of the comments that were made, and I would urge the sponsor to consider longer follow-up for patients and also to collect patient-reported outcomes because I haven't seen that.

The final point, in the briefing document from the FDA, there was a mention of at least 50 percent deaths within 30 days of the drug remestemcel-L, and I don't think I heard an

explanation for that from the sponsor or from the expert. It may be that this is expected in this severe patient population.

DR. HOFFMAN: Do you want to address that, Dr. Grossman?

DR. GROSSMAN: Yes. Sure. Thank you. I can address that. First of all, there's a higher number of deaths in GVHD trials, and we very carefully looked at all of the SAEs and deaths across our GVHD trials in total because that's how you really can make those comparisons, especially the ones that had a placebo group. We do not have any increase in SAEs or deaths in remestemcel versus placebo.

DR. HOFFMAN: Okay. I think we're going to stop the discussion at this point and move on to the vote. Dr. Yu is going to provide the instructions for the voting.

DR. YU: Yes. Thank you. We will be using email to submit our vote for this meeting. Voting members, please reply "all" to the voting email you received in order to submit your vote. After

everyone has submitted their vote, the vote will be compiled while we take a brief break. The vote will then be displayed on the screen. I will read the vote from the screen into the record.

Next, Dr. Hoffman will go down the roster and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in this same manner until all questions have been answered or discussed.

Before I ask a member of the FDA to please read the questions, do any of the panel members today have any questions about the logistics of the voting?

(No response.)

DR. YU: Okay. Seeing no hands, would a member of the FDA please read the voting question?

DR. GEORGE: Thank you. This is Bindu George again. Question 3 is the voting question. Do the available data support the efficacy of remestemcel-L in pediatric patients with steroid-refractory acute GVHD? Thank you.

DR. HOFFMAN: Okay. If there are no questions or comments concerning the wording of the question, we'll now begin the voting. Voting committee members, please email your vote now to the FDA advisory committee staff as just instructed and don't forget to reply "all" and then we're going to take a 10-minute break to compile the votes, so stay tuned.

(Voting.)

DR. YU: Good afternoon. Everyone has voted. The vote is now complete. I will read the vote from the screen into the record. The vote is 8, yes; 2, no. There were zero abstained and zero no votes. Thank you.

DR. HOFFMAN: Okay. Are we going to a clear slide? At least what I have is not. It says it's in progress.

DR. YU: Hi. Dr. Hoffman, just give us one moment.

DR. HOFFMAN: Okay, but count the absentee ballot.

DR. YU: Hi. Dr. Hoffman?

DR. HOFFMAN: Yes?

DR. YU: I have the slide up. If you don't see it at this moment, can I ask you to hang up, disconnect, and try back in?

DR. HOFFMAN: Just my phone or the whole thing?

DR. YU: You can actually just close your browser and come back into the meeting, and see if that works for you. We'll give you a second.

(Pause.)

DR. HOFFMAN: Now that the vote is complete, we'll go down the list and have everyone who voted state their name, their vote, and if you want to, you can state the reason why you voted as you did into the record. We'll start with Dr. Garcia.

DR. GARCIA: Thank you, Dr. Hoffman.

Jorge Garcia. I voted yes. I do believe the question perhaps to me was a bit too narrow and simple, but based upon the available data, I do believe this agent has efficacy in the disease in question. Do I believe it's better than any other existing agents? I don't know. Do I believe

it's a safe agent? I do.

Do I believe with 15 years of experience, no overlapping side effects, in a diseased setting where there is clearly an unmet need -- I think that agent has shown some efficacy.

DR. HOFFMAN: Thank you.

Dr. Halabi?

DR. HALABI: Yes. Susan Halabi. I voted yes, and I believe that the drug has activity. Even though I was 51 percent for voting yes versus 49, it was really a struggle to make a decision, but I was persuaded by the clinical experts who made the argument that it may not be possible to do a randomized trial. I'm also hopeful that the sponsor will try to address some of the concerns that we have made in the next randomized trial.

DR. HOFFMAN: Thank you.

Dr. Hinrichs?

DR. HINRICHS: Christian Hinrichs. I voted no. The reason why is that I think that we need to continue to make regulatory decisions about drugs based on rigorous high-quality science, and I think

that this single-arm study that was performed did not represent that, and it's not compelling that there is --

(Audio lost.)

DR. HOFFMAN: Did we lose you?

(No response.)

DR. YU: Hi, Dr. Hoffman. This is Joyce. Please move on if we don't hear from Dr. Hinrichs, and we can come back to him.

(No response.)

DR. YU: Dr. Hoffman?

(No response.)

DR. YU: Hi. Dr. Hinrichs, if you can hear us, we'll continue with you. Dr. Hoffman momentarily lost connection.

DR. HINRICHS: Dr. Hoffman lost connection, too?

DR. YU: Yes. Please proceed with your justification.

(No response.)

DR. YU: Hi. Dr. Hinrichs, we're going to try to get Dr. Hoffman back. Please proceed with

your justification.

DR. HINRICHS: Okay.

Again, my justification was based on the need for rigorous science and careful clinical trials, especially in the pediatric patient population. I don't think that this single-arm study gives us that kind of rigorous data that we should be using to make these sorts of decisions.

DR. YU: Thank you, Dr. Hinrichs.

We're going to pause for one moment while we wait for Dr. Hoffman.

(Pause.)

DR. YU: Good afternoon, everyone. This is Joyce Yu. In the interest of time, I'm going to have Dr. Sung please state his vote and his justification. Thank you.

DR. SUNG: My name is Anthony Sung, and I voted yes. While I agree with Dr. Hinrichs of the importance of rigorous studies, including randomized clinical trials, I think back to Dr. Baird's slide on single-trial requirements and demonstration of a clinically meaningful effect on

a potentially serious outcome.

With respect to Dr. Przepiorka's earlier comments, I still cannot help but think that ruxolitinib received FDA approval with a single-arm trial, and I believe this study shows actually better data for the same indication.

Although the landscape is a little different in that ruxolitinib is FDA approved for patients 12 and older, there's still a gap for patients younger than 12, and I believe that this fills that gap for patients in that age range.

Now, for patients who are 12 and older, I do think randomized clinical trials are needed to provide further evidence, and it sounds like the sponsor's already planning such a trial with ruxolitinib as a control, which in my mind would be appropriate.

DR. HOFFMAN: Okay. I'm sorry. This is Dr. Hoffman. I was unceremoniously dismissed. It looks like we're up to Dr. Bunin.

DR. BUNIN: Hi. Nancy Bunin. I voted yes. I do think there are additional studies that need

to be done on this drug. GVHD studies -- and I've participated in more than a few -- are extremely messy and not as clear-cut as looking at a cancer drug for a variety of reasons. I do think this may fill a gap. We use many drugs for GVHD which are not approved. For example, we use rux for many kids less than 12 for chronic GVHD.

Much of the experience I think is anecdotal, but I do think it may fill a hole and additional studies will be needed. But what strikes me most is the safety profile of this drug, which is much safer than the many other immunosuppressives we use to treat graft-versus-host disease.

DR. HOFFMAN: Thank you.

Dr. Finestone?

DR. FINESTONE: Sandra Finestone. I voted yes, based on a need and compelling efficacy.

DR. HOFFMAN: Okay. Dr. Kamani?

DR. KAMANI: Hi. This is Naynesh Kamani. I voted yes, and my reasons are similar to those expressed by other members. Clearly, this is not a randomized trial demonstrating efficacy over

placebo or efficacy over best available treatment, but a 65 to 70 percent complete remission or overall response at day 28 is impressive in a subset of patients who have a fairly dismal prognosis. There's also an unmet need for approved drugs for this indication.

Just to reiterate what Dr. Bunin said, the dozen or more than a dozen drugs that are often used to treat these patients all have toxicity profiles, which are probably much worse than the ones with remestemcel, so I voted yes. Thank you.

DR. HOFFMAN: Ms. Pearl?

MS. PEARL: Hi. This is Diane Pearl. I voted no, initially taking the question word for word on efficacy and after listening to everyone's compelling medical information. But the parents and me, and re-reading and thinking everything, I would like to change my vote to yes. I believe patients and parents deserve more choices, and this drug may provide that hope, especially as there is just not much out there. I'd like to see more trials and scientific data as well, and I think

they will prove that in the future. Thank you.

DR. HOFFMAN: I'll let Dr. Yu correct me if I'm wrong. But if you do want to change your vote, please send another email to that effect so it's on the record.

MS. PEARL: I did, right after I --

DR. YU: Hi. Dr. Hoffman?

DR. HOFFMAN: Yes?

DR. YU: Thank you, Dr. Hoffman.

Ms. Pearl, that's not necessary. Thank you.

MS. PEARL: Okay. I'm so sorry. This is --

DR. HOFFMAN: No worries.

MS. PEARL: -- heartfelt and a lot to digest as a parent who has been through two transplants. But my heart does say overwhelmingly yes, and thank you to everyone for saving children's lives.

DR. HOFFMAN: Thank you.

Dr. Walters?

DR. WALTERS: Yes. Mark Walters. I voted yes. I was also on the fence for all the reasons stated, and in the end, I was persuaded by the

public voice and the patient efficacy arguments, and my own clinical practice facing those situations with families as well. Thank you very much.

DR. HOFFMAN: Okay. This is Dr. Hoffman. I voted yes, and I don't think I have additional reasons beyond what many of my colleagues have already voiced and what I said toward the end of the question discussion, that I find the clinical evidence compelling. Even though it is not randomized, it's a product that's hard to characterize. And because there were no significant safety signals that were new or different or worse, on balance, I felt that I would vote yes.

Before we adjourn, are there any last comments from the FDA?

DR. GEORGE: This is Bindu George. No, I don't have any comments. I just want to thank the committee, as well as the participants of the open public hearing.

Let me check with Dr. Wilson Bryan if there

are any additional comments or questions.

Adjournment

DR. BRYAN: Yes. Thank you. I'd just reiterate what I said this morning. This has been a very important discussion for us because this is the first MSC product that we've brought to the advisory. It's a complex product, and as indicated, we have concerns about the application. But we also have concerns about the unmet need, and I think the thoughtful deliberations by this committee will help us to think about those concerns.

(Whereupon, at 5:24 p.m., the afternoon session was adjourned.)