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OPEN PUBLIC MEETING

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

ATTENDEES

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Eric Crombez, M.D.	Ultragenyx Gene Therapy
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Steven Shapero, B.S.	Patient Representative - Childhood Cerebral Adrenoleukodystrophy (CCALD)
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Miranda McAuliffe	Caregiver
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OPENING REMARKS: CALL TO ORDER AND WELCOME

MR. MICHAEL KAWCZYNSKI: Good morning and welcome to the FDA Center for Biologics Evaluation and Research 72nd Meeting of the Cellular, Tissue, and Gene Therapy Advisory Committee. I'm Mike Kawczynski, and I will be helping moderate today's activities. This is a live public meeting, so please note that if we do run into any technical issues, we may have to momentarily pause the meeting in order to address those.

But bear with us. This is a meeting where we even have international partnerships and participants, so we appreciate you joining us today. With that being said, I want to get this meeting started and hand it off to my colleague and DFO, Christina Vert, and our chair for today, Dr. Lisa Butterfield. Dr. Butterfield, are you ready kick us off?

DR. LISA BUTTERFIELD: All right. Good morning, everyone. Thank you, Michael. I'm Lisa Butterfield. I'll be your chair today, and I'd like to welcome all of the members of the Committee, our

regulatory colleagues, the participants we have for today as well as tomorrow, and the public who are viewing remotely.

Just a moment of housekeeping, I'd like to remind everyone during the Q&A to use the "Raised Hand" function. That's how I'll see you and how I'll be able to call on you so that we can have a robust discussion of the important matters of the day. With that, for the roll call, I'd like to hand it off to our designated federal officer today, Ms. Christina Vert, please.

ADMINISTRATIVE REMARKS, ROLL CALL, INTRODUCTION OF COMMITTEE, CONFLICT OF INTEREST STATEMENT

MS. CHRISTINA VERT: Thank you, Dr. Butterfield. Good morning, everyone. This is Christina Vert, and it is my great honor to serve as the designated federal officer, DFO, for today's 72nd Cellular, Tissue, and Gene Therapies Advisory Committee Meeting. On behalf of the FDA, the Center for

Biologics Evaluation and Research, and the Committee, I am happy to welcome everyone for today's virtual meeting.

Today the Committee will meet in open session to discuss the two biologic licensing applications, BLA 125755 and BLA 125717 from bluebird bio, Inc. Today's meeting and the topic were announced in the Federal Register Notice that was published on April 14, 2022. I would now like to introduce and acknowledge the excellent contributions of the staff in the Division of Scientific Advisors and Consultants, including the director, Dr. Prabha Atreya, who is my backup and co-DFO for this meeting.

Other staff are Dr. Sussan Paydar, Ms. Tonica Burke, Ms. Joanne Lipkind, Ms. Karen Thomas, who have provided excellent administrative support in preparing this meeting. I would also like to thank Mr. Mike Kawczynski in facilitating the meeting today and his many hours of work preparing for the meeting. Also, our sincere gratitude goes to many CBER and FDA staff working hard behind the scenes trying to insure that

today's virtual meeting will also be a successful one.

Please direct any press and media questions for today's meeting to FDAs Office of Media Affairs at fdaoma@fda.hhs.gov. The transcriptionist for today's meeting is Ms. Ora Giles. We will begin today's meeting by taking a formal roll call of the Committee members and temporary voting members.

When it is your turn, please make sure your video camera is on and you are unmuted and state your first late name, organization, expertise of the roll, and when finished, you can turn your camera off so we can proceed to the next person. Please see the member roster slides in which we will begin with the chair. Dr. Butterfield, please go ahead and introduce yourself.

DR. LISA BUTTERFIELD: Thank you. Good morning again. My name is Lisa Butterfield. I am the vice president of research and development at the Parker Institute for Cancer Immunotherapy as well as an adjunct professor in microbiology and immunology at University of California, San Francisco. My expertise

is in tumor immunology, cancer immunotherapy with vaccines, cell therapies and biomarkers.

MS. CHRISTINA VERT: Thank you. We next have Dr. Ahsan, but I don't think she's present at the moment. So we'll move on. Thank you, Dr. Fox. Go ahead.

DR. BERNARD FOX: My name is Bernard Fox. I'm the Harder Family Chair for Cancer Research at the Earle A. Chiles Research Institute, which is a division of the Providence Cancer Institute. My expertise is in preclinical and clinical translational work in cancer immunotherapy with a focus on cancer vaccines and adoptive immunotherapy, as well as biomarkers.

MS. CHRISTINA VERT: Thank you. Dr. Lee.

DR. JEANNETTE LEE: Good morning. My name is Jeannette Lee. I'm a professor of biostatistics and a member of the Windsor P. Rockefeller Cancer Institute at the University of Arkansas for Medical Sciences. My area is biostatistics in clinical trials. Thank you.

MS. CHRISTINA VERT: Thank you. Dr. Ott.

DR. MELANIE OTT: Good morning. My name is

Melanie Ott. I'm the director of the Gladstone Institute of Virology at the University of California, San Francisco. I'm also a professor of medicine at UCSF. My expertise is molecular virology, especially in the area of HIV and antiviral vectors.

MS. CHRISTINA VERT: Thank you. Dr. Shah.

DR. NIRALI SHAH: Hi, this is Nirali Shah. I work at the pediatric oncology branch in the National Cancer Institute, and I focus on CAR T-cell therapy primarily in hematologic malignancies in children and young adults.

MS. CHRISTINA VERT: Thank you. Okay. Now we will go on to our temporary voting members. Ms. Anspach.

MS. SYLVIA ANSPACH: Hi, my name is Sylvia Anspach, and I am the parent representative for cerebral adrenoleukodystrophy.

MS. CHRISTINA VERT: Thank you. Dr. Coffin.

DR. JOHN COFFIN: My name's John Coffin. I am professor of molecular biology and microbiology Tufts University in Boston, Massachusetts. My expertise is

in basic retrovirology, retrovirus replication, and HIV pathic replication and pathogenesis, particularly interested in the integration mechanism consequences and specificity.

MS. CHRISTINA VERT: Thank you. Dr. Crombez.

DR. ERIC CROMBEZ: Good morning. I'm Eric Crombez. I'm the chief medical officer for gene therapy and inborn errors of metabolism at Ultragenyx. My training is in pediatric clinical genetics and biochemical genetics, and I am serving as the industry representative.

MS. CHRISTINA VERT: Thank you. Dr. DiPersio.

DR. JOHN DIPERSIO: Hi, I'm John DiPersio, and I'm the chief of the division of oncology and deputy director of the Siteman Cancer Center at Washington University School of Medicine. And I focus on AML genomics and cellular therapies, including CAR Ts directed towards hematologic malignancies.

MS. CHRISTINA VERT: Thank you. Dr. Dueck.

DR. AMYLOU DUECK: Hi, I'm Amylou Dueck. I'm an associate professor of biostatistics at Mayo Clinic

in Scottsdale, Arizona. And my expertise is in biostatistics in clinical trials.

MS. CHRISTINA VERT: Thank you. Dr. Hawkins. I mean, Dr. Gordeuk, go ahead. Sorry.

DR. VICTOR GORDEUK: My name's Victor Gordeuk. I am professor of medicine at the University of Illinois at Chicago. I'm director of the Sickle Cell Center here. My expertise is in clinical and translational research in sickle cell disease and other benign hematological conditions.

MS. CHRISTINA VERT: Thank you. Dr. Hawkins, go ahead.

DR. RANDY HAWKINS: Yes, good morning. Randy Hawkins, I'm a physician in private practice and at Charles University. My specialty is internal medicine and pulmonary critical care medicine. I'm the alternative consumer representative for these two meetings. Thank you.

MS. CHRISTINA VERT: Thank you. Dr. Stephanie Keller.

DR. STEPHANIE KELLER: Hi, I'm Dr. Stephanie

Keller. I'm a pediatric neurologist here at Children's Healthcare of Atlanta in Atlanta, Georgia. I'm also an associate professor of pediatrics and neurology for Emory University. And I'm the medical director of neurogenetics and the director of our leukodystrophy care center in Atlanta.

MS. CHRISTINA VERT: Thank you. Dr. Jaroslaw Maciejewski.

DR. JAROSLAW MACIEJEWSKI: This is Dr. M. I am attending physician and hematologist at the Cleveland Clinical Foundation Taussig Cancer Center. I run a laboratory interested in bone marrow failure and leukemias, including immunogenetics and the genetics of myeloid neoplasia.

MS. CHRISTINA VERT: Thank you. Dr. Donna Roberts.

DR. DONNA ROBERTS: Hi, I'm a professor of neuroradiology at the Medical University of South Carolina.

MS. CHRISTINA VERT: Thank you. Mr. Steven Shapero.

MR. STEVEN SHAPERO: Yes, hi, I'm Steven Shapero. And I live in Montana. And I'm the patient representative, and ALD runs in my family and has directly impacted my brother and his family and myself and my family.

MS. CHRISTINA VERT: Thank you. Dr. Singh.

DR. NAVDEEP SINGH: Hello, my name is Navdeep Singh. I'm an assistant professor at the University of Toledo at the College of Nursing. And I'm also a patient representative. I have beta thalassemia; I was diagnosed when I was nine months old.

MS. CHRISTINA VERT: Thank you. Dr. Janelle Trieu.

DR. JANELLE TRIEU: Hi, my name is Janelle. I'm a clinical pharmacist for specialty home infusion. And I am also a patient representative born with beta thalassemia.

MS. CHRISTINA VERT: Thank you. Okay. There are a total of 19 participants, 15 voting and 4 non-voting members today. And I thank you all for your introductions. I would also like to acknowledge CBER

leadership. Dr. Bryan is present, and Dr. Marks may be joining us in the meeting at another time. I will now proceed to reading the conflict of interest statement for the public record. Thank you.

The Food and Drug Administration is convening virtually today, June 9, 2022, the 72nd Meeting of the Cellular Tissue and Gene Therapies Advisory Committee, CTGTAC, under the authority of the Federal Advisory Committee Act, FACA, of 1972. Dr. Lisa Butterfield is serving as the chair for today's meeting.

The morning session of June 9, 2022, open session will include presentations of the effectiveness and product-specific safety results from the clinical trials in BLA 125755 for elivaldogene autotemcel to treat patients younger than 18 years of age with early cerebral adrenoleukodystrophy who do not have an available and willing antigen match sibling hematopoietic stem cell donor.

The afternoon session will include presentations of safety concerns relevant to both products described in BLA 125755 and also BLA 125717

for betibeglogene autotemcel to treat patients with beta thalassemia who require regular blood cell transfusions, followed by Committee discussion and voting on BLA 125755. The topic is determined to be a particular matter involving specific parties. With the exception of industry representative members, all regular and temporary voting members of the CTGTAC are appointed special government employees, SGEs, or regular government employees, RGEs, from other agencies and are subject to federal 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 including, but not limited to, 18 USC Section 208 is being provided to participants in today's meeting and to the public. Related to the discussion at this meeting, all members, RGE and SGE consultants 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 spouse and minor child and,

for the purpose of 18 US Code 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and development agreements, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment. They may include interests that are current or under negotiation. FDA has determined that all members of this Advisory Committee, both regular and temporary voting members, are in compliance with federal ethics and conflict of interest laws.

Under 18 USC Section 208, Congress has authorized the FDA to grant waivers to special government employees and regular government employees who have financial conflicts of interest when it is determined that the agency need for the special government employees services outweighs the potential for a conflict of interest created by the financial interest involved or when interests of the regular government 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.

Based on today's agenda and all financial interests reported by Committee members and consultants, there have been no conflict of interest waivers issued under 18 US Code 208 in connection with this meeting. We have the following consultants serving as temporary voting members: Dr. John Coffin, Dr. John DiPersio, Dr. Amylou Dueck, Dr. Stephanie Keller, Dr. Jaroslaw Maciejewski, and Dr. Donna Roberts.

We have two voting patient representatives, namely Ms. Sylvia Anspach and Mr. Steven Shapero. Additionally, we have the following consultants serving as temporary non-voting members: Dr. Victor Gordeuk, Dr. Navdeep Singh, and Dr. Janelle Trieu. Dr. Eric Crombez, of Ultragenyx Gene Therapy, will serve as the alternate temporary industry representative at today's meeting. Industry representatives are not appointed as special government employees and serve only as non-voting members of the Committee. Industry representatives act on behalf of all regulated industry

and bring general industry perspectives to the Committee.

Dr. Randy Hawkins is serving as the alternate temporary consumer representative for this Committee meeting. Consumer representatives are appointed special government employees and are screened and cleared prior to their participation in this meeting. They are voting members of the Committee. We have the following federal speaker today who has been screened for his conflicts of interest and cleared to participate in today's meeting: Dr. Stephen Hughes, senior investigator, HIV Dynamics and Replication Program from the NCI from NIH.

In disclosures of conflicts of interest with speakers and guest speakers follow applicable federal laws, regulations, and FDA guidance. FDA encourages all meeting participants, including open public hearing speakers, to advise the Committee of any financial relationships they may have with any effected firms, its products and, if known, its direct competitors.

We would like to remind regular 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 that participants need to inform the DFO and exclude themselves from the discussion, and their exclusion will be noted for the record. This concludes my reading of the conflicts of interest statement for the public record. At this time I would like to hand over the meeting to our chair, Dr. Butterfield. Thank you.

DR. LISA BUTTERFIELD: Great. Thank you, Christina. And so, with all of that, I would like to welcome Dr. Wilson Bryan, the Director of OTAT FDA for the opening remarks from FDA.

FDA OPENING REMARKS

DR. WILSON BRYAN: Good morning and welcome on behalf of the FDA, the Center for Biologics Evaluation and Research, and the Office of Tissues and Advanced Therapies, or OTAT. Over the next two days this

Committee will consider two Biologics License Applications, or BLAs, from bluebird bio Inc.

The two products for discussion are elivaldogene autotemcel, or eli-cel, a gene therapy for the treatment of cerebral adrenoleukodystrophy and betibeglogene autotemcel, or beti-cel, a gene therapy for the treatment of beta thalassemia. The two products both use a lentiviral vector to deliver a gene. As you will hear, we are concerned that the vector has the ability to cause hematologic malignancies in the patients who receive these products.

Because this safety concern relates to both products, we have a relatively unusual format for the agenda over the next two days. This morning we will hear about the efficacy and safety of eli-cel for the treatment of cerebral adrenoleukodystrophy. This afternoon we will hear about the risk of hematologic malignancy with respect to both products. We will then ask the Committee to discuss and vote on issues related to the safety and effectiveness of eli-cel.

Tomorrow morning we will hear about the efficacy and safety of beti-cel for the treatment of beta thalassemia. Tomorrow afternoon we will ask the Committee to discuss and vote on issues related to the safety and effectiveness of beti-cel. We are fortunate to have experts on each topic serving on the Committee, but the Committee members are slightly different for each topic. We very much appreciate the Committee's willingness to indulge us in this somewhat unusual agenda.

We are asking this Committee to consider critical clinical questions regarding safety and effectiveness. The two applications also have CMC or manufacturing issues. However, we are working with bluebird to address those issues and do not have CMC questions for this Committee.

Cerebral adrenoleukodystrophy is similar to many extremely rare genetic disorders. It's a bad disease with limited treatment options. Also, as with many rare diseases, development of products to treat CALD can be particularly challenging due to the limited

number of study subjects, due to the limited natural history data, particularly in pre-symptomatic disease to support study design and interpretation, and due to disease heterogeneity.

In this setting, as we will hear today, a single arm study of limited duration with an external control group can be extremely difficult to interpret. We must not forget that, as with many of these rare genetic disorders, there is a tremendous unmet need for effective treatments for CALD. However, patients should not be subjected to products that are ineffective or have an unfavorable benefit/risk profile. This eli-cel BLA is particularly challenging due to issues with the evidence of effectiveness as well as our concerns regarding safety, particularly the risk of hematologic malignancy.

And we ask this Committee to weigh these issues in the setting of a desperate clinical situation. We are truly grateful to bluebird bio and the scientists and other professionals who have brought this product to this stage of development. We are also

grateful to the patients and their caregivers who participated in the clinical trials that will be discussed today. The FDA thanks the participants in today's open public hearing. It is critical that we hear from patients and patient advocates, particularly regarding the benefits and risks associated with eli-cel.

Many individuals are not able to participate today, and we appreciate and will carefully consider the written comments that we receive regarding eli-cel. We want to thank all the members of this Committee who have given their time to participate in today's discussion. I also want to thank the members of the FDA review team and the Advisory Committee staff who have worked tirelessly to prepare for today's meeting. I now turn to Dr. Butterfield to continue with the agenda.

DR. LISA BUTTERFIELD: All right. Thank you very much, Dr. Bryan, for those remarks. So, with that, let's begin our work of the day on efficacy and safety, and so I would like to welcome a series of

presentations from the applicant bluebird bio. And we'll start with Ms. Eggimann.

APPLICANT PRESENTATIONS: INTRODUCTION

MS. ANNE-VIRGINIE EGGIMANN: Thank you, Dr. Butterfield. Thank you, Dr. Bryan. Good morning. I'm Anne-Virginie Eggimann, chief regulatory officer at bluebird bio, Inc. We thank the FDA, the panelists, and the patients who participated in our clinical trials, as well as their families for making this meeting possible. Over the next two days we look forward to discussing the development of our lentiviral vector gene therapies for the treatment of rare and severe genetic diseases.

The first product we will discuss this morning is elivaldogene autotemcel, also known as eli-cel, developed for the treatment of early active cerebral adrenoleukodystrophy, or CALD. CALD is an ultra-rare, pan-ethnic, life-threatening, neuro --

MR. MICHAEL KAWCZYNSKI: Could you give us --

oh, one moment please. We want to make sure your slides are up, so just give us one second. bluebird, you want to go ahead and give it a shot now?

MS. ANNE-VIRGINIE EGGIMANN: Sure. The first product we will discuss this morning is elivaldogene autotemcel, also known as eli-cel, developed for the treatment of early active cerebral adrenoleukodystrophy, or CALD. CALD is an ultra-rare, pan-ethnic, life-threatening, neurodegenerative disease that impacts the brain of boys typically between the age of 4 and 10. Patients with early CALD urgently need a treatment option that can stabilize their neurological function.

The second product, which we will discuss primarily tomorrow, is betibeglogene autotemcel, also known as beti-cel, which is developed for the treatment of patients with beta thalassemia who require regular red blood cell transfusions. These transfusions are required for survival as these patients cannot produce enough of their own hemoglobin. In addition, this afternoon we will discuss the safety of lentiviral

vectors, or LVVs, based on our experience with eli-cel and beti-cel as well as a third LVV gene therapy in clinical development for the treatment of sickle cell disease called lovotibeglogene autotemcel, or lovo-cel.

Eli-cel and beti-cel are two different products. However, they share some key features. They're both first-in-class, one-time gene therapies that consist of the patient's own blood stem cells that have been genetically modified ex vivo with a lentiviral vector. Both products address the underlying cause of the disease they aim to treat by adding functional copies of a gene into the patient's blood stem cells. These gene addition is permanent and resulting gene expression is expected to be life-long.

Treatment steps for both products are also similar, as shown on the next slide. First, cells are collected from the patient. These cells are then shipped to the manufacturing facility, where they're transduced with the LVV to produce the drug product. After testing, the frozen drug product is shipped to the hospital. As for allogeneic transplant, the

patient undergoes conditioning to clean the bone marrow niche before drug product administration. The drug product is then thawed and infused back to the patient. Despite these key features, eli-cel and beti-cel are separate and distinct gene therapies with key differences.

Eli-cel uses Lenti-D LVV, which has a ubiquitous promoter to add the ABCD1 gene into the patient's cells. After engraftment, the transduced cells differentiate and migrate to the brain to produce functional ALD protein to stabilize CALD. In contrast, beti-cel uses a different lentiviral vector, BB305 LVV, which has a lineage-specific promoter. BB305 LVV adds the Beta A-T87Q-globin gene in the patient's cells to ultimately produce red blood cells that contain beti-cell-derived adult hemoglobin.

Today and tomorrow we'll present robust evidence supporting a separate and distinct benefit/risk assessment for eli-cel and beti-cel, both uniquely positive for the disease they intend to treat. Tomorrow, we will show that beti-cel provides a high

rate of durable transfusion-independence and trends of improvement in iron overload and erythropoiesis. Its safety profile reflects known side effects of mobilization and conditioning, and during beti-cel clinical development there was no deaths, no malignancy, and no BB305 LVV mediated safety event.

In summary, beti-cel is a potentially curative option for patients with beta thalassemia who require regular red blood cell transfusions. Today, we will focus on eli-cel. We will show that eli-cel is efficacious in treating early active CALD as compared to untreated patients and compared to the standard of care allogenic transplant. Eli-cel can stabilize CALD and, in certain circumstances, provide a survival advantage compared to allotransplant.

Eli-cel has important identified risks, which must be considered, including the risk of myelodysplastic syndrome, or MDS. Because of the fatal nature of CALD and the inherent morbidity and mortality of allotransplant, benefit/risk evaluations of eli-cel show that it is an essential, life-saving therapy for

patients with mismatched donors and a meaningful option for those with a matched, unrelated donor. The proposed indication for eli-cel is for the treatment of patients with early active cerebral adrenoleukodystrophy who are less than 18 years of age and do not have an available and willing HLA-matched sibling donor.

Comprehensive data supporting the efficacy and safety of eli-cel were collected in five clinical trials conducted over the past decade and (inaudible) numerous fruitful interactions with the FDA. Shown in purple are studies conducted in patients with CALD who are either untreated or treated with allogenic transplant. These studies provided context for our two eli-cel studies, shown in light blue, that treated a total of 67 patients. We are committed to the follow-up of patients for 15 years post-treatment in our long-term follow-up study and, after approval, in our registry study.

This is our agenda for today. This morning you will hear an overview of CALD and the summary of

the data supporting a positive benefit/risk assessment of eli-cel and a proposed indication. A number of additional key experts will be with us today to answer questions. Thank you. And now I would like to invite Dr. Eichler to provide an overview of CALD, a devastating disease with a high unmet need.

APPLICANT PRESENTATIONS: CEREBRAL ADRENOLEUKODYSTROPHY

DR. FLORIAN EICHLER: Thank you. My name is Florian Eichler. I'm a neurologist at Mass General. I have no financial interest in the outcome of this meeting, but my institution has received funding for the clinical trial as well as for my consulting on this program.

So what is adrenoleukodystrophy? Adrenoleukodystrophy is a single gene disorder due to mutations in the ABCD1. ABCD1 encodes a peroxisomal half transporter that is responsible for importing very long-chain fatty acids into the peroxisome, hence, very long-chain fatty acids accumulate across multiple

tissues. There are four main forms of adrenoleukodystrophy that range in severity. Childhood cerebral adrenoleukodystrophy is the most severe form, and approximately 40 percent of boys, mostly between the ages of 4 and 10, develop this devastating phenotype.

I want to illustrate here a boy who came to my clinic. You can see this boy six months before arrival, precocious, very active here in a karate class, high-functioning. And then, on the right you see the boy after onset of cerebral adrenoleukodystrophy, six months after coming to my clinic. He is at this point nonverbal. He has trouble walking and has vision difficulties. You can see the marked sensory attacks here causing him to stumble and need assistance. These boys do not suffer from development delay but rather from regression after onset of demyelination in the brain.

Importantly, the lesions were already progressing at the time he was asymptomatic. Now this disease strikes boys in the prime of their development

and affects multiple neurologic domains. To measure this progressive disease, Gerald Raymond developed a 25-point neurologic function score that encompasses the many effected domains. These range from cognition to vision to swallowing, gait difficulties, incontinence, to seizures.

From these we define six major functional disabilities, or MFDs, because they are clinically meaningful and unambiguous measures of cerebral ALD disease burden: loss of communication, cortical blindness, tube feeding, wheelchair dependence, no voluntary movements, and total incontinence. These MFDs were used to define a binary endpoint, the MFD-free survival. Let me emphasize three points here. First, specific definitions of these event terms have been provided to all investigators who are experts in the care for cerebral ALD patients and who are trained to detect these events.

Second, in separate research on the test characteristics, even physicians who are naïve to the MFD assessment reliably detected the presence of MFDs

in all simulated scenarios, with 97 percent inter-rater agreement, as described by Raymond and colleagues. Third, patients who progress to this stage typically develop multiple MFDs concurrently or in short sequence, further supporting that the binary MFD-free survival endpoint is a robust measure.

As I mentioned before, active cerebral ALD can progress swiftly. The boys usually develop normally, many performing at a high level, then develop attention deficit and personality changes. They go on to have vision and hearing problems, develop gait problems, and then often are vegetative or dead within one to two years. It's important to note that the brain MRI changes occur prior to onset of symptoms, and you can see the earliest signs of disease on brain MRI. As shown in the bottom panels, lesions spread within the white matter of the brain and in a symmetric conflict fashion take over the entire white matter over time, spreading like wildfire and destroying neurologic function as it progresses.

A scoring system was developed by Daniel Loes

that accounts for lesion growth as it effects different anatomical regions. This system ranges from 0 to 34, with the lower numbers showing smaller lesions, the higher numbers larger lesions, as illustrated on the right. Early cerebral ALD is defined as Loes scores from 0.5 to 9 and NFS of 0 or 1. If white matter lesions are present on MRI, we determine whether the lesion is active using a contrast agent such as gadolinium. Gadolinium enhancement is a strong predictor of rapid disease progression and impacts treatment decisions. It indicates the breakdown of the blood/brain barrier, which is visible as garland of contrast enhancement on brain MRI.

You can see here work from the group at Hopkins and Elias Melhem, which showed that patients who gadolinium enhancement on their MRI had rapid lesion progression on follow-up. Whereas those patients without gadolinium enhancement showed less or no growth of their lesion. Gadolinium enhancement is a pathognomonic sign of active, meaning progressive, cerebral ALD. It is a trigger for treatment either by

bone marrow transplantation or, in our case, enrollment in the ex vivo gene therapy trial. This reflects the international recommendations for the diagnosis and management of patients with adrenoleukodystrophy.

We've known for several decades that allogeneic stem cell transplantation, if the graft takes, can slow or stop cerebral ALD progression and improve survival compared to no treatment, shown here on the left. The effect of allogeneic stem cell transplantation also extends into functional outcomes if performed in the early stages of disease, shown here on the right. In those boys that are treated too late, the lesion is too large, and these boys suffer from neurologic disease progression despite transplantation.

The goal of treatment is to halt disease. Treatment does not reverse deficits. Because of this, it is absolutely critical to monitor these boys by MRI to detect active disease as early as possible. Once the boys have active cerebral ALD, it is an absolute urgency to proceed to treatment, as they would unfortunately otherwise progress and experience rapid

neurologic decline. While effective, allogeneic stem cell transplantation has substantial risks. Among these are transplant-related mortality, graft failure, and graft versus host disease.

We have learned over the years that outcomes are typically more favorable if transplantation is performed using cells from an unaffected HLA-matched sibling donor, but only approximately 10 percent have such a donor. The remaining 90 percent of patients may have a matched unrelated donor or may only have HLA-mismatched donor options. In conclusion, cerebral ALD is characterized by inflammatory cerebral demyelination leading to progressive, irreversible loss of neurologic function across different domains and death if left untreated. It is striking boys in the prime of their development, and progression can be swift.

Allogeneic stem cell transplantation is effective if performed at the early stage of cerebral involvement. As you will see in the following presentations, patients without matched sibling donors have substantial risks associated with allogenic

transplantation, particularly for those with only an HLA-mismatched donor. We think that ex vivo gene therapy using autologous cells is therefore particularly appropriate for these patients and provides benefit and new options for them. Thank you.

APPLICANT PRESENTATIONS: EFFICACY

DR. JAKOB SIEKER: Thank you, Dr. Eichler. I'm Jakob Sieker, the eli-cel clinical development physician at bluebird bio. Over more than a decade, despite its rarity, the clinical program collected data on over 250 CALD patients across five trials. ALD-101 is a retrospective study that defined the natural course of untreated CALD and historic outcomes of allogenic stem cell transplantation. ALD-101 informed the selection of the primary endpoints for the pivotal eli-cel study and defined the benchmark that efficacious treatments must exceed.

While allogenic stem cell transplantation is not an approved treatment, the data reflect that

patients who are identified at an early stage of active disease are rarely left untreated. Early detection and treatment of appropriate patients before loss of neurologic function occurs is desirable but impacted the available data on untreated patients. This introduces the need for careful consideration of the program's data in totality. Sixty-seven boys with early active CALD were treated with eli-cel in clinical studies.

ALD-102 is the completed pivotal eli-cel study and described eli-cel safety and efficacy in 32 patients. ALD-104 is a second eli-cel study with a similar design providing additional efficacy and safety information. Procedural differences between the studies pertain to the mobilization regiment, lymph node (phonetic) depleting agent, and post-infusion GCFUs. Enrollment and treatment in ALD-104 are complete. Follow-up is ongoing.

After two years in the eli-cel treatment studies patient enrolled in the long-term follow-up study LTF-304. Available LTF-304 durability and long-

term safety data are integrated in this presentation. ALD-103 is a partially retrospective and partially prospective non-interventional study. It enrolled 59 boys with early or advanced CALD who received allogenic stem cell transplantation in or after 2013. ALD-103 serves as a contemporaneous external control to the pivotal eli-cel Study 102.

Today I will present eli-cel's efficacy in three parts: first, eli-cel compared to no treatment; second, eli-cel compared to allogenic stem cell transplantation; and third, the durability of eli-cel's effects. I want to start with the comparison of eli-cel to no treatment. The primary efficacy analysis was a comparison of eli-cel to a pre-specified benchmark that reflects the course of untreated CALD. Further, we will compare eli-cel to an untreated patient population with early active disease and address the FDA's observations. The pivotal eli-cel Study ALD-102 met the prespecified success criterion for the primary efficacy endpoint.

This endpoint was major functional disability-

free survival at two years after treatment. At this timepoint, 29 out of 32 eli-cel treated patients, or 90.6 percent, were alive and free of MFDs. The confidence interval lower bound was 75 percent and clearly exceeded the pre-specified benchmark of 50 percent show here as an orange line. The MFD-free survival endpoint included MFD, death, or second transplantation events. After Study ALD-102 was complete, three cases of myelodysplastic syndrome, or MDS, were reported.

In order to capture all major events, the event-free survival was analyzed. Event-free survival includes all the elements of MFD-free survival plus MDS. From here on I will present event-free survival. The event-free survival at two years in the ALD-102 population is identical to the primary analysis. To reflect the total eli-cel treated populations I will present the pooled results of both eli-cel studies from here on.

In the total eli-cel population the event-free survival at two years was 91 percent, also, clearly

exceeding the pre-specified benchmark. I will now address an FDA observation. The pre-specified benchmark was in large parts derived from an untreated patient population with active CALD in Study ALD-101.

FDA observed that this untreated population had more advanced disease and likely progressed more rapidly than the treated population, which had early active disease. Therefore, it raises the question if the 50 percent benchmark and the two-year timepoint are appropriate to assess whether eli-cel is superior to no treatment. We can address this observation in two ways. First, we can evaluate the proportion of event-free survival at several years beyond the two-year timepoint.

Second, we can use a population derived by FDA that represents early active CALD without treatment. If we look beyond two years, eli-cel continues to exceed the benchmark at three, four, and five years after treatment, assuaging any concerns about baseline dissimilarities and the potential effect on time to progression of disease. When we planned this primary

efficacy analysis with the FDA, the planning showed that to present two-year data for the initial cohort of 17 patients. We present to you today with over five years of follow-up on this cohort.

The second way to address FDA's observation is to compare eli-cel to the untreated population derived by the Agency that reflects early active CALD. The Agency applied an imputation strategy that resulted in the subgroup of seven untreated patients who will eventually develop documented active disease but were at an early stage around the first available MRI. Five of these patients developed MFDs or died. Shown here in green is the Kaplan-Meier curve of event-free survival from CALD diagnosis.

Using this conservation imputation strategy, these untreated patients developed major functional disability at a substantial rate within two years from CALD diagnosis. As noted by the FDA, the median time to event was 20.4 months after diagnosis for the five patients who experience events. Eli-cel compared favorably to no treatment. Added here in blue is the

Kaplan-Meier curve of event-free survival for eli-cel treated patients from infusion. Estimated event-free survival at two years was 92 percent after eli-cel, which compared favorably to the 57 percent estimated for no treatment.

At seven years, 87 percent of eli-cel treated patients were estimated to be event-free compared to 38 percent of untreated patients. Based on this exploratory analysis, eli-cel reduces the risk of developing events by 72 percent compared to no treatment. Due to the occurrence of MFDs after seven years, and the low number of patients with follow-up beyond this time point, the event-free survival is considered not reliably characterized beyond seven years.

You've seen that eli-cel compares favorably to no treatment. Now I'm going to show you how it compares to allogeneic stem cell transplantation without matched sibling donor and address FDA's observations of the similar baseline characteristics between the treatment groups. Dr. Eichler explained

that matched sibling donors typically have favorable outcomes and would receive allogeneic transplantation. Therefore we focus on the population without matched sibling donors who would be eligible to receive eli-cel according to a proposed indication statement.

Only patients with early active disease were used for efficacy comparisons between eli-cel and allogeneic stem cell transplantation. Baseline characteristics of these populations were comparable. The median ages at CALD diagnosis and stem cell infusion were slightly higher in patients treated with allogeneic stem cell transplantation. However, the baseline characteristics most critical to CALD progression, including the NFS less MRI score and the gadolinium enhancement status, were similar.

Approximately 95 percent of patients had a baseline neurologic function score of zero in both populations. Median Loes score was two and identically in both populations. All patients had gadolinium enhancement at enrollment or prior to treatment. Because of the high similarity among these critical

characteristics we conclude that it's appropriate to compare these efficacy populations. Event-free survival after eli-cel, shown here in blue, compared to favorably to allogeneic stem cell transplantation in purple.

The estimated two year survival rates were 92 versus 71 percent, respectively. This benefit was also observed in the propensity score adjusted analysis that adjusts for minor baseline differences. The patients treated with allogeneic stem cell transplantation without matched sibling donor shown here either received cells from a matched unrelated donor or from a mismatch donor, and results for these groups are shown on the next slide. Here are the results for patients who had a matched unrelated donor. These are comparable to eli-cel.

Next, I will show you an additional curve with the results for those who only had mismatched donors. These patients experienced frequent early events, largely representing second transplantation due to graft failure. The event-free survival at month 24 was

92 percent after eli-cel and 43 percent have HLA-mismatched transplantation. We agree with the Agency that eli-cel's benefit is most apparent for patients who only have mismatched donor options.

I want to remind you that the definition of event-free survival, as shown here, considers MFD, death, MDS, and second transplantation as events. We consider graft failures, as observed in the allogeneic stem cell transplantation group, as events. These are major events with prolonged hospitalization, increased risk of death, disease progression, or other complications. Since the Agency observed that graft failures are not commensurate with death or MFD we would be prepared to show pertinent sensitivity analysis if raised during Q&A.

You've seen that eli-cel compares favorably to allogeneic stem cell transplantation without matched sibling donor, particularly with mismatched donors. Now I'm going to show the durability of eli-cel's effect using direct clinical measures of neurologic function and cognition. The neurologic function score

covers a broad range of pertinent symptoms, including the major functional disabilities and symptoms of lesser severity. At two years after eli-cel treatment, 89 percent of evaluable patients had no change from their baseline score.

The majority of patients maintained their baseline score beyond two years after treatment, including 86 percent with no change from baseline at year five. Lastly, the performance intelligence portion data, shown here, reflect the performance of pertinent subscales from age-appropriate Wechsler Test. These functional tests are recognized as sensitive measures of cognitive ability and demonstrate that at two and five years after eli-cel treatment, the majority of patients maintained normal IQs.

In summary, eli-cel compares favorably to no treatment. The pivotal eli-cel study met the primary efficacy success criterion. 90.6 percent of patients were alive and free of MFD at month 24 post-treatment. The confidence interval lower bound of 75 percent clearly exceeded the pre-specified 50 percent

benchmark. Eli-cel continued to exceed the pre-specified benchmark at three, four, and five years after treatment.

Further, eli-cel reduces the risk of developing events by 72 percent compared to an imputed, untreated population with early active CALD derived by FDA. Dr. Eichler showed you that allogeneic stem cell transplantation is effective and the standard of care for patients with early active CALD. Therefore, we present the data in context of transplantation.

These data demonstrate that event-free survival after eli-cel compared favorably with allogeneic stem cell transplantation without matched sibling donor. For the populations used here, differences in baseline characteristics were either absent or minor, and propensity score adjusted analysis support the primary conclusions.

It is important to note that the event-free survival rate after eli-cel is similar to allogeneic stem cell transplantation with a matched unrelated donor, which also achieved 90 percent event-free

survival at month 24. In contrast, the event-free survival rate after eli-cel is higher than for HLA-mismatched transplantation, with a rate of 43 precent at month 24 for the latter.

Further, eli-cel's efficacy is durable. Eli-cel maintained an event-free survival rate of 87 percent through seven years of follow-up. And lastly, the majority of eli-cel treated patients maintained their baseline neurologic function and normal performance IQ. And now I would like to turn it over to Dr. Demopoulos for the safety and benefit/risk assessment.

APPLICANT PRESENTATIONS: SAFETY AND BENEFIT/RISK

DR. LAURA DEMOPOULOS: Thank you, Dr. Sieker. My name is Laura Demopoulos. I'm a safety physician at bluebird bio. In this section of the presentation I'm going to describe the safety data from the eli-cel development program. A key driver for the development of an autologous treatment option for CALD patients was

the morbidity and mortality of immune incompatibility events following an allo-graft transplant.

The next several slides thus provide comparative data between eli-cel and allotransplants relating to these complications. A primary safety success criterion was prospectively established for the program and was defined as the proportion of eli-cel treated patients in Study ALD-102, shown on the left, versus allo-treated patients in study ALD-103, shown on the right, who experienced acute or chronic graft versus host disease in the 24 months after treatment.

As expected, autologous treatment with eli-cel did not result in GVHD events while just over half of patients in TP-103 experienced acute or chronic GVHD. This difference was highly statically significant, and the primary safety success criterion was met. Events with a fatal outcome effected one patient, or 1.5 percent of eli-cel treated patients, seen here at TP-102/104. This patient had clinical and radiologic evidence of rapid disease progression starting almost immediately after eli-cel treatment. He then developed

four major functional disabilities followed by cardio-respiratory arrest two years after treatment.

In contrast, there were 15 deaths in the allo population of TP-103, representing just over one quarter of patients. Two were in the matched sibling donor, or MSD, subgroup, and 13 were in recipients of an allo-graft from a donor that was not a matched sibling, shown here as the NMSD subgroup. Death has occurred disproportionately in the NMSD subgroup. Of the 15 deaths, 9 were considered transplant-related and 7 followed the occurrence of GVHD.

The striking difference in death rates between eli-cel and allo-treated patients underscores the significant potential for transplant-related death following allo graft treatment, primarily among those without a matched sibling donor and particularly following the occurrence of GVHD. Another manifestation of immune incompatibility is engraftment failure. This figure depicts the proportion of patients with successful primary neutrophil engraftment.

All eli-cel patients engrafted successfully at a median of 13 days after treatment. Ninety percent of patients in TP-103 overall had successful primary engraftment, with all failures in the NMSD subgroup. Following primary neutrophil engraftment, all eli-cel treated patients followed for two years maintained engraftment. In contrast, about a quarter of allo patients in TP-103 had engraftment failure by two years, as did about a third of NMSD recipients.

Nine of the ten allo-treated patients with either primary or secondary engraftment failure required subsequent allotransplants, and three of these nine patients died on study. Having reviewed the comparative data for GVHD, death, and engraftment failure the next several slides describe safety findings specific to the eli-cel treatment regiment, which comprises mobilization apheresis, conditioning and eli-cel treatment.

Serious adverse events eli-cel treated patients were generally attributed to conditioning, eli-cel or CALD. Of the 67 patients treated, just over

half had any serious adverse event. Treatment emergent serious adverse events occurring in at least two patients are tabulated here, with febrile neutropenia and pyrexia being most common. Serious adverse events attributed to eli-cel and serious seizures will be discussed in more detail shortly.

Due to the disease under study, serious neurologic events are of particular interest. Seven patients treated with eli-cel were effected. Of these, two had major functional disabilities in association with another neurologic SAE. The first of these is the patient I described previously who died, having developed serious dyskinesia followed by multiple MFDs. The second patient developed transverse myelitis seven months after treatment. He subsequently developed an MFD of total incontinence, which was thought to be a consequence of transverse myelitis.

Five patients had serious seizures, all with onset two or more years after eli-cel treatment. Four of these patients are otherwise clinically stable and have had follow-up ranging from one to five years since

seizure onset. The fifth patient has unfortunately developed additional neurologic symptoms including gait disturbance and visual impairment. Adverse drug reactions due to eli-cel itself occurred in eight, or about 12 percent, of patients.

Five patients had eli-cel-related serious adverse events. Three of these were cases of myelodysplastic syndrome, and that'll be discussed in more detail shortly. Two patients had prolonged pancytopenia following treatment. One of these was subsequently diagnosed with MDS, while the other has parvovirus. One patient had an event of BK viral cystitis, which resolved with supportive care. Three patients had non-serious events of eli-cel infusion-related vomiting and nausea.

As mentioned, three patients treated with eli-cel were diagnosed with myelodysplastic syndrome identified as likely mediated by Lenti-D lentiviral vector insertion, thus representing insertional oncogenesis. The topic of lentiviral vector safety and insertional oncogenesis will be discussed in detail

this afternoon. Two of these three patients presented similarly. They had timely neutrophil engraftment, but their time to platelet engraftment was markedly longer than for other subjects, just over 100 days.

Further, integration site analysis, or ISA, an exploratory assay used to identify specific vector insertion sites in the stem cell genome and to monitor chronal dynamics identified vector containing clones contributing at least 50 percent of analyzed cells in both patients at month six. Each had a vector insertion in MECOM, a known proto-onco gene. No driver mutations were identified in either subject, and their bone marrow biopsies showed dysmegakaryopoiesis. Both were diagnosed with single lineage MDS effecting megakaryocytes within two years of eli-cel treatment. Both have since undergone allotransplant and are in remission.

A third patient in the eli-cel program was more recently diagnosed with MDS, approximately seven and a half years after he was treated. He had had stable and polyclonal bone marrow recovery but then

presented with severe thrombocytopenia and circulating blasts, which contained the lentiviral vector. ISA showed a clone with a PRDM16 insertion, which contributed more than 50 percent of analyzed cells. PRDM16 is proto-onco gene similar to MECOM. He underwent chemotherapy followed by allotransplant and is in early recovery.

Given the importance of insertional oncogenesis, specific monitoring for MDS will be implemented in the post-marketing setting. Extensive data analyses for early detection and risk mitigation reinforce the importance of a routine CBC at least every six months as the basis for this monitoring. Patients with specific CBC abnormalities will be evaluated to determine the underlying cause. Further, early markers of risk include peripheral blood vector copy number at month six and evidence of clonal hematopoiesis. These will be routinely assessed in the post-marketing registry study, REG-502.

Close follow-up will be facilitated by restricting eli-cel access to a limited number of

expert qualified treatment centers, where we anticipate approximately 10 patients per year will be treated given the rarity of the disease. This framework establishes the basis for continual reassessment of benefit/risk, and any subsequent changes to monitoring can be rapidly communicated. Conclusions based on the safety data are as follows. The primary safety success criterion of a significant reduction in GVHD was met. Notably, eli-cel treatment entirely avoided key immune-mediated complications of allotransplant, including graft versus host disease, graft failure, and transplant-related mortality.

Adverse drug reactions related to eli-cel include myelodysplastic syndrome, pancytopenia, viral cystitis, and infusion reactions. As described, a comprehensive post-marketing surveillance plan for malignancy will be established. What follows next is an integrated view of the benefit/risk balance of eli-cel treatment derived from the programs efficacy and safety data in the context of the natural history of CALD and existing treatment options.

The assessment of the benefit/risk profile of eli-cel is complex. Untreated, CALD can result in devastating neurologic decline and death in childhood. Allotransplant is the only available therapeutic option and has good outcomes when a matched sibling donor is available. Unfortunately, only about 10 percent of effected children have a matched sibling donor. NMSD allo grafts have significant morbidity and mortality resulting from immune incompatibility.

As Dr. Sieker presented, outcomes are heterogenous in this subgroup, depending on whether the donor is a matched unrelated donor or a mismatched donor. Thus defining the optimal use of eli-cel requires balancing the known benefits and risks of an NMSD allo graft against the demonstrated benefits and gene therapy-specific risks of autologous eli-cel therapy. A Cox proportional hazard ratio analysis was performed to provide eli-cel versus allo comparative data for both event-free survival, shown in the top panel, and overall survival in the bottom panel.

The eli-cel population in this analysis

comprises all 67 treated patients. And the allo comparator includes those subjects from the ALD-103 study who matched eli-cel eligibility criteria and fit the proposed indication, abbreviated as TPES-103 NMSD. Also shown are the allo component subgroups, that is recipients of matched unrelated or mismatched allo grafts. Recall that for purposes of this analysis, events included MFDs, deaths, second transplant, as well as the three cases of myelodysplastic syndrome in the eli-cel treated patients.

This analysis demonstrates that the advantage of eli-cel is more apparent for patients who only have mismatched donor options in whom eli-cel reduces the hazard of an event or death by more than 90 percent and that eli-cel may be an acceptable alternative treatment option for those with a matched unrelated donor. This graphic depicts an integrated approach to considering treatment in patients with CALD.

As is the case for all patients with life-threatening diseases, patients with CALD benefit from having multiple treatment options. The shaded

horizontal bar represents the spectrum of allotransplant histocompatibility. Those with a matched sibling donor should undergo allotransplant, as the risk of immune complications is low and long-term benefit has been established. Patients with only mismatched donor options should be treated with eli-cel, as the rate of early morbidity and mortality after allotransplant in this group is extremely high.

Patients with matched unrelated donors fall in a spectrum where considerations beyond histocompatibility may weigh in favor of either treatment. These factors are shown in the white box in the center. Some of these are assessed clinically, while others reflect personal preference and circumstance. The aggregate weight of these considerations will determine which options should be used.

Accordingly, the approval of eli-cel for the treatment of patients without a matched sibling donor will allow for individualized treatment decisions and improved patient care. Thank you and I'd like to turn

it over to Dr. Christine Duncan to provide a clinical perspective.

APPLICANT PRESENTATIONS: CLINICAL PERSPECTIVE: THE ROLE OF ELI-CEL

DR. CHRISTINE DUNCAN: Thank you, Dr. Demopoulos. I'm Christie Duncan. I'm the medical director of Clinical Research and Development in the Gene Therapy Program at Boston Children's Hospital and the in-patient director of our Pediatric Stem Cell Transplant Service. My clinical expertise is in the cellular therapy of children who are diagnosed with rare neurometabolic disorders. Thank you to the FDA and this Advisory Committee for today's discussion of eli-cel.

It is my honor to offer my clinical perspective on the role of eli-cel in the future landscape of the treatment for cerebral ALD. In over 12 years I've treated 43 patients with cerebral ALD with allogeneic stem cell transplant or eli-cel. One

of the most important things I have learned in treating these children is that there's no average, there's no typical patient. Each child is unique in the presentation of their cerebral disease.

Some have long family histories of many effected relatives. Others were identified because of a diagnosis of a sibling who in many cases was too advanced for treatment, has died, or is neurologically devastated. Some boys are diagnosed because their own neurologic or adrenal symptoms, and thankfully, a growing number of boys are diagnosed because of newborn screening. There's also diversity in the therapeutic options available to boys with cerebral ALD. Cellular therapy is not effective for boys with advanced disease, and neither allogeneic transplant nor gene therapy is advised in that setting.

Allogeneic transplant is a consideration for patients with early stage disease. This is a complex process that occurs at the hands of highly trained providers at certified specialized centers. Planning a transplant requires the understanding and balancing of

many factors, including the selection of a donor, the stem cell source, chemotherapeutic conditioning regiment, and graft versus host disease prevention treatment.

We do not have enough time today to discuss all of the elements of transplant care, nor are all of those factors pertinent to our discussion. I would like to talk about the aspects of transplant care that are highly relevant to the discussion of eli-cel. Data over decades has demonstrated that for patients who have HLA-match related donors, who do not have an ABCD1 gene mutation the risks associated with allogeneic transplant are convincingly outweighed by the potential benefits.

Stem cell transplant is the standard of care for patients who have acceptable available related donors. You'll note that matched sibling donor is a planned exclusion in the indication for eli-cel. Unfortunately, due to the genetic nature of this disease, match related donor transplants are uncommon. Per the data between 2013 and 2015 show that only

approximately of 10 percent of allotransplants for this disease use related donors.

For the majority of cerebral ALD patients unrelated donor transplantation is complicated. International registries are searched to find appropriate, unrelated donors. For approximately 75 percent of Caucasian donors patients with Western European ancestry an acceptable donor can be identified. This is not the case for all other racial and ethnic groups. For Hispanic patients in the United States an appropriate donor can be identified for approximately 40 percent of patients and for less than 20 percent of African American patients. The current unrelated donor pool is not sufficient for all patients, particularly non-Caucasian ones.

Those who cannot find an acceptable unrelated donor need different options. Based on those data, one could argue that the most appropriate role for eli-cel is in patients who do not have a fully related, match related, or unrelated donor. I disagree. The risks of transplant are significant for those who have

mismatched unrelated donors and those who have matched unrelated donors. Those risks include greater risk of graft failure, graft versus host disease, and death compared to patients treated with related donors.

Not all matched unrelated donors are the same. There are factors such as the donor age, sex, and others that impact outcome. And I'm happy to discuss those further in the Q&A if considered. Those are facts. Those are not merely academic considerations. They are the realities of unrelated donor transplantation. I've transplanted a young boy with cerebral ALD three times in the same hospitalization, the second and the third transplants performed in the ICU due to graft failure.

He survived to hospital discharge and died a year later of complications of treatment disease. I spent hours trying to find appropriate mental healthcare for children suffering from depression and anxiety as a result of the complications of treatment and the prolonged isolation that follows allogeneic stem cell transplant.

And I stood next to the mother and the father of a patient as we watched their son die after suffering myocardial infarction at age nine directly as a result of chronic graft versus host disease -- a myocardial infarction at age nine years old. That was not academic for any of us. Boys who do not have a match related donor need options for alternative therapies. The other thing we must remember is the impact of this horrific disease and complex treatments on the patients and families.

As you've heard, these patients come to treatment discussions in the setting of trauma that can come from the experience of death or neurologic deterioration of another child or family member. The trauma may come from receiving a new diagnosis and learning what that means for their child. And our team spend many hours over days to weeks trying to support families in their trauma and to prepare them for the road ahead: a road that involves a long time in a hospital, a road that involves immune suppressing medications, and a road that involves frequent visits

and common readmissions to the hospital. And that road is often far from home.

We have to consider their access to longer term care and how patients and families will navigate the time, energy, and cost of treatment, and more. I have met with and treated dozens of patients with cerebral ALD, and I know that we need more. And I know that we can do better.

I had hoped that things would be crystal clear with the development of an autologous gene therapy. I've been pleased to see how well an autologous transplant can be tolerated in the short term compared to allogeneic transplant with less time spent in the hospital, fewer urgent care visits, and less post-transplant medications with fewer side effects of those drugs.

Further, I've been pleased to see that the completed pivotal eli-cel study was a success based on the primary efficacy and safety endpoints. The supporting MFS, Loes score, and neuropsychological testing helped confirm that for me, and provide

additional insights about the treatment process. Clearly, I hoped that there will be no insertional oncogenesis, that none of my patients would develop myelodysplasia or cancer. But this happened, and we take this issue extremely seriously.

I was consenting physician for all 26 boys treated at our center, including two of the three boys who developed myelodysplasia. I told their mothers about the MDS diagnosis, explained what happened to the best of our understanding, and have been their physician through the next steps of care. I also shared the news with the families of every other patient we treated at our center, and those are not easy conversations.

While I know that the FDA decision regarding eli-cel is not based only on the perceptions and feelings of patients and their family members, I feel a responsibility to share their voice. When told about the MDF, not one family expressed anger or regret. They expressed concern for the effected children. They said they knew of the risk, and they all wanted to know

how we are moving forward.

As I told you before, I'm used to difficult situations and outcomes treating children with cerebral ALD with cellular therapies. These are intense and arduous therapies. MDS after eli-cel is an important consideration, but it is not the only consideration. We need to balance the potential risks and benefits of therapeutic options available to each patient. We need to educate patients and families and move forward together as we determine which patients benefit most from eli-cel.

At the end of it, one spectrum is a patient has a matched sibling donor with all other factors being favorable. I'm comfortable with allogeneic transplant for that patient. At the other end of the spectrum is a patient who has no related or unrelated donor options. We need an option for that patient. In between those ends of the spectrum are multiple layers of complexity, and we need to allow for open dialogue about the possibilities. These are case-by-case discussions often with no clear-cut answers.

Having multiple therapeutic options allows for better treatment conversations and I believe better care. Patients and families benefit from options, however complex they may be. Allowing for informed decision making between our healthcare team and our families should be our goal. I ask you to support eli-cel as a treatment option for our patients without matched sibling donors, and I hope that we have adequately explained to you the critical need for children with cerebral adrenoleukodystrophy. Thank you.

FDA PRESENTATION: ELIVALDOGENE AUTOTEMCEL (ELI-CEL): BLA 125755 CLINICAL CONSIDERATIONS FOR EFFICACY AND SPECIFIC SAFETY IN EARLY CEREBRAL ADRENOLEUKODYSTROPHY

DR. SHELBY ELENBURG: Good morning. I'm Dr. Shelby Elenburg. I'm a medical officer in Office of Tissues and Advanced Therapies CBER FDA. I will be presenting FDA's review of the evidence provided to support efficacy in BLA 125755 for elivaldogene

autotemcel, or eli-cel, in the treatment of early cerebral adrenoleukodystrophy in males less than 18 years of age without an available and willing HLA-matched sibling hemopoietic stem cell donor. My colleague, Dr. Leah Crisafi, will be presenting FDA's prospective on product specific safety.

I will briefly review the pathophysiology and disease background for cerebral adrenoleukodystrophy, or CALD, the eli-cel product, and clinical development program including an overview of the primary eli-cel study ALD-102. I then will present the data supporting efficacy and the identified review issues. Dr. Crisafi will review product-specific safety issues and the benefit/risk summary to complete this morning's presentation.

Cerebral adrenoleukodystrophy, or CALD, is a rare, x-linked neurodegenerative metabolic disorder caused by mutations in the ABCD1 gene that lead to accumulation of very long-chain fatty acids, or VLCFAs, that start a neuroinflammatory cascade. CALD develops in approximately 40 percent of the roughly 1 in 20,000

males effected by the broader x-linked adrenoleukodystrophy. It presents between approximately 3 to 10 years of age, initially with attention deficit hyperactivity disorder-like symptoms, behavioral concerns, or adrenal insufficiency before progressing into neurologic dysfunction.

Once symptomatic, if left untreated, neurologic deterioration to a vegetative state and ultimately death typically occurs by the second decade of life. CALD is heterogeneous, and some patients have slow disease progression and could remain asymptomatic for many years. Unfortunately, there is no way to predict an individual patient's rate of progression or how long after diagnosis symptoms will begin.

There is no FDA approved treatment for CALD in the United States, but allogeneic hematopoietic stem cell transplants, or allo-HSCT, is the standard of care performed shortly after diagnosis when there is the earliest evidence of cerebral involvement on brain MRI and often before the onset of symptoms.

It has traditionally been thought that the

ideal donor for HSCT is an HLA-matched sibling donor of the patient. It is also generally thought that HSCT from alternative donors is associated with increased HSCT-related risks, including graft rejection, graft versus host disease, and transplant-related mortality. As you have heard, the most commonly used scoring system to rate clinical severity of disease in CALD has been neurologic function score, or NFS. A score of 0 to 25 is assigned based on 15 symptoms across 7 domains. A score of zero is asymptomatic or normal, and a higher score indicates more symptomatic and severe disease.

The major functional disabilities, or MFDs, are a subset of the NFS that are considered largely irreversible, clinical neurologic changes, and CALD. The MFDs were chosen by the applicant based on impact on independent functioning. The six MFDs are indicated by red boxes in this figure and are loss of communication, cortical blindness, tube feeding, wheelchair dependent, loss of voluntary movement, and total incontinence.

Cerebral adrenoleukodystrophy, CALD, is diagnosed radiographically once there's evidence of brain involvement with characteristic demyelination on MRI. And, therefore, the diagnosis of cerebral ALD can be made prior to the onset of symptoms. Loes score is a scoring system developed to grade demyelination on brain MRI and CALD based on location and extent of disease and presence or absence of focal and/or global atrophy. A score of 0 to 34 is assigned where 0 indicates a normal MRI, or absence of disease, and higher scores correlate with more severe radiographic disease.

Early disease physically corresponds to a Loes score between 0.5 and 9, with scores above 9 considered advanced disease. Gadolinium is a contrast agent now routinely utilized in CALD brain MRIs. Presence of gadolinium enhancement, or GdE+, is indicative of active inflammatory demyelination associated with increased risk of disease progression and higher five-year mortality. Hematopoietic stem cell transplant is typically performed once early active CALD is diagnosed

based on MRI findings.

MRI findings are thus used for guiding treatment decisions and for monitoring of radiographic disease progression following transplant. The drug product elivaldogene autotemcel, or eli-cel, is a lentiviral vector, LVV, gene therapy product intended to replace the deficient ABCD1 gene. It will be discussed in further detail in the cross-product safety discussion later this afternoon.

As you have heard from bluebird bio, the clinical development program includes several studies. The primary trial for eli-cel is ALD-102, a Phase 2/3 trial completed in March 2021. An additional Phase 3 trial, ALD-104, is ongoing. Both are open label, single arm, multi-center international studies of eli-cel in males less than 18 years of age with early active CALD who were to be followed for at least two years for safety and effectiveness.

Although ALD-102 and ALD-104 are similarly designed studies, conditioning regiments were different between the two studies. After completion of ALD-102

or ALD-104, subjects are supposed to enroll in the long-term follow-up study, LTF-304, for a total of 15 years of follow-up. The external control data used to support this application comes from two additional studies. Study ALD-101 is a completed retrospective natural history study of untreated and allo-HSCT treated CALD patients. Study ALD-103 was a combined retrospective and prospective observational study of CALD patients treated with allo-HSCT intended as a contemporaneous comparator for Study ALD-102.

It is worth noting that both control studies included at least some retrospective data collection. In addition, although Study ALD-101 data was collected in 2011 and 2012, it was important to understand that some of the ALD-101 subjects were diagnosed and/or treated 10 to 20 years, or more, prior to the treatment of subjects in ALD-102 with eli-cel. This is critical to understanding some of the differences in study populations I will tell you about in this presentation, as ALD-101 subjects were diagnosed when diagnostic methods were not as sophisticated, and patients were

often diagnosed at more advanced stages of disease.

Study ALD-102 was the primary study submitted by bluebird bio to support the safety and effectiveness of eli-cel. Subjects were eligible to enroll if they were males 17 years of age or younger with active CALD, which was defined by elevated VLCFA levels, brain MRI demonstrating Loes score between 0.5 and 9, and gadolinium enhancement. They also had to have an NFS of zero or one.

The intent was to enroll CALD subjects with early active cerebral disease who are asymptomatic or minimally symptomatic and have a high risk of disease progression. Throughout this presentation I will often refer to this early active disease population, which is also the population thought most likely to benefit from HSCT, as the primary comparator. Subjects were excluded from Study ALD-102 if they had a 10 out of 10 HLA-matched sibling donor.

The primary efficacy endpoint was number and proportion of subjects achieving month 24 major functional disability-free survival compared to a

benchmark value of 50 percent derived from analyses of the natural history study ALD-101. There are a lot of populations that will be mentioned throughout this presentation, and the strictly ALD-102 eligible population are important to understand. Strictly ALD-102 eligible is terminology chosen by the Applicant to define populations in the external control studies ALD-101 or ALD-103 who were supposed to have the same baseline early active disease defining criteria as the subjects enrolled in eli-cel study ALD-102: an NFS of zero or one, Loes score between 0.5 and 9, and GdE+ MRI.

As it is incredibly important, I remind you that this is the early active disease population who have no symptoms or very mild symptoms and are at high risk of disease progression. In subjects who received allogeneic HSCT, the strictly ALD-102 eligible population are named TPES. I ask you to please remember this term, TPES, as I will use it frequently throughout the presentation to refer to the early active disease population that received HSCT and that

would have been eligible for involvement in the primary eli-cel study.

The TPES-101 population in Study ALD-101 included 26 subjects, and TPES 103 in Study ALD-103 included 27 subjects. In the untreated population of Study ALD-101, there was only one subject who met the strictly ALD-102 eligible criteria. This may be explained by the fact that gadolinium status was not routinely assessed at the time subjects in Study ALD-101 were diagnosed and thus, for many subjects, gadolinium status was unknown.

By the time gadolinium was assessed in these untreated subjects, many already had advanced symptomatic disease with NFS and Loes scores outside the criteria listed on this slide and, thus, were not strictly ALD-102 eligible. The primary efficacy endpoint was number and proportion of subjects achieving month 24 major functional disability-free survival compared to a clinical benchmark from the natural history study.

To achieve MSD-free survival at month 24

following eli-cel treatment a subject must be alive, not have developed any of the six major functional disabilities, or MFDs, not have received rescue cells or hematopoietic stem cell transplant, and not have withdrawn from the study or been lost to follow-up. The benchmark for success was greater than 50 percent of subjects achieving month 24 MFD-free survival. The benchmark was derived from two populations in the retrospective natural history study, ALD-101.

Population number one was a cohort with presence of gadolinium enhancement on brain MRI who were untreated and never received HSCT, referred to as UTG-101. Throughout this presentation I will often refer to this cohort simply as population number one. It is worth noting that population number one is not strictly ALD-102 eligible and the majority of this population had more advanced disease with higher NFS and Loes scores than the eli-cel study cohort.

The MFD-free survival for population number one at month 24 following the first GdE+ MRI was 21 percent with an upper bound of the 95 percent

confidence interval of 45.6 percent below the 50 percent benchmark value. Population number two was the strictly ALD-102 eligible HSCT treated population, or TPES-101, without a matched sibling donor, referred to as no match sibling donor, or NMSD. Remember that the indication for eli-cel is children with early active CALD and no available matched sibling donor. Thus, population number two of the benchmark is the target population for eli-cel.

I will use NMSC in this presentation to refer to subjects who had HSCT from donors other than matched sibling donors who are referred to as MSC. The month 24 MSC-free survival for population number two following HSCT was 76 percent with a lower bound of the 95 percent confidence interval of 50.1 percent. The 50 percent benchmark is thus above the upper bound of the 95 percent confidence interval for month 24 MFD-free survival in the untreated GdE+ population and the same as the lower bound of the 95 percent confidence interval in the TPES-101 NMSC population.

Success on the primary endpoint was apparently

designed to show eli-cel is better than no treatment and at least similar to treatment with HSCT. Thirty-two boys aged 4 to 14 years with CALD were enrolled and treated with eli-cel in Study ALD-102 and followed for two years for safety and efficacy. Before I show you study results, it is important for you to understand the key baseline disease characteristics and demographics for cohorts used in the analysis of the primary efficacy endpoint of month 24 MFD-free survival.

UTG-101 in the first column is the untreated GdE+ population, or population number one of the benchmark. TPES-101 NMSD in the middle column is the strictly ALD-102 eligible HSCT population with no matched sibling donor or population two of the benchmark. And TP-102 in the last column is the cohort treated with eli-cel in ALD-102, highlighted with the dark blue box.

Please look at the top two rows. As you can see, median age and age at diagnosis were higher in the benchmark population than in subjects in ALD-102. More

concerning are the baseline, Loes score, and NFS differences, shown in the third and fourth rows and highlighted with the red box for the benchmark population. These baseline characteristics are very different between population number one and population number two.

You can see in the bottom row that the baseline NFS of zero is the same in study ALD-102 and population number two, indicating most subjects treated with eli-cel and HSCT in these groups were asymptomatic at baseline. But the baseline NFS for the untreated population number one of 3.5 is much higher, is outside the criteria for early disease, which I remind you is an NFS of zero or one, and indicates that most of the untreated subjects were symptomatic at baseline.

Additionally, looking at the range of NFS for population number one the upper limit of 25 is the maximum NFS and indicates some untreated subjects had major functional disabilities at baseline. Drawing your attention to the third row above this for Loes scores, you see again that population number one is

much more advanced with a median Loes of 11, again outside the criteria for early disease, which I remind you is a Loes score between 0.5 and 9.

While the differences between populations is most striking when looking at untreated population number one, the Loes scores at baseline are also higher in the TPES group for population number two compared to Study ALD-102 subjects treated with eli-cel. These differences in baseline characteristics suggest that eli-cel subjects were treated at an earlier stage of disease which may have biased results in favor of eli-cel.

This slide shows the results for the primary efficacy endpoint of month 24 MFD-free survival, comparing eli-cel to the untreated population number one from the clinical benchmark and the strictly ALD-102 eligible TPES populations from studies ALD-101 and 103. The figure shows the 50 percent benchmark with an orange dotted line. For each cohort the dot in the middle of the vertical line represents the point estimate for month 24 MFD-free survival, and the line

represents the 95 percent confidence interval.

Population number one of the benchmark is represented by the UTG-101 green line on the left of the figure, with the entire line below the 50 percent benchmark. The first red dot and line represents TPES-101, and the next red dot and line represents TPES-103. Both of these groups were treated with HSCT and had early active disease. As you can see, both lines were above the 50 percent benchmark. Eli-cel is represented by two lines. The important line to focus on is the dark blue line to the far right denoted all TP-102, which represents the entire eli-cel cohort of 32 subjects in Study ALD-102.

The dark blue eli-cel line is clearly above the 50 percent benchmark. In this eli-cel cohort there were three failures of MFD-free survival by month 24 for a point estimate of 90.6 percent month 24 MFD-free survival, with a 95 percent confidence interval of 75 percent to 98 percent, clearly exceeding the 50 percent benchmark. There was only one MFD in a subject who developed total incontinence at month nine.

The other two subjects were counted as failures because, at the investigator's discretion, they received rescue allo-HSCT at month 13 for one subject and month 17 for the other, due to the investigator's assessment of progressive radiographic disease on brain MRI, including worsening Loes scores. While the results look impressive for eli-cel, during the review process FDA discovered several issues that led us to question the interpretability of these results. The most pressing concern is comparability of populations as just discussed.

While the untreated population appears clearly inferior on the primary efficacy endpoints of month 24 MFD-free survival in the figure, I remind you that these subjects had very advanced symptomatic disease at baseline, and it does not seem relevant to compare their 24 month outcomes to the outcomes of subjects with early, mostly asymptomatic disease who received HSCT and eli-cel. I will now elaborate on these comparability concerns.

As I mentioned to you in a previous slide, we

have multiple issues with the benchmark that was used in the primary analysis. First and foremost, the populations that were used to determine the benchmark were not comparable to the subjects treated with eli-cel in Study ALD-102. Population number one had considerably more advanced and symptomatic disease at baseline, so their outcomes at month 24 would be expected to be worse. Because there is no comparable untreated population with early active disease and we do not know the expected timing between development of MRI lesions and onset of symptoms, we are not confident that 50 percent is an appropriate benchmark to demonstrate the treatment effect of HSCT compared to no treatment in the early active disease population.

Additionally, as shown in the demographics table, HSCT population number two was not strictly comparable to the eli-cel cohort in ALD-102 with older age and higher, more advanced Loes at time of treatment. To reiterate, the difference between the benchmark populations and the eli-cel cohort suggests subjects treated with eli-cel in Study ALD-102 were

treated at an earlier, less-advanced stage of disease, which would bias results in favor of eli-cel.

Our second issue with the benchmark calculation pertains to the imputation strategy that was used for subjects who had to have a repeat HSCT for failure to engraft. In population number two of the benchmark, subjects who received a second transplant after the first HSCT failed to engraft were counted as failures of MFD-free survival and many of the failures of MFD-free survival were from repeat HSCT rather than from MFDs or death.

This imputation strategy made the performance of the benchmark population number two look worse and biased the results in favor of eli-cel. No eli-cel subjects received repeat treatment with eli-cel or rescue cells, and eli-cel subjects who were treated with rescue allo-HSCT were treated due to progressive disease, not engraftment failure. We do not feel repeat HSCT for engraftment failure in the HSCT population is the same as disease progression, MFD, or death, and should not be imputed as such.

In addition to concerns for comparability and imputation methods contributing to bias, two other main contributors to potential bias were identified. The first is retrospective data collection in Study ALD-101 could have resulted in selection bias. Also, the major functional disabilities were derived from Study ALD-101 data, and there is concern about bias not only due to knowledge of treatment effects, but also due to the subjective nature of some MFD assessments. In particular, tube feeding and wheelchair dependence may be more temporary or related at times to convenience rather than true need.

Finally, 24 months may be insufficient time to assess MFD-free survival. Few events occurred by 24 months in the eli-cel and HSCT populations. Most events constituting failure were HSCT, either rescue HSCT in the eli-cel population or repeat HSCT in the HSCT population. MFDs and deaths by 24 months were rare, and most were seen in the untreated population, as would be expected.

However, as discussed previously, the

untreated population number one in the benchmark is not an appropriate untreated comparator group, as the subjects had quite advanced disease at baseline and some even had MFDs at baseline. While we know that disease progression will occur if CALD is left untreated, we do not know the timeframe of disease progression following diagnosis of early active asymptomatic disease and thus cannot be confident that progression would have occurred in the two years following diagnosis.

Additional reviewer-initiated analysis of the Study ALD-101 untreated population indicated that some of these subjects may be slow progressors and remain asymptomatic for many years. We therefore cannot be confident that the subjects with early active disease would have experienced disease progression in two years if not treated with HSCT, as in population in number two, or with eli-cel. And there is no way to predict which CALD patients will be slow progressors. As HSCT is now largely routine upon diagnosis of early active cerebral disease, there likely never will be an

appropriate untreated comparator. And the comparison between HSCT and eli-cel is critical.

Only additional long-term follow-up of similar populations could help elucidate the relative efficacy of eli-cel compared to HSCT on MFD-free survival for CALD patients with early active disease. With all of these uncertainties it is unclear if eli-cel is efficacious on month 24 MFD-free survival. Now I will review some of the secondary and exploratory analyses done by the Applicant. Relative efficacy of HSCT and eli-cel for many of these endpoints were assessed over time in time to event analyses, rather than specifically assessed at month 24.

The secondary endpoints had no pre-specified hierarchical order, so we consider them as exploratory. The populations used for these analyses differs somewhat from those used in the benchmark and primary endpoint analyses. So I'll first show you another demographics and baseline disease characteristics table. In this table I will show you the key baseline features for the eli-cel treated cohort and the HSCT

comparators for the analyses of relative efficacy. The applicant's main comparator cohort is the strictly ALD-102 eligible HSCT cohort with no match sibling donor in Study ALD-103 or TPES-103 NMSD.

I remind you that Study ALD-103 was the more contemporaneous HSCT study. Baseline features for the TPES-103 NMSD population, which included only 17 subjects, are shown in the first column. As you can see in the second and last columns, we pooled some populations to increase the robustness of some of the exploratory analyses, largely to maximize data due to the rarity of disease and limited number of children treated in each of the study cohorts.

In the righthand column, demographics of eli-cel cohorts are shown. From Study ALD-102 or cohort TP-102, already reviewed, and a pooled group in the far right column to include subjects from ALD-102 and 16 subjects with at least 24 months of follow-up in the ongoing eli-cel study ALD-104. We pooled the eli-cel cohorts because we wanted to see if adding additional eli-cel subject's with at least 24 months of data

provided additional support for efficacy. As you can see by comparing the two eli-cel columns on the right, this pooled population has similar baseline features to the subjects in Study ALD-102 alone.

In the second column, the table shows that the TPES-103 NMSD cohort pooled at the TPES and MSD population in Study ALD-101 or population number two of the benchmark, whose demographics were already reviewed. As mentioned, there were only 17 subjects in the TPES-103 NMSD main comparator group. Of these only nine, or 53 percent, had at least 24 months of follow-up after HSCT, and long-term data beyond 24 months is scant. We therefor pooled the TPES NMSD population in order to evaluate outcomes following HSCT in a TPES NMSD population with longer duration of follow-up.

I would like to draw your attention to the Loes score in the third row and highlighted by a red box for the TPES NMSD population. As the Applicants showed you in their presentation, Loes scores were similar for eli-cel in the two far right columns and TPES-103 NMSD in the first column. However, once

populations were pooled, we again see that the baseline Loes score for TPES NMSD populations, as shown in the second column, is higher or more advanced than the eli-cel population.

We are concerned that the differences in demographics and disease characteristics indicate the eli-cel subjects may have been treated at an earlier stage of disease, which would bias in favor of eli-cel. You have already seen a similar Kaplan-Meier curve in the Applicant's presentation. I am showing you this Kaplan-Meier estimate of time to event for MFD-free survival to show you how results comparing eli-cel and HSCT were presented by the Applicant in the original BLA submission.

This figure shows the estimates of MFD-free survival over time in the study ALD-102 eli-cel cohort TP-102 represented by the blue line; the TPES-101 NMSD cohort, or population number two from the benchmark, represented by the green line; and TPES-103 NMSD, represented by a red line. The Applicant focused on this TPES-103 NMSD group as the primary comparator for

eli-cel for relative efficacy analyses. I remind you that the TPES NMSD populations are subjects who were treated with HSCT from donors other than a matched sibling and who had early active disease. They are the target population for eli-cel.

MFD-free survival probability as a percentage is shown on the Y-axis and months since relative treatment or treatments on relative day one is shown on the X-axis. I want you to draw your attention to the first six months following treatment where the observed difference between the eli-cel line and the HSCT line was largely driven by the Applicant's imputation of repeat HSCT for engraftment failure as an event. Again, as previously discussed, we do not feel repeat HSCT for engraftment failure is similar to disease progression, MFDs, or death.

We have several other concerns with this analysis that I will now discuss. Our other issues with this comparison are reminiscent of our issues with the Study ALD-101 benchmark analysis. The main concern other than the repeat HSCT imputation is the lack

comparability between treatment groups, as reviewed in the demographics slide. Another point of concern is that bias may have been introduced through retrospective data collection for all Study ALD-101 data and some of the Study ALD-103 data and during the assessment of MFDs, as previously discussed.

Another important concern that interferes with interpretability is that only nine, or 53 percent, of the subjects in the Applicant's primary comparator group, TPES-103 NMSD, completed at least 24 months of follow-up. This resulted in significant amounts of missing data. Longer term data beyond 24 months is scant and is primarily available in the TPES-101 NMSD population, of which 17 of 27 subjects had at least 24 months of data. Few MFDs or deaths during the limited duration of follow-up make relative efficacy difficult to interpret.

In conclusion, the comparison of eli-cel results in Study ALD-102 to TPES-103 or TPES-101 NMSD cohort by a Kaplan-Meier estimate of MFD-free survival over time is not easy to interpret given all of these

uncertainties and potential biases. It is important to keep in mind as I review the rest of the efficacy results that these limitations effected analysis of all other secondary and exploratory efficacy endpoints as well. As previously discussed, in an attempt to increase the robustness of our analysis of MFD-free survival, we asked the Applicant to conduct several exploratory analyses that involve pooling of HSCT cohorts and eli-cel cohorts.

We also asked for a more conservative imputation strategy. To be conservative, failures of MFD-free survival for allo-HSCT cohorts included MFD and death only. We asked that repeat HSCT not be imputed as failure since all repeat HSCT was performed due to graft failure and not progression of disease. For eli-cel cohorts failure of MFD-free survival included MFD, rescue allo-HSCT, death, and myelodysplastic syndrome, or MDS.

Following BLA submission, three cases of MDS, a form of cancer that is very rare in children, were diagnosed in subjects treated with eli-cel. Due to the

morbidity and mortality associated with MDS we feel it is reasonable to impute it as a failure. MDS will be discussed in the safety presentation and in much more detail this afternoon.

In this exploratory analysis where the repeat HSCT was not imputed as failure and myelodysplastic syndrome was imputed as failure, the outcomes of MFD-free survival over time are pretty much identical between the pooled eli-cel cohort and the TPES NMSD cohorts, except at the very beginning and at the end. The reason for the dip in the blue eli-cel line at the end is a subject who developed myelodysplastic syndrome approximately seven and a half years after treatment. The reason for the small dip in the HSCT line at the beginning interested us.

Understanding that CALD is a devastating disease with unmet medical need we wanted to see if there was a subpopulation for which there was more robust efficacy data. When looking at line listings of the data, there appeared to be a trend toward early failures of MFD-free survival in subjects who received

HSCT from HLA-unmatched donors regardless of relatedness of donor to subject. To elaborate, even though it is traditionally understood that matched sibling donors are the ideal HSCT donors, the pattern we saw indicated subjects who received transplants from HLA-unmatched donors seems to do more poorly than recipients of HLA-matched donor HSCT, even if the donor wasn't related to the CALD recipient.

In other words, subjects with both matched sibling donors and matched unrelated donors seems to do well compared to subjects who received HSCT from unmatched donors. To explore this pattern and the slight difference in MFD-free survival during the first few months in the NMSD analysis I just showed you we asked the Applicant to conduct another exploratory analysis comparing long-term outcomes between eli-cel and TPES-101 and 103 recipients of HSCT from HLA-matched and unmatched donors.

In this exploratory analysis, pooled eli-cel TP-102 and TP-104 are again represented by the blue line. Pooled TPES-101 and 103 subjects with HLA-

matched donors are represented by the red line and pooled TPES-101 and 103 subjects with HLA-unmatched donors are represented by the green line. The same imputation methods are used in this analysis where repeat HSCT and HSCT-treated control is not imputed as failure and myelodysplastic syndrome in eli-cel subjects is imputed as failure.

Here we see that eli-cel and matched donor HSCT are nearly identical, but please look at the unmatched donor HSCT green line. It is strikingly different with a significant drop to near 80 percent at six months. After 12 months it parallels the curve for eli-cel and HSCT from matched donors. Although there appeared to be similar rates of major functional disabilities in the matched donor and unmatched donor populations, please look at the table at the bottom of the slide.

First MFD occurred earlier at 19 months in subjects with HLA-unmatched donors compared to 35 months in subjects with HLA-matched donors. Deaths occurred much sooner in the unmatched donor population

at six months compared to 23 months in the matched population. It is important to recognize the limited data however, in that only 17 boys received unmatched donor HSCT, only 12 of whom were followed past 12 months. Nonetheless, with this observation of earlier events in the HLA-unmatched HSCT population, we asked the Applicant to do a Kaplan-Meier analysis of overall survival rather than MFD-free survival.

Essentially, we wanted to compare only death with no imputation for missing data due to repeat HSCT or major functional disabilities. The cohorts in this analysis are the same as the previous, where the blue line is the eli-cel population, the red line is the pool of HLA-matched donor HSCT TPES population, and the green line is the pool of HLA-unmatched donor TPES population.

Estimates for overall survival over time are nearly identical for eli-cel and TPES subjects with HLA-matched donors, irrespective of relatedness of donor to subject. However, the population who received transplant from HLA-unmatched donors had considerable

early mortality. Again, I will ask you to focus on the green line in the first six months. Nearly 20 percent died in the first six months following treatment compared to zero percent in the other cohort.

Following month 24, the cohorts mirror each other. However, at month 24, both eli-cel and the HSCT population with HLA-matched donors maintained around 90 percent survival while the HSCT population with HLA-unmatched donors maintained only around 75 percent survival. However, due to other limitations already discussed and few subjects and events, the results are difficult to interpret, particularly as deaths in the HLA-unmatched cohort may be related to increased toxicity of HSCT in this population. To increase the robustness of the efficacy review, changes in neurologic functions score, or NFS, and Loes score from baseline were also analyzed.

This figure shows change in NFS from baseline to month 24 for individual subjects in Study ALD-102 with each subject shown by a different line. NFS stayed largely unchanged for the majority of subjects,

and only a few increased above NFS of one. The blue line represents the subject who developed major functional disability, whose rapid disease progression up until the subject's death at 22 months.

The Applicant defined stable NFS as change of less than or equal to three from baseline and score remaining less than or equal to four at month 24. While most subjects maintained stable NFS by this definition, it is not clear that this definition is appropriate. Any increase in NFS confers worsening neurologic symptoms that may be significant to independent functioning.

Regardless, change in NFS for eli-cel subjects in the 24 months following treatment was similar to allo-HSCT subjects in the TPES groups. This is likely due to the short duration of follow-up in studies where 24 months may be insufficient time to see NFS changes in boys with early active CALD. While the NFS changes I just showed you were similar between eli-cel and HSCT-treated subjects, some troubling signals were seen when we evaluated change in Loes score from baseline to

month 24.

This table compares the pool of eli-cel and TPES groups. For pooled eli-cel populations the first red box at the top highlights that only one eli-cel treated subject, or 2.9 percent, experienced a decrease or improvement in Loes score at month 24 compared to 13.3 percent in the pooled HSCT population. However, the increases or worsening of Loes scores are more concerning. I would like to draw your attention to the bottom red box where we see that eli-cel populations were more likely to experience worsening Loes score with increase of four or more at month 24.

Nearly 50 percent of the eli-cel population had a Loes score increase of four or more at month 24 compared to only 20 percent for the TPES HSCT population. This raises the concern that eli-cel is less efficacious than HSCT. However, it is unclear if MRI changes predict later clinical disease progression. The predicted value of the difference in Loes scores could only be elucidated with more time in follow-up.

In summary, although the primary eli-cel study

ALD-102 was successful on its primary efficacy endpoints, the many issues with the derivation of the benchmarks makes the results difficult to interpret. Furthermore, similar issues were seen in the comparative analyses for other efficacy endpoints, namely comparably issues between populations, imputation methods, and potential bias. The short duration of follow-up in all studies made it especially difficult to assess efficacy due to the unpredictable timing of onset of symptoms and progression of disease in the target population of early active CALD.

The rarity of endpoint events in the TPES NMSD and eli-cel populations further complicate the assessment of relative efficacy. We did identify a population of subjects who did exceptionally poorly with HSCT, namely, the HSCT recipients of HLA-unmatched donors, who had approximately a 20 percent early mortality rate in this small series. This may be the more appropriate target population because the risk of early mortality with HSCT in this population is so great.

Yet longer term outcomes following eli-cel are unclear compared to HSCT and even no treatment. It is important that any population to be treated with eli-cel has a favorable benefit that outweighs our worries and safety concerns that will now be discussed. I will now turn it over to Dr. Leah Crisafi to discuss product specific safety.

DR. LEAH CRISAFI: Thank you, Shelby. My name Leah Crisafi. I am a co-reviewer in OTAT, and I will briefly present FDA's assessment of the safety of eli-cel. The safety issues I will cover include the occurrence of engraftment failure and three important types of adverse events that occurred during the eli-cel study. These adverse events relate to low blood counts, opportunistic infections, and, most critically important for this product, cancer that appears to be the result of lentiviral mediated insertional oncogenesis. I will conclude with information about the duration of follow-up that contributes to our uncertainty of the ultimate safety profile of eli-cel.

I will start with the engraftment failure.

Conditioning for eli-cel involves administration of high dose chemotherapy that kills the cells in the bone marrow, creating an available compartment to be repopulated with the autologous cells containing the lentiviral vector. This repopulation is referred to as engraftment. A clinical measure for evaluating engraftment is peripheral blood counts, and engraftment of the bone marrow is considered a failure when blood counts do not return to a prespecified level after transplant.

Neutrophil engraftment failure was defined by the Applicant as failure to achieve three consecutive absolute neutrophil counts of at least 0.5 times 10 to the 9th cells per meter by 42 days. By this definition, no subject failed to engraft. However, the Applicant's definition did not account for the use of granulocyte colony stimulating factor, abbreviated G-CSF. Because G-CSF increases neutrophil production, the FDA determined that ongoing G-CSF administration should preclude achieving neutrophil engraftment.

And we determined that six subjects who the

Applicant classified as engrafted were receiving G-CSF and did not meet the target neutrophil count of 42 days in the absence of recombinant G-CSF administration. We considered these six subjects to have neutrophil engraftment failure. Platelet engraftment was defined by the Applicant as three consecutive platelet counts of at least 20 times 10 to the 9th per liter without platelet transfusion in the preceding seven days.

While the Applicant did not define platelet engraftment failure, FDA determined that the safety assessment of eli-cel should include an assessment of resumption of platelet production, and it made sense to parallel the definition per neutrophil engraftment failure. We therefore used the definition for platelet engraftment failure that is provided on this slide. And with this definition, we determined that 14 out of 64 subjects had platelet engraftment failure.

In addition to the unexpected cases of engraftment failure, there were persistent cytopenias that I will go over in the next several slides. Severe neutropenia, defined as neutrophils less than 1 times

10 to the 9th per liter was present in 21 percent of subjects at day 60 and persisted in 11 percent of subjects at day 100. Severe thrombocytopenia was present in 15 percent of subjects at day 60 and 8 percent at day 100.

These severely low blood counts put subjects at risk for infectious and bleeding complications for the first several months after eli-cel administration. And such low counts are not anticipated to occur after transplant of sufficient numbers of autologous stem cells that are derived from peripheral blood. For many subjects platelet, hemoglobin, and white blood cell values never returned to their baseline level. The figure on the right demonstrates medium platelet counts over time for subjects who had normal platelet counts at baseline.

The black horizontal line denotes no change from baseline. The figure demonstrates that platelet counts did not return to baseline for the duration of follow-up, although the median platelet count for all subjects was within the normal range starting at six

months post-eli-cel and continuing for the duration of follow-up. Next is the change in hemoglobin levels from baseline. We can see in this figure that hemoglobin did not return to baseline levels until more than two years after eli-cel administration. However, the median hemoglobin level was in the normal range starting at six months.

Last are the white blood cells. These figures show neutrophils and lymphocyte count changes from baseline with data separated by study. In both years, Study ALD-102 data are in blue and Study ALD-104 data in red. The figure on the left demonstrates that neutrophils did not recover to baseline during the seven year follow-up period. Although, neutrophil counts were in the normal range starting at two months post-eli-cel.

The figure on the right shows that it took at least two years to recover lymphocyte counts to baseline. Although lymphocytes were in the normal range starting at nine months post-eli-cel. The long-standing reductions in most blood cell types after eli-

cel administration were not expected and have not been explained. FDA is concerned that the process of transforming the precursors of these cells into eli-cel may have a detrimental effect on their subsequent ability to generate normal populations of blood cells.

Now I will briefly touch on the second adverse event of special interest: opportunistic infections. Eighty-six infections were reported in 34 of 67, or 51 percent, of eli-cel treated subjects. The 23 most significant opportunistic pathogens of the 86 infections are categorized by time of onset and listed here. The top row has the infections that were either serious or severe, and on the bottom are infections that were not classified as serious or severe. There were six central line infections and five bacteremia. Also notable are numerous viral infections that are not generally problematic in an immunocompetent patient but may cause significant morbidity in the immunocompromised patient.

The third type of adverse event I will discuss is the single most important safety issue for eli-cel:

insertional oncogenesis. Three of 67 children treated with eli-cel have developed cancer so far. All three cases were diagnosed within the last year, and all three children have gone on to receive hematopoietic stem cell transplant for treatment of their cancer. FDA is concerned that with more time to follow subjects more will be diagnosed with cancer.

There are a number of subjects who are currently being closely watched due to concern that they may be developing a hematologic malignancy. And, in addition, it is concerning that nearly all subjects who received eli-cel have integrations into the parietal oncogene MECOM that is implicated in two of the three cancer cases diagnosed thus far. Given the overall short period of follow-up for most subjects, it is important to consider the possibility that many more eli-cel treated subjects will be diagnosed with hematologic malignancy over time.

Lastly, I will speak to FDA's concern regarding the relatively short period of follow-up for many of the subjects who have been treated with eli-

cel. In order to understand and mitigate the risk of a delayed adverse event resulting from permanent modification of the genome, FDA has long recommended that subjects treated with an integrating vector be followed for safety for 15 years. Keeping in mind the expectation for 15 years of follow-up data to characterize long-term risks of integrating vectors, I would like to highlight the comparatively short duration of follow-up data that we have to characterize the safety of eli-cel.

The figure on the right shows the duration of follow-up for the 67 subjects who received eli-cel in Studies ALD-102 and ALD-104. Of the 32 subjects who were treated in the initial study, ALD-102, 27 subjects are still being followed for lentiviral vector safety related outcomes. Of those 27 subjects, the duration of follow-up ranges from approximately two to seven years. For Study ALD-104, which treated its final subject in July 2021, the duration of follow-up data ranges from approximately 1 to 27 months. A final point to note here is that the first subject treated

with eli-cel has the longest duration of follow-up. And he is also one of the three who has developed cancer.

We don't know how many more of the subjects who were treated after him will also go on to develop a hematologic malignancy. I will conclude by briefly presenting on the challenging topic of the benefit/risk assessments. Even though the primary study, ALD-102, was successful on its primary endpoint, our overall assessment is that the efficacy of eli-cel is difficult to determine given limitations in study design, lack of comparability between eli-cel treated subjects and extremal controls, and that 24 months is an insufficient duration for assessing death and major functional disability in boys with early active CALD.

Nonetheless, we understand that CALD is a terrible disease, and therefore, we conducted additional analyses to assess if there may be a subpopulation with CALD for whom eli-cel offers a favorable risk/benefit assessment. We noted that boys without HLA-matched donors who receive HSCT have a high

early mortality, and therefore, eli-cel appears to offer a survival benefit compared to unmatched HSCT, especially in the first six months.

However, the study interpretability issues make it difficult to assess the long-term outcomes in these boys in the extent that eli-cel offers a treatment benefit compared to no treatment at 24 months with respect to survival or major functional disability. The uncertainty regarding efficacy following eli-cel treatment is particularly challenging in the context of serious safety concerns, including the development of life-threating hematologic malignancy.

Benefit/risk needs to be considered in the context of the condition that is being treated. This is truly challenging based on the available data, given the uncertain benefit and uncertain magnitude of the life-threating risk of hematologic malignancy. We thank you for your attention and look forward to the Committee's discussion about this complicated benefit/risk analysis.

CLARIFYING QUESTIONS TO PRESENTERS

DR. LISA BUTTERFIELD: All right. Thank you very much to all of the speakers, those from bluebird bio and those from FDA. So we now have almost 30 minutes for Q&A, and so I'd like to open it up to members of the Committee. And remember, I'm looking for your hands to go up electronically, and then I will call you on you to ask your question. So the first question I see is from Dr. Coffin, please.

DR. JOHN COFFIN: Yeah. I have a bunch of questions about the insertional oncogenesis, but I assume -- I'll save those for this afternoon where I assume there'll be a more (audio skip) discussion of that. But I do have a question regarding the clinical outcome of MDS with current treatment methods. And perhaps, Dr. Duncan could address that, what the clinical experience is with treating that (inaudible).

DR. JAKOB SIEKER: Yes, thank you. I will ask Dr. Duncan.

DR. CHRISTINE DUNCAN: Thank you for that important question. So the current data that we have published in blood in 2018 shows that in pediatric patients diagnosed with MDS, the event-free survival is approximately 75 percent.

DR. JOHN COFFIN: Okay. And that -- I'm sorry, event-free, that's five years survival? I don't quite understand that.

DR. CHRISTINE DUNCAN: Yeah, so, based on that data that's pooled from multiple different studies with different endpoints, but it can be projected to three and a five year survival, approximately 75 percent in pediatric patients.

DR. JOHN COFFIN: Okay. Thank you.

DR. CHRISTINE DUNCAN: Thank you.

DR. LISA BUTTERFIELD: All right. Thank you very much. So, I also have -- next we'll move to Dr. Fox and then Dr. Ott, Dr. Shapero, Dr. DiPersio, and Dr. Hawkins. Dr. Fox, please.

DR. BERNARD FOX: Yeah, so I think this question is directed to Dr. Duncan, but it's really to

comment on Dr. Elenburg's presentation, particularly on, I think it's slide 27, where Dr. Elenburg was summarizing the change in the Loes score.

And I would like to know, especially the last line, where it looks like the Loes score goes up by greater than four in 17 patients in the pooled TP-102 and TP-104 score compared to only six patients, or 20 percent, in the pooled HSCT scores. So can you comment on that? That would be directed again to Dr. Duncan on the clinical side.

DR. JAKOB SIEKER: Dr. Duncan, please.

DR. CHRISTINE DUNCAN: Thank you for that question. Yes, we do see change in the Loes score -- oh, sorry. Yes, if you please bring up slide one. So there are changes in the Loes score, but I think one of the important things to know about that is when we look at the Loes score and see how that was reflected in the NFS score, the changes on the MRI are not reflected in changes in the neurologic function scores of the patient. So we do expect to see some change in Loes score over time but really want to focus on the

clinical significance of that and the individual patients.

DR. BERNARD FOX: So is your impression that having more patients with a greater increase in Loes score is not clinically significant? Did I misinterpret that?

DR. CHRISTINE DUNCAN: In our patient population that's correct.

DR. BERNARD FOX: And do you have an explanation for why that would be different in the patients who got the stem cell transplant?

DR. CHRISTINE DUNCAN: So I think that there are differences, and particularly if you look at the ALD-101 scores and the 102, of how close the MRIs are being followed, and these are being followed very closely across the study. And we did our best to correlate those as carefully as we can.

And just one more point about the function in the patient. If you could please bring up slide one, so we can look to see the changes in the Loes score and how that impacts the IQ across that and neurologic

functioning of the patients and don't see a significant impact of those change in the Loes score on the patients who have a change -- I'm sorry -- impacted the neurologic function, the IQ, in the patients who had changes in their Loes core.

DR. BERNARD FOX: And if you compared this to the patients who had stem cell transplant, how would that compare?

DR. CHRISTINE DUNCAN: I would expect to see this quite similar. One of the challenges with the IQ scoring is that that is not routinely done at every center in the same way for the patients who are treated with allogeneic stem cell transplant. And we certainly wish that it was, but I think we were able to follow the IQ scores much more robustly in our study because we were paying such close attention to it because of the importance of that outcome.

DR. BERNARD FOX: Thank you.

DR. CHRISTINE DUNCAN: Thank you.

DR. LISA BUTTERFIELD: All right. Thank you very much. Let's move to Dr. Ott, please.

DR. MELANIE OTT: Yes, hello. I have a question to Dr. Demopoulos. It might also cross over to the discussion this afternoon, but I appreciate that there is more surveillance being done to check for malignancies in patients who have received transplants. My question is what is done proactively? And my concrete question is what happens with the HFCs once they get transfused? What is being done as a quality control here? How much time is there, and is there any integration site sequencing done at that time?

DR. JAKOB SIEKER: Dr. Demopoulos.

DR. LAURA DEMOPOULOS: Thanks for that question. You're right. We've paid a lot of attention to how we can identify these cases and whether or not there is a way for us to easily and proactively identify patients at risk for the development of MDS. Could I have slide one up please? You probably won't be surprised that in a small sample size such as our population and a small number of events that it was very unlikely that we were ever going to identify anything that clearly explained to us why these

particular children had these events.

And so you can see here a list of some of the factors we looked at in groupings of patient characteristics, baseline disease characteristics, drug product characteristics, the treatment regiment, and post-treatment factors. None of these had a significant correlation with the development of MDS versus not except for two. Those were the ones that I called out in the main presentation, so that is time to platelet engraftment, which was longer in two of the three patients effected with MDS, and both 6 and 12 month measures of peripheral blood vector copy number, which increased in patients who were effected with MDS.

So these factors, unfortunately, are post-treatment measures, so they don't allow us to prospectively identify patients at risk and consider other treatment options. But they do potentially give us a window into considering whether or not patients at risk can be identified early. And that was one of the features that I identified in the main presentation, and that will be one component of the post-marketing

surveillance for this clinical complication.

DR. MELINDA OTT: Can you give us a brief idea of what is done before transplantation with the transfused HFCs?

DR. JAKOB SIEKER: Yes, I would like to ask Dr. Shestopalov to come up and discuss the release criteria we have the eli-cel drop product.

DR. ILYA SHESTOPALOV: Hello, I'm Dr. Ilya Shestopalov. I'm the analytical product lead for eli-cel. So, slide one up, please. To answer your question, we have six potency assays as part of product release, three of which specifically look at how well we transduced the cells. And one key aspect of that is vector copy number, which is measuring on average how many copies per cell there are among the cells in the drug product.

It's been theorized that a more -- higher vector copy number would lead to more integrations, which increases the possibility of then having insertional oncogenesis. What we see in practice, as Dr. Demopoulos mentioned, is that actually we find the

vector copy number's related to efficacy, so you need sufficient vector copy number to produce enough ALTP protein to treat the disease. But the products that were given to the three patients that went on to have MDS were actually right around the median of our cohort.

Can I have slide three up, please? So, as you can see, the three blue dots in the right are the vector copy numbers for those products, and you can see that right around the mean of our cohort. So it doesn't actually bear out that higher vector copy numbers lead to insertional oncogenesis. It points out to it's more of a random event and patient-specific factors are involved. And we'll be discussing that this afternoon.

DR. MELINDA OTT: Thank you.

DR. LISA BUTTERFIELD: Thank you very much. We'll now move to Dr. Shapero followed by Dr. DiPersio, Dr. M, Dr. Roberts, Dr. Shah, and Dr. Keller. Lots of questions.

MR. STEVEN SHAPERO: Yes. Hi, thank you. I'm

not a doctor, but that's okay. Is there any chance that Dr. Eichler is still in the room? I have a question for him.

DR. JAKOB SIEKER: Yes, he's in the room.

MR. STEVEN SHAPERO: Great. Okay. Great. Thank you. My question is this. I know that in the standard care allo-HSCT cases, when they give the treatment, it often takes months, 12, 24 months before we start to see improvement or the disease stops progressing in these patients. I'm curious if in the eli-cel trials we saw the same thing, or did it behave differently with regard to that lag?

DR. FLORIAN EICHLER: Yes, very good question. Clinically my impression is it's very similar, and so we generally see following these kind of stem cell transplantations where there's eli-cel or allogeneic stem cell transplantation a rise in the Loes score over time. But we also see diminishment of contrast enhancement showing that this is now attenuation of the active cerebral ALD form. And that seems to be critical to our clinical judgement that this is now

effective attenuation of active disease.

MR. STEVEN SHAPERO: But it's similar between the two techniques, yes?

DR. FLORIAN EICHLER: It is similar.

MR. STEVEN SHAPIRO: Thank you.

DR. LISA BUTTERFIELD: Terrific. Thank you. Dr. DiPersio.

DR. JOHN DIPERSIO: Yeah. Thank you. So I had a question for Dr. Duncan. Maybe just she'd like to comment on this. But obviously, as a leukemia physician and someone who focused on transplantation immunology and having taken care of many transplant patients -- and this is important for how the FDA looks at the data -- the importance of a single treatment providing benefit over a long period of time versus a transplant which requires an enormous amount of ongoing effort needs to be considered. That's the first thing.

And so, in the leukemia world, we actually determine whether something's better or worse than another treatment by using something called a Griffith score, which is a combination of GvHD and relapse

disease. And this was really left out of your analysis from the FDA side. I think it would be interesting to look at that and compare. Obviously, in the gene therapy arm there's not going to be any graft versus host disease, and so that's going to be zero. But it would be important to look at survival based on not only progressive debilitation and problems, but also with graft versus host disease acute and chronic.

Because sometimes you trade a little diminishment in the Loes score by a lot of extra GvHD. And so the life of a patient can actually be dramatically worse. And so I think that's left out, and that's a very important assessment that was not included. I had another question about just -- I'll ask them all at the same time -- just the issue of I know there was no correlation between the vector copy number and the incidence of MDS, but I'm wondering was there also a correlation between the CD34 per kilogram infused and the platelet recovery?

In other words, were the three patients that were really slow in their recovery, did they get the

lowest number of CD34 cells? And I guess I assume that the MDS cases came from both the (inaudible) populations, but I'd like to hear someone comment on that. And the final issue is mobilization was always with G, or was it with G and plerixafor for some of these patients and not for others? And I'll just listen for now.

DR. CHRISTINE DUNCAN: Thank you. There's some really important points. I think I do want to talk about the first one, and I think you've made an excellent point about sort of the quality of that survival for a patient. And so survival, obviously, the most important thing, but we need to think about the survival and what that quality is. And the way I think about this is that we have a neurologically devastating fatal disease and two imperfect therapies. Then we have to try and weigh those risks and the benefits of each of those.

And so, when we think about autologous stem cell transplant and we think about that graft failure rate of the primary graft failure rate, we're talking

about around a 40 percent survival. So patients with primary graft failure after allogeneic stem cell transplant. And just a little bit of an aside to comment on that, with all respect to the FDA reviewers, neutrophil graft failure is not defined by the use of GCSF and autologous stem cell transplants. GCSF is the standard for all patients, or almost all patients, particularly those with non-malignant diseases. And so I don't think that targeting our patients with graft failure is in fact accurate.

So if you look at an autologous patient who has graft failure, needing a second transplant, has primary graft failure, that survival rates around 42 percent. So I think that that's an issue. And then I think we have to think about graft versus host disease because we have become very good at keeping patients alive. We know how to support patients, but the quality of that survival really matters. So just to bring up the slide one, please. So just, in full disclosure, these are pediatric allogeneic stem cell transplant patients who have graft versus host disease.

So this is not specific to ALD patients because we really needed to look at a large number of patients. So this is about 1,500 patients. And if you look at the top line this is the risk of mortality, so non-relapsing mortality, which even is occurring 10, 15 years later with graft versus host -- patients who had acute graft versus host disease. If you have Stage 3, Grade 3 -- excuse me, Grade 3 acute GvC or Grade 4, you're non-relapse mortality at 5 and 10 years is significantly higher than other patients. And that is matched unrelated donors and that is mismatched unrelated donors making up the bulk of it.

And not only does that graft versus host disease exist, those are patients who have their overall development effected by things. They are pediatric patients who are on steroids for many years in some cases, which can effect organ function and other things. And then just please, in slide one, this is a slide from a pivotal study run by Smita Bhatia, the bone marrow transplant survivor study, where we look at patients who received allogeneic stem cell

transplant and long-term outcomes.

And we see that patients who receive, especially allogeneic transplant, long-term have greater functional impairment and activity impairment and poorer general health compared to their siblings and then compared to patients who received standard chemotherapy for oncologic diseases that don't have transplant. So it is not just whether you're alive or dead. It is what your impairment is like, what your function is like, what your quality of your life is like.

And so I think we really have to think about those questions, and I do appreciate the opportunity to do so. I think your second question -- I want to make sure I get these all, or actually I'm just going to go to your last one quickly. For the mobilization piece, in ALD-102 all patients were mobilized with GCSF with the opportunity to use plerixafor. Plerixafor is not mandated across -- in ALD-102. In ALD-104, all patients received GCSF, and all patients received plerixafor across the study.

And you were absolutely right, the MDS cases did occur across those studies. So the first two patients who were diagnosed with MDS received busulfan fludarabine conditioning. And the last patient we spoke about received busulfan cyclophosphamide, so all patients receiving myeloablative conditioning, which you also have to think about in regards to the late and longer-term effects. And then, finally, just to comment that there's been a lot -- and there are probably others in the room who would like to comment on this as well -- trying to identify those features related to the vector copy number and the platelet and grafting. And anything that we can highlight from those --

DR. LISA BUTTERFIELD: And I'm going to ask to keep this very short because we've got the afternoon.

DR. CHRISTINE DUNCAN: Yep. Okay. I'm sorry. Just to say we were not able to identify anything specific to the product related to vector copy number and the development of MDS. I apologize.

DR. LISA BUTTERFIELD: Thank you very much.

DR. CHRISTINE DUNCAN: I believe those were all four. Thank you.

DR. LISA BUTTERFIELD: We're going to move to Dr. M and then Dr. Robert Shaw and Dr. Keller.

DR. JAROSLAW MACIEJEWSKI: Can you guys hear me?

DR. LISA BUTTERFIELD: Yeah.

DR. JAROSLAW MACIEJEWSKI: It's a little bit not obvious. Okay.

DR. LISA BUTTERFIELD: We can't see you, but we can hear you.

DR. JAROSLAW MACIEJEWSKI: Thank you very much for that presentation. The allogenic bone marrow transplant does have variability in terms of -- variability in terms of the quality of transplant, different possibilities as to how to set up a bone marrow transplant in the setting, institutional differences.

Can it be that -- and the fact that the patient (inaudible) over several years, can it be that under current condition the most recent patients on

recent transplant or a modified allo regiment or use of (inaudible) or use of new FDA approved drugs for GvHD would improve the high risk transplant that has been used as a comparator group? This one question that I have.

And I have another question related to the fact that the material that you provided has several cases of integration site into MECOM EV1, which do not fulfill criteria understand of MDS but would be considered something that either (inaudible) in two of the (Inaudible) if it was equivalent. Obviously, it's not a natural mutation because two of them have a sort of mild single lineage cytopenia, the low platelet count. If we add this, how do you assess the risk of this being a (inaudible) teacher of the myelodysplastic syndrome, which is of course a chronic --

DR. LISA BUTTERFIELD: And we're going to again hold the MDS --

DR. JAROSLAW MACIEJEWSKI: Oh, thank you.

DR. LISA BUTTERFIELD: -- discussion to the afternoon.

DR. JACKOB SIEKER: Okay. So we can answer the first question about how the ALD transplant population compares to the experiences of today. And I would like to ask Dr. Duncan to answer that.

DR. CHRISTINE DUNCAN: Thank you for the question. One thing just to remind the panel is that for ALD-103 trial the last patients enrolled in that, that trial was closed in 2019. And so we did attempt to have a more contemporaneous population to look at, so that is one thing to consider. It just -- in my experience as a transplanter, there are things that have certainly improved over time, many of our supportive care medicines, our ability to treat graft versus host disease. But unfortunately, we haven't seen those outcomes change really what we're seeing in ALD.

So I think the experience that we present in the study is very reflective of what we see currently. That is one point to that. And I think the other question about haploidentical transplant, there's been a lot of discussion, much movement in the

haploidentical transplant world in recent years. And so, just for those who aren't familiar, that's using someone who is half-matched, typically a related donor, as a transplant with certain modifications done either to the cellular product or to the patient after transplant.

I think that that is encouraging for many diseases. Unfortunately, the data has not turned out as well as we would hope for ALD. Albeit there are limited studies, but the largest study that was done, which is of nine patients -- and that's partially because of the small number of patients who are treated -- showed a 45 percent graft failure rate. And so we have not found haploidentical transplant to be ideal in this disease and certainly with high risks also associated with infection and other things as we go forward.

And so I think the other challenge, obviously, with haploidentical transplant is in this genetic disease your availability of donors is actually cut probably pretty much in half because we're unlikely to

use a mother who is heterozygous mutation as a donor. So haploidentical, great for many diseases, but not really ideal for ALD. Thank you.

DR. LISA BUTTERFIELD: Thank you very much. Dr. Roberts.

DR. DONNA ROBERTS: Yes, thank you. I had a follow-up question from Dr. Fox for Dr. Elenburg's slide 27 as well and the discrepancy between the increase in Loes score and neurologic function. And my question is, besides Loes scores, were the MRIs evaluated at all for size and lesion volume over time? Hello? Can you hear me?

DR. LISA BUTTERFIELD: Yes, that was for Dr. Elenburg.

DR. DONNA ROBERTS: For the sponsor.

DR. JAKOB SEIKER: Okay. This is a question for, yes -- so I would like to ask Dr. Raymond to comment on the relationship to Loes score and NFS.

DR. GERALD RAYMOND: So, good afternoon. I'm Dr. Gerald Raymond. I'm professor of neurology and genetic medicine at Johns Hopkins, and I've been in the

ALD field for over 30 years. So the question is whether we use volume metrics compared to the Loes score, and have we found that to be useful?

And the honest answer is at this point, volume metrics, while being an additional feature, have not been shown to be of any additional benefit to the Loes score as a simple measure of measuring disease burden. Unfortunately, we have looked at a variety of research methods over time, and I've been involved in many of those studies. And once again, the gold standard still is the Loes score using a T2 flare weighted imaging.

DR. JAKOB SEIKER: Dr. Raymond.

DR. LISA BUTTERFIELD: Thank you. We've got time for two more questions. Dr. Shah and then, finally, Dr. Hawkins.

DR. NIRALI SHAH: Hi, so I have -- can you hear me okay?

DR. JAKOB SEIKER: Yes.

DR. NIRALI SHAH: I have two questions. One, I was struck by this asset with the ALD-102 Study -- you didn't see any events related to (inaudible) in

almost seven years. But you had two events in the ALD-104 Study, and I was just wondering if anything had changed between the two studies that could have possibly lead to that increased incidence?

Particularly since the follow up period for that one is shortened. And then the follow-up to that is for the clinical team, what incidence of MDS do you think would be acceptable for this type of population given what you're seeing?

DR. JAKOB SEIKER: I would like to ask Dr. Demopoulos to review our current understanding of the three MDS cases that occurred in the two studies, ALD-102 and 104. Dr. Demopoulos.

DR. LAURA DEMOPOULOS: Thanks. That's an important topic. With regard to the distribution of the patients with MDS, yes, two were in the 104 Study, and one was in the 102 Study. We spent quite a lot of time and a lot of effort with our statistical colleagues attempting to determine whether or not any differences on the patient characteristics or treatment characteristics between the two studies might have in

any way influenced the uneven distribution, albeit it's three patients. So it was always going to probably break unevenly some way.

The short answer is we were not able to identify anything that appeared to be a so-called smoking gun that would have helped us to say treatment or patient factors could be adjusted in some way that would allow for risk mitigation. As to your second question regarding what level of MDS is acceptable, I don't actually think there's any great answer to that question. I think we've seen from many of the presentations and some of the comments that the medical need for patients certainly without good donor options and even among those who may have some degree of matched unrelated donor option -- the medical need is still very high.

And the early mortality rate that we've seen is still in the range of about 10 to 20 percent in the proposed indication. Our current data estimate that our MDS event rate now is in about five percent of patients, and so, we still see that our current MDS

rate compares favorably to the early fatalities that occur in patients having transplants who don't have a matched sibling donor.

DR. NIRALI SHAH: Thank you.

DR. LISA BUTTERFIELD: All right. A very short final question from Dr. Hawkins, please.

DR. RANDY HAWKINS: Thank you very much. To Dr. Duncan a comment and a question. Thanks for your presentation, including a brief presentation on the effects of quality of life for family and patients, the disparity of needs and availability of certain ethnic groups, such as African Americans and Hispanics. In your shared decision making, do families realize that MDS is cancer?

I did hear you say -- give some response to that. And two of your cases I viewed developed MDS. I don't know how long it's been, how much time's elapsed, but what type of allotransplant did they receive? Do you have a status update? And finally, those who develop seizures (audio skip).

DR. CHRISTINE DUNCAN: I lost a little bit of

the question on the seizures. Sorry, go ahead, I'm sorry. Please, go ahead.

DR. RANDY HAWKINS: How well are the seizures controlled in those five patients who developed seizures as an adverse event?

DR. CHRISTINE DUNCAN: Okay. So kind of the first question, so when we do talk to the families about MDS, we do explain that this is considered a pediatric cancer. And we've spoken about how those patients need to be treated. Both boys received allogeneic transplants. One child, just speaking about, again, slide one and that availability of unrelated donors, is a patient who was Hispanic who had absolutely no unrelated donors available in the registry. And so we needed to use that patient's father as a donor -- a haploidentical donor, which obviously has some concerns, but there were no other options for that patient.

The second patient had -- that I've treated received an allogeneic stem cell transplant with an imperfect donor because they did not have a matched

family donor available as well. And so I'm not sure if someone else would like to comment on the seizures. I think Dr. Raymond would like to comment on the seizures, but we do talk to the families. We do explain a transplant consent, a gene therapy consent. They're pretty brutal. And we get very honest about the risks, the benefits, and trying to characterize those for the individual patient as best we can.

DR. RANDY HAWKINS: Thank you. And seizure control in a neurological disease.

DR. GERALD RAYMOND: Can I have slide one up? So once again, seizures are a complicated thing in a neurologically injured patient, and our patients have a variety of reasons to have seizures. However, when we look at the seizure outcomes and the five serious seizure disorders -- or the five serious seizures, the seizures have generally been singular or well-controlled. And so they have not been medically refractory, and they are controlled in certain situations with medication.

DR. RANDY HAWKINS: Thank you very much.

DR. LISA BUTTERFIELD: All right. Thank you very much for an important Q&A session. We now are going to take what will serve as a lunch break. We will come back though on time at the top of the hour. So a very short, 20 minute lunch break please. Thank you very much.

MR. MICHAEL KAWCZYNSKI: Hold on, everybody. Studio, take us to clear.

[BREAK FOR LUNCH]

OPEN PUBLIC HEARING

MR. MICHAEL KAWCZYNSKI: All right. And welcome back from our break to the Open Public Hearing. I'm going to hand it back to our Chair, Dr. Lisa Butterfield, and our DFO, Christina Vert. Take it away.

DR. LISA BUTTERFIELD: Thank you very much. Welcome back. Welcome to the Open Public Hearing session. Please note that both the Food and Drug

Administration, FDA, and the public believes 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's 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 expenses in connection with your participation in this 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 the issue of financial relationships at the beginning of your statement, it will not be -- it will not preclude you from speaking. So with that, let me turn

it over to Christina Vert for the Open Public Hearing.

MS. CHRISTINA VERT: Thank you, Dr. Butterfield. Before I begin calling the registered speakers, I would like to add the following guidance. FDA encourages participation from all public stakeholders in its decision-making process. Every Advisory Committee meeting includes an Open Public Hearing, OPH session, during which interested persons may present relevant information or views.

Participants during the Open Public Hearing session are not FDA employees or members of this Advisory Committee. FDA recognizes that the speakers may present a range of viewpoints. The statements made during this Open Public Hearing session reflect the viewpoints of the individual speakers or their organizations and are not meant to indicate Agency agreement with the statements made. Okay. Now we'll go on with the first speaker. Amy Waldman.

DR. ADELINE VANDERVER: Hello. This is Adeline Vanderver at the Children's Hospital of Philadelphia.

DR. AMY WALDMAN: And this is Amy Waldman, also at the Children's Hospital of Philadelphia.

DR. ADELINE VANDERVER: I don't have any disclosures with bluebird bio to present. Although bluebird bio has, in the past, presented -- support educational activities at the Children's Hospital of Philadelphia related to leukodystrophy education.

DR. AMY WALDMAN: And I have consulting fees for data review with bluebird bio.

DR. ADELINE VANDERVER: We are from the Leukodystrophy Center of Excellence in the Children's Hospital of Philadelphia, which I direct.

DR. AMY WALDMAN: And I am the medical director for our clinical program at the Children's Hospital of Philadelphia. And today we are speaking about diversity in X-linked adrenoleukodystrophy. Next slide, please.

We would like to share our collective experience in our leukodystrophy program, taking care of newborns with ALD. Our current population is over 40 affected children with pre-symptomatic ALD who are

identified predominantly through newborn screening, many of them through Pennsylvania and New Jersey, and are aging into high risk for cerebral ALD. Next slide, please.

One of CHOP's core values -- you can keep going to the next slide, please -- one of CHOP's core values is reducing health disparities. And we are committed to this through our Center for Outcomes Research; the National Provider Services, which has provided education throughout the U.S. and internationally; the Global Leukodystrophy Initiative, led by Dr. Vanderver, providing outreach for patients and physicians.

And of note, our leukodystrophy program has a catchment area that is mostly outside of the tri-state area. Seventy-nine percent of our patients are not from our local tri-state region. And in our experience availing our patients of our bone marrow transplant collaborative, many of our patients have not had an ideal match. Next slide, please.

We would like to just review the data, which

you have already discussed I'm sure, this morning with Dr. Miller et. al., on outcomes related to transplants. Next slide, please. And in this -- one of the papers looking at the outcomes, over 30 -- oh, excuse me, only 30 percent of children had a related marrow transplant. And transplant related mortality is higher, as everyone knows, among unrelated donors, perhaps in part due to higher conditioning needed to save engraftment. Next slide, please.

I was thrilled to hear this morning some discussion about the health disparity and the odds of finding a match. Next slide, please. As was already discussed, with our African-American population only having a 29 percent chance, and it increases, as you see here. Next slide, please. Racial disparities in transplants has been studied. And this is not specific to ALD. Next slide, please.

As you can see here, transplant related mortality is higher among ethnic minorities, particularly African-American patients shown on the right and our Asian population shown on the left. Next

slide, please. And in thinking about survival and functional outcomes in boys -- I'm sure this data has also been published. This data was collected from five study center in the U.S., as you know, from Minnesota, Kennedy Krieger, North Carolina, Duke, and of course, France where the population of treated and untreated was still about 64 percent Caucasian or 70 percent in the untreated arm.

So in conclusion, diversity is present among our ALD families. Historically, the likelihood of finding an ideal unrelated donor match is lessened in under-represented minorities. Newborn screening is agnostic to race and ethnicity. Transplant related mortality increases among our unrelated donors and ethnic minorities.

And we ask the FDA to please consider health disparities -- and I'm glad to hear that you have already discussed it a bit this morning -- in that not every young boy will have an eligible donor for a standard autologous transplant. Thank you for the opportunity to speak today.

MS. CHRISTINA VERT: Thank you. Next speaker is Josh Bonkowsky.

DR. JOSH BONKOWSKY: Thanks. This is Josh Bonkowsky. I'm speaking on behalf of our Leukodystrophy Center and our transplant teams here at the University of Utah and Primary Children's Hospital which is part of Intermountain Healthcare. Next slide, please.

So, we provide care for the state of Utah as well as the Intermountain West. Next slide, please. This is a very large geographical area. It's about 400,000 square miles that we provide centralized care for. Even though it's a less population dense area because of the large geographic area, it still ends up being responsible for care of about 1.7 million children in this catchment area. Next slide, please.

Historically, this region has been obviously a rural area, but it's now -- this region has the fastest growing states in the United States including Idaho, Nevada, Utah, and Arizona. And the population is shifting significantly with this population growth and

now has almost a quarter minority population in these states. Next slide, please.

In this region there are urban areas so, for example, where the hospital is located is a urban area, but much of the region is what's classified as rural or frontier. And many of the patients that we take care of come from these very far outlying regions and have to travel significant distances and times to reach care with us. Next slide, please.

So, the hospital itself then becomes a referral center for all of these patients who need any sort of specialty care, including specifically in this context for ALD, adrenoleukodystrophy. For any kind of specialized care related to ALD that means that for any kind of care they're having to travel often more than or up to 500 miles to reach us and that -- to be able to access both their leukodystrophy care and the transplant teams. Next slide, please.

So, if we look back over about the past decade of care for ALD patients, including for patients who have cerebral ALD, we identify these patients through

several sources. In some cases they have known family history and we've been able to follow them for those reasons. There's now newborn screening occurring in several states including Utah and Idaho in this region and then, of course, if they present with new symptoms, so, for example, new cerebral ALD symptoms. Next slide, please.

So, these are the patients that we've statistically had with cerebral ALD in the past five years. So, the first patient presented with new cerebral ALD symptoms. He was too late to qualify for transplant, and he died basically a year after his presentation. A second patient in 2017 also presented with new cerebral ALD, again, too late for a transplant and died two years later.

The third patient was known since birth because of family history. He was being monitored. When he developed cerebral ALD, he did have an allotransplant. And as of this time, most recently, he's doing great. Totally normal neurologic exam, in school -- a real success.

In 2020, our fourth patient developed new symptoms of cerebral ALD. He did get the ex vivo gene therapy transplant program through Boston. We're following him here currently. He also looks great. I just saw him a few weeks ago -- totally normal.

At this point, in 2022, we're following five boys at risk for developing cerebral ALD with monitoring, both MRIs and labs. Next slide, please.

So, in conclusion, we're often receiving these ALD patients from rural and other underserved communities. As part of their care, transplant, whether it's allo or ex vivo gene therapy, is a critical tool for their treatment. We -- having the availability of ex vivo gene therapy is really critical for us as we discuss treatment options for families.

We, of course, discuss risks. But as you can see, with our experience the alternative to treatment is worsening and often leading to death in the patients we take care of. Thank you very much for your time.

MS. CHRISTINA VERT: Thank you. Okay. Our next --

MR. BENJAMIN KOCH: I'm --

MS. CHRISTINA VERT: -- speaker is -- go ahead.

MR. BENJAMIN KOCH: I'm sorry.

MS. CHRISTINA VERT: Next speaker is Benjamin Koch. Go ahead.

MR. BENJAMIN KOCH: How's it going? My name is Benjamin Koch. I'm 19-years-old. I had a stem cell transplant to mitigate adrenoleukodystrophy when I was 8 years old. And I'm going to be talking about that.

So, I -- my story starts with my brother. My brother was diagnosed before me. And I was diagnosed early because my parents were trying to see if I or either of my siblings were donors for him. And in that, they discovered that I also had adrenoleukodystrophy. On the Loes scale, my brother was 10 and I was a one. So I was very lucky that mine was discovered early on even though his was significantly more progressed.

My parents, mom and dad, both moved the two of us down to North Carolina to Duke to go get stem cell

transplants. We had two young sisters that stayed in New York. And we were moved from school, removed from friends, removed from everything. We had to have a lot of preliminary checks, checkups, and testing. And then we were both admitted to the hospital. He was about 20 days ahead of me.

We had 10 days of intense chemotherapy to essentially wipe out our immune systems. That was probably the hardest 10 days of my life, like nothing I will ever, ever experience. You know, I would not wish it on my worst enemy. I remember struggling. You know, we had to re-learn how to walk. I remember it being difficult just to wake up and find the strength to have a day in the morning. That was really difficult. I couldn't really be a kid.

I was in the hospital for two months. But the first milestone that -- after engrafting that was a big one was a hundred days. But once you get to a hundred days it's not much of a celebration because it's like are we really going to be able to do this for another 200-plus more days to get to one year. One year is

when you're really able to resume a new life.

Once becoming outpatient, I had two places I could go -- the hospital or my apartment. I had to wear masks everywhere. I could not be around anybody that was not wearing gloves and a mask. We had to wipe down food and groceries. I couldn't eat fast food that wasn't prepared in the last 15 minutes. We had to be careful. And careful was really, really like -- careful is saying it lightly.

We were concerned about graft versus host disease. We were concerned about really just being able to live. My parents had to administer medicine to us for a year being concerned about, you know, like anti-viral, anti-fungus. Being -- just -- again, being able to live (audio skip).

MS. CHRISTINA VERT: Benjamin?

MR. MICHAEL KAWCZYNSKI: I think he lost his audio. We will -- I will try to bring him back to finish up. Let us go to the next one at the moment. And we will go to --

MS. CHRISTINA VERT: Okay.

MR. MICHAEL KAWCZYNSKI: Is that all right?

MS. CHRISTINA VERT: Yeah, that's fine. Go ahead, Kirsten Finn.

MS. KIRSTEN FINN: My name is Kirsten Finn. I'm the mother of a boy who was diagnosed with ALD at age four, and we had to intervene immediately. We experienced significant barriers to accessing care for our son. In fact, our son almost did not make it to treatment because of these barriers. Thinking back on that time fills me with a crippling fear that I cannot shake to this day.

It is a devastating fact that many boys will continue to be diagnosed in a manner similar to our son, who will require immediate intervention. And some will never make it to treatment and will be condemned to the cruelest of fates, with their parents having to watch their suffering and deterioration, powerless to stop it. No parent should ever be told they have to take their child home to slowly deteriorate and die when a successful and qualified treatment is available.

An ALD diagnosis is terrifying. To be told

your child is facing a silent killer, one that could cruelly and savagely rob him of every functional ability he has before it takes his life, is deeply traumatic. The mere memory of that moment can stop me dead in my tracks, unable to catch my breath. The emotional pain and anticipatory grief I experienced was so intense and deeply visceral that I quite simply wanted to crawl out of my own skin. I would have endured any amount of physical pain to not have to experience that emotional trauma.

This is not something I have to explain to any ALD parents. The fear and devastation caused by this disease instinctively binds us as a community. No words are needed. The only thing that allowed us to endure was knowing we had a path towards treatment with an expert physician who understood our child's disease. And this gave us the hope we needed to move forward. Devastatingly, many children will not be able to find a suitable match on the registry or may have complicated medical factors and co-morbidities to consider. Both of these patient populations must have options

available to them.

The physicians involved in treating ALD compassionately and directly communicate the risks involved in such a way that there can be no room for confusion or misunderstanding. So many questions and fears came crashing down upon me as we considered what our options might be. What if I make the wrong choice? Am I choosing an option that will cause my son additional suffering? Am I making a choice that will hasten my son's death? There must be choice.

I recall conveying to our specialist how truly excruciating it was to be making this decision for our son. He was only four, and I would have to decide something that would forever alter the course of his life and that could potentially result in his death. However, I also told him that if I was four and I was facing an insidious, relentless monster of a disease like ALD that I would want him to get in there and take it out. And I will never regret it.

And I can tell you in honesty today that if our son could not find a match on the registry and that

gene therapy was our only option, that knowing all of the risks, we would proceed to treatment and we would not look back. The alternative to no treatment is simply not acceptable.

It would be exceedingly difficult, if not impossible, to find a patient population more excruciatingly and acutely aware of the risks involved in the treatment options available to us. The moral injury of not having this life saving option to patients, parents, and providers alike can neither be overlooked nor understated.

One ALD mother of a boy who could not make it to transplant, who also had a child who beat childhood cancer, confided to me once. She said, I wish it was cancer. At least with cancer you can fight.

As you consider how to proceed on this matter, I implore you to consider how you would feel and what you would do if your child were facing this disease and gene therapy, the only option you had, was withheld. The right to refuse treatment will always be there. Parents must have the right, with full understanding of

the risks involved, to choose. Anything less condemns these children to a life of severe disability and suffering. It is a death sentence. Thank you.

MR. MICHAEL KAWCZYNSKI: Christina, we do have --

MS. CHRISTINA VERT: Yeah?

MR. MICHAEL KAWCZYNSKI: -- we do have Benjamin back.

MS. CHRISTINA VERT: Okay. Benjamin, why don't you go ahead and finish your statement.

MR. BENJAMIN KOCH: Yeah. I just wanted to wrap it up by saying my life with ALD was incredible. I had spent a year isolated from all people. I spent a year suffering. I had to watch my brother die in front of my eyes because, A, his was a lot more progressive, but, B, because transplant was the only option. Transplant takes a long time to happen.

That was the biggest part for me. I wish -- as I said, I would not wish this on to my worst enemy. And even though I'm never going to forget it, it's something where -- the struggle is the one thing that

I'm going to remember.

MS. CHRISTINA VERT: Thank you. Thank you for sharing. Next speaker, Jennifer Mahoney.

MS. JENNIFER MAHONEY: Hi. My name is Jennifer Mahoney, and I live in Glen Head, New York with my husband, John, and our daughter, Ava, and our son, Colin.

Ever since I was a child, we talked about this mysterious walking disease that my uncle and my mother both had. It was something that developed in their forties and seemed to be progressively getting worse. My uncle was more severely affected by this walking disease, as we referred to it as, but was younger than his sister, my mother. He had been in Vietnam, and after years of unsuccessful attempts at a true diagnosis they concluded it might have been from Agent Orange or some sort of cerebellum pressure on his nerves.

They did not answer a lot of his unanswered symptoms that gradually took away his ability to play tennis, play golf, then general walking ability. He

went from a walker to a wheelchair for long distances to a motorized scooter all the time over the course of 30 years.

It was not until Colin, my son, was born in 2016 that this mysterious walking disease would be diagnosed after all these decades. Nine days after Colin was born, we got the call that something on his newborn screening came up, and it was called ALD. Once I looked it up and saw what the symptoms were, I knew right away that this was what my mom had and -- this is what my mom and uncle had been suffering from.

It was probably the worst day of my life, and everything seemed to be crashing down around me. Through the support of fellow ALD moms that I was able to get in touch with, and then as well our neurologist specialist Dr. Eichler at Mass General, we eventually began to see the progress of the treatments for cerebral ALD, which included a gene therapy trial. I was introduced to families that had been given this amazing opportunity for their child and saw how great most of the boys were doing for years after.

This potential treatment that was waiting for FDA approval was the reason we were able to be able to enjoy life again and see the hope in our son's future. With a traditional stem cell transplant there are major risks involved for those without a perfect sibling donor match. The graft versus host risk can be life threatening and continue for the rest of their lives. With gene therapy we didn't have to worry about the potential issues or drawbacks because they use their own stem cells.

I know obviously, as well as you, that there have been a few children that have developed some complications with this treatment. However, the majority of boys are thriving and living a life that would not be possible without this gene therapy. We need alternative treatments that will save all of our son's lives. And bluebird's treatment is doing that. It would be a tremendous setback for the entire ALD community if this therapy was not available to give our boys the best possible outcomes in life.

MS. CHRISTINA VERT: Thank you. Next speaker,

Miranda McAuliffe.

MS. MIRANDA MCAULIFFE: Thank you. My name is Miranda McAuliffe. My son was diagnosed with X-linked adrenoleukodystrophy at birth thanks to the New York State Newborn Screening Program and the passing of Aidan's Law in 2013. He is now six years old and currently asymptomatic. He has blood work done every six months to check for adrenal insufficiency and he has MRIs of the brain done every six months to monitor for cerebral ALD. While we can see that his adrenals are affected through his lab results, he has not yet needed medical intervention.

As scary as it was receiving this diagnosis when my son was 12 days old, I soon realized that the knowledge of this disease at birth is a gift. Treatment is most effective when given at the earliest signs of the disease, and his monitoring protocol allows for detection before symptoms are likely to arise. I am so grateful for the screening and grateful for the medical technology that allows our family to stay one step ahead of ALD.

If my son develops the cerebral form of ALD in childhood, our family will have limited options. You see, my son is an only child. In addition to having ALD myself, I also have primary ovarian failure. Growing our family would have been another healthcare struggle that quite frankly my husband and I did not feel equipped to tackle emotionally or financially. And so our son will never have a match sibling donor if he is ever recommended for the treatment of cerebral ALD. This is a burden that weighs heavily on our family.

I once again find gratefulness in the midst of this diagnosis. I know we are fortunate that an allotransplant can halt progression of this disease. But graft versus host disease has scared me since before I became a part of the ALD world. We watched a family friend suffer from it before my son was born. His donor was his sister. I have met many ALD families with children who are still struggling with it and some who have died from it. Its severity and unpredictability frightens me.

I know how to prepare for ALD. But I find it impossible to prepare mentally or physically for graft versus host disease, especially knowing my son will never have a sibling match. The progress made by eli-cel gives me so much hope.

The FDA will be reviewing this treatment almost exactly one month after my son's next scheduled MRI, a pivotal one at six and a half years of age. I apologize. It is my hope that the FDA will approve this treatment on the scheduled PDUFA date of September 16th, 2022, so that it is available for my son, if needed, and for others less fortunate than us who are statistically less likely to find a match in the registry.

Aside from my own plea, I also would like to leave the Committee with two other thoughts that are both true and terrifying. There are several gene therapy treatments for rare diseases being developed at this time. Gene therapy treatment for cerebral ALD is unique because it is halting a disease that, if left to its own course, will result in deterioration and death.

There is no way to manage cerebral ALD. Children without access to treatment will die.

And number two -- and I'm so glad this has already been touched upon, but it's worth saying again. ALD families that are Black or African-American, Asian, and Hispanic have less than a 50 percent chance of finding a match in the registry while the cerebral ALD deterioration clock is ticking. An approved gene therapy treatment for cerebral ALD will help close this inequitable gap in healthcare. Thank you for this opportunity to share my family's story.

MS. CHRISTINA VERT: Thank you. Next speaker, Katherine Mullen.

MS. KATHERINE MULLEN: Hi. My name is Katherine Mullen. My wife and I adopted our oldest son through the Massachusetts Foster Care system in 2018 when he was four years old. His younger brother was born just prior to the adoption being finalized.

We first heard of ALD when we got a phone call from a social worker saying that a test had come back from the baby's newborn screen and that our happy and

healthy four year old had a 50 percent chance of having what she termed a degenerative condition. After testing, he too was diagnosed with ALD. We began educating ourselves on the condition and talking to the medical team.

The idea of a bone marrow transplant was terrifying, but it was not a foregone conclusion that it would be necessary. And one of the things that came up while we were educating ourselves was the clinical trial for gene therapy which was having a lot of success treating cerebral ALD. Somewhere in my subconscious, I think we always assumed this would be an option.

In April of 2021, our older son's regular MRI showed the start of a lesion. We were devastated. Initially, we were also told that the gene therapy trial would not be an option, as it was full. This news was almost as devastating as the lesion itself. We immediately made an appointment to do his HLA testing, but our hopes were very low. Our son is biracial, and we knew the odds of finding a good HLA

match for a person of mixed race is significantly reduced. And our son is a mix of minority groups that already have lower odds of finding a match.

Knowing this, we went into an already terrifying ordeal with diminishing hope that he would have a good outcome. We were exceedingly lucky, and he did in fact have a 12 out of 12 match. So we began moving forward with the process for traditional BMT. A couple of weeks before he was supposed to be admitted, we were informed that a spot had opened on the gene therapy trial and that our son would be able to go through gene therapy if we so chose.

And so, we were faced with a decision: a traditional BMT with a long track record of success and decades of follow-up data, or gene therapy with a similar success rate but far fewer patients and less than 10 years of post-transplant data. We agonized over the decision. We considered the various risks of each, compared success rates, discussed both transplant data, and worried that whichever choice we made it would be the wrong one.

Ultimately, knowing all of the risks, we chose to enroll him in the gene therapy trial. One of the primary deciding factors was our fear about the possibility of GvHD following the traditional BMT which has the potential to be severe and sometimes deadly. Another primary decision factor was how quickly he would be able to return to normal daily activities. Our son is on a social emotional IEP and had already lost more than a year of social development due to COVID and the transition to remote school.

He was admitted to Boston Children's Hospital on June 28th and received his transplant on July 6th, 2021. We are now almost a year out from transplant, and we are so thankful that he was able to do gene therapy. Had he done a traditional BMT he would likely still be on restrictions and would have lost another whole year of in-person learning at school. Following gene therapy, his labs improved so rapidly that he was cleared to start school in the fall and returned only one day later than the rest of his classmates.

We have watched him make social strides that

would not have been possible for him if he were still doing remote learning. He has attained his blue belt, competed in martial arts tournaments, and is showing leadership skills on the baseball field with his little league team. His labs have been so good that his transplant doctor told us he no longer needs any special monitoring, and his neurologist was pleased with his six-month post-transplant MRI.

Our son would not be where he is today had it not been for gene therapy, and I feel that it was absolutely the right choice. Of course, we also adopted his little brother who is now approaching the age window where lesions are most common. As his brother is Hispanic, he has less than a 50 percent chance of finding a match according to bethematch.org. Our fear is having to go through this again and that without gene therapy as an option our youngest will have a much more difficult path.

MS. CHRISTINA VERT: Thank you. Next speaker, Paul Orchard.

DR. PAUL ORCHARD: Hello. My name is Paul

Orchard. I'm a pediatrician at Bethesda Pediatrics at the University of Minnesota. The University of Minnesota has been very interested in adrenoleukodystrophy and initiated transplants here back in the 1990s. We've done well over a hundred allogeneic transplants for ALD. And we've been involved in the clinical trials of bluebird on the 102 and 104 studies enrolling I think it's 17 patients. So, in -- what I'd like to do is briefly address my views of efficacy and then safety and summarize at the end what my recommendations would be.

So, it was my understanding that on the one or two studies in terms of efficacy, three patients were taken off study due to progression so would be considered treatment failures. One of those patients regressed quickly and was not thought to be a patient that should be offered allogeneic transplant. Of the other two patients who received allogeneic transplant, one died going through the transplant process, the other is stable to the best of my knowledge.

In terms of efficacy data, I think it's quite

clear that eli-cel shows superiority related to no therapy. Demonstrating superiority or inferiority in terms of transplants is more difficult. The parameters such as neurologic functional score, the Loes scores, seizures, neuropsych data who are all important in this regard. And I think we're just going to have to have more experience with more patients to be able to sort this out.

In terms of safety, I ordinarily think of this in two global parameters. One is the early difficulties, and the other are late concerns. Related to the early problems, we ordinarily think of transplantation in terms of peri-transplant mortality, meaning the number of patients that die by day 100. As was shown earlier in the 103 study, it was approximately 25 percent of patients died by day 100. In our hands -- this is a large, experienced allogeneic center for ALD -- I would estimate it more to be 15 percent, recognizing that most of these patients are treated with unrelated donor grafts.

The complications resulting in mortality with

treatment in eli-cel is zero as I understand it. So, there's 67 patients. And as these patients become neutropenic and have thrombocytopenia and other issues related to the chemotherapy, one would anticipate that the peri-transplantality's not going to be zero, but it may well be in the one or two percent. And if that's true, then the peri-transplant mortality associated with allogeneic transplant is likely to be an order of magnitude higher.

In terms of late complications, clearly myelodysplasia concerns all of us. Three out of the 67 patients thus far, so roughly five percent of these, have developed myelodysplasia. Of these, all were transplanted and thus far have been doing well. But the follow-up is very short here. But it's -- I think it's important to understand that the development of myelodysplasia is not a death sentence. And treatment failures both from progression as well as myelodysplasia can be treated with allogeneic transplant, which is the therapy they would be getting anyway if eli-cel was not available.

So, from my standpoint, I would certainly recommend that we have another option to offer patients because clearly there are situations where the allogeneic transplant risks are very high. Giving informed consent and making sure that the risk benefits are well understood by the families ends up being very important. But certainly as the transplanter I would like the opportunity to have other therapies available. Thank you.

MS. CHRISTINA VERT: Thank you. Next speaker is Elisa Seeger.

MS. ELISA SEEGER: Hi. My name is Elisa Seeger, and I'm the founder of the ALD Alliance. My son, Aidan, was diagnosed with ALD in 2011. He was just six and a half years old. I remember when we were looking for treatment options learning about gene therapy. And even at that time, over 10 years ago, gene therapy is what I would have chosen if that was an option for us. But it was not. Aidan did receive a transplant at Duke. He, again, was a late diagnosis. And he passed away 10 months later having been in-

patient for all of those 10 months.

In the latter part of 2012 I started a foundation in his honor. Our primary focus is newborn screenings. And we had Aidan's Law signed here in New York where we became the first state to start testing for ALD. And I'm grateful to say today we are at 29 states that are testing with more states coming on board in 2022 and 2023.

So, we are really in dire need of more treatment options for our boys because we are diagnosing them much earlier, giving them the chance of having that time for early treatment. Sixty-seven children have received this treatment thanks to bluebird bio's clinical trials. The majority of them are doing really well, particularly one I'll talk about now. It's a family I'm very close to.

Brian was one of the first boys to receive gene therapy for ALD. Brian, like other patients not of Caucasian descent, had a less than 50 percent chance of finding a match for transplant. Brian did not have a compatible match. The gene therapy saved his life.

He is now a healthy boy who attends school and loves Harry Potter. His older brother, who was diagnosed too late for treatment, no longer walks, talks, or eats, and needs round the clock care.

We understand as an advocacy organization that works with a lot of ALD families -- we do understand that gene therapy, much like allogeneic transplant, does not come without risks. It is our job as an advocacy organization to educate families about these risks and facilitate important conversations about their treatment options so that parents can make informed decisions for their children.

Eliminating the need for finding a match and eliminating the side effects of graft versus host disease are both viewed as tremendous advantages by the parents we interact with. Again, many ALD children will not have a bone marrow or cord blood match as an option.

As our organization continues to advocate for newborn screening, we hope that the FDA will keep pace with our efforts by providing sufficient treatment

options for all boys receiving a diagnosis of cerebral ALD. Our country's federal leadership has committed to advancing health equities for all of its citizens. If eli-cel gene therapy treatment is approved by the FDA this September, all families receiving a timely diagnosis of cerebral ALD will be granted the opportunity for their child to go on and live a normal, healthy life regardless of their ethnic background and ability to find a match.

We respectfully request that the FDA Advisory Committee members take these points into consideration during this meeting and the FDA complete its review and approve eli-cel gene therapy treatment as quickly as possible thereafter for treatment of patients with early cerebral ALD. Thank you, so much.

MS. CHRISTINA VERT: Thank you. Next speaker. Next speaker, Jillian Smith.

MS. JILLIAN SMITH: Hi. Thank you, very much. I just want to thank you for the opportunity to speak about the importance and lifesaving need for gene therapy for ALD patients. My son, Grady (phonetic),

was diagnosed with ALD on August 17th, 2018, at the age of seven.

Grady was a late find patient with zero family history, known as a spontaneous mutation. He had a progressed Loes score of 10. We were originally told that Grady would not be a candidate for treatment and most likely pass within one to three years. After a second opinion, we were told he would be a candidate for bone marrow transplant. Grady was not given the choice of gene therapy due to the progression of his disease and a neurological deficit that had already begun.

We were extremely blessed to find out a couple weeks later that Grady had a fully matched unrelated donor and was then scheduled for admission on September 11th, 2018, with a transplant date set for September 20th, just 34 days after being diagnosed. Grady's fully matched, unrelated donor was unable to donate marrow at the last minute, so Grady did receive peripheral cells. Knowing this, we still went through with the decision because had we not he would most

likely pass or live in a painful vegetative state.

Although my son has had an amazing outcome and a very successful transplant, Grady has been dealing with chronic GvHD of liver, eyes, skin, joints, and fascia since transplant. We are going on almost four years now on a horrible emotional and physical roller coaster of weekly and biweekly visits. Had gene therapy been an option, this never would have happened. Grady has had many upon many readmissions, biopsies, MRIs, ultrasounds, x-rays, and thousands of intrusive tests.

On top of all the lingering medical issues, my son now deals with severe depression and anxiety mostly caused by PTSD of medical situations. Multiple times a week I find my son crying, stating that he does not want to live his life like this any longer. Grady's growth has also been extremely impacted. His muscles and bones have been affected from high dose Prednisone, the main drug to treat GvHD. He has only grown three to four centimeters since transplant almost four years ago.

Not to mention all the drugs that we have tried for GvHD that have caused so many side effects, including one being med induced Lupus that filled his knees with so much fluid that it made it hard for him to walk, which my poor Grady thought was progression of ALD taking his ability to walk from him. My son and our lives are forever changed, not only by ALD, but mostly GvHD.

My once gifted athlete, who was a basketball and football obsessed boy making one handed catches emulating his favorite Boston NFL player, now struggles to keep up with his peers. I have also lost my job due to constant admissions and appointments. And other -- my other children have also lost so much as well.

Grady is here and living with ALD, and we are forever thankful. But our family has not truly been able to even enjoy this amazing, uncommon outcome due to lingering medical complications from his allotransplant. And we are still constantly at worry of losing our baby in some way to GvHD. GvHD, to our family, feels like a price that we have paid for Grady

doing so well with ALD.

I also would like just to take one second, if you don't mind. There are many ALD parents today listening in on today's public meeting. And it has been extremely hurtful to us to listen to members of the FDA focus on even mentioning cost and saying disgusting things like G-tubes and wheelchairs could be used as convenience.

I want to leave with you saying that I pray none of you are ever put in our shoes with your children. I pray they all live healthy, beautiful lives. But maybe, if you lived in our world for even five minutes, your thoughts on this decision today might be much different. Thank you, very much.

MS. CHRISTINA VERT: Thank you. Next speaker, Bradford Zakes.

MR. BRADFORD ZAKES: Thank you. Good afternoon. My name is Brad Zakes, and I'm the father of Ethan Zakes who lost his life to cerebral ALD at the age of 10 years old. My family's story is unfortunately not unlike the thousands of other

families around the world that are impacted by this devastating disease each year.

Our son, Ethan, from all outward indications was born a perfectly healthy baby boy. Ethan developed at a normal rate, was a good student, good athlete, and involved in a number of activities outside of school. There was absolutely no indication that there was anything wrong with our son. It wasn't until Ethan reached the age of eight years old that he started to show the most subtle of early symptoms. Although our son had been a good student, we started receiving reports from his teachers that he was having difficulty staying on task and following the written instruction.

Unfortunately, Ethan, like the vast majority of young boys born with this disease, without having a known family history, was classically misdiagnosed as having attention deficit hyperactivity disorder or ADHD. We spent the next two years on a diagnosis odyssey meeting with numerous pediatricians and behavioral specialists only to watch our son's symptoms continue to worsen over this period of time.

It was only after he started having some difficulties with his balance and speech that his pediatrician suggested he undergo a CAT scan which revealed the abnormalities in the white matter of his brain, ultimately leading to a conclusive diagnosis of cerebral ALD. At the time of our son's official diagnosis, the progression of his disease was still early enough that he was considered a good candidate for an allogeneic stem cell transplant.

Unfortunately, as we have heard from others this morning, Ethan did not have a matching sibling donor that would have allowed us to move quickly with treatment. Even though we live in the Seattle area with some of the best transplant facilities at our doorstep, it still took several months to find a suitable donor for our son. I have no doubt that if Ethan had undergone his transplant immediately upon being diagnosed with the disease, he would still be here with us today. Instead, our family agonizingly waited months for a suitable donor while we watched our son's condition steadily deteriorate before our eyes.

Regrettably, by the time Ethan underwent his transplant the disease advanced to the point that it could not be stopped. Our son lost his life a short six months from the time of his initial diagnosis. I'm here today to stress the fact that this is a disease where time equals brain. There's simply no other way to put it. For those young boys that are born with ALD without a known family history, more times than not the simple reality is that they are going to face delays in finding a suitable donor. Whether it's days, weeks, or months, any delay is simply unacceptable. As my family only knows too well, the outcome in these situations is not a positive one.

Having access to an alternative therapy that can be deployed quickly, without delay would simply be a game changer in the lives of young boys born with this devastating disease. I can definitively state that had eli-cel been a treatment option for our son, we would have been grateful to be provided an alternative therapy as opposed to watching our son slowly slip away from us while waiting for a donor

match to be identified.

In the case of ALD, the time spent waiting for a suitable donor is often nothing short of a death sentence for these young boys. Eli-cel is desperately needed as an alternative therapy that can effectively fill this treatment gap. I strongly urge that you consider this therapy for approval to help save the lives of future young boys born with this devastating disease. Thank you.

MS. CHRISTINA VERT: Thank you. Next speaker is Nina Zeldes.

DR. NINA ZELDES: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Nina Zeldes, a senior fellow at the center. We analyze scientific data to provide objective health information to patients, health professionals and policymakers. We do not accept funding from drug or medical device companies. We have no conflicts of interest.

We agree with FDA scientists in their summary that, "The uncertainty regarding efficacy at 24 months

following treatment is particularly problematic in the context of the recent discovery of a serious safety concern, the development of MDS, a life-threatening malignancy which occurred in three subjects." We share the concerns of the FDA that two of this -- two of the events are definitely related to the product, and the third is highly likely to be related.

You will recall that the FDA points out that, "The verity of the condition in the absence of a provoking event and the lack of known association between MDS and CALD are other factors that have influenced our concern regarding a causal relationship." Also, as FDA highlighted in the materials, the growth of clones with proto-oncogene integration sites may point to these clones having a selective advantage and may evolve into cancer.

We also share FDA's concern about the cause of a tumor (inaudible) leukemia that were observed following treatment with a related LVV-based product. (audio skip) patients with sickle cell disease. We also agree with the FDA that because most of the

subjects had less than two years follow up data, longer follow up data will uncover additional cases of MDS as a potentially life-threatening complication of treatment.

Please take these concerns into consideration as you conclude whether the data convince you that the likely benefits outweigh the likely risks. Thank you for your time.

MS. CHRISTINA VERT: Thank you. This concludes the Open Public Hearing. And I will now pass the meeting back over to Dr. Butterfield.

DR. LISA BUTTERFIELD: I want to thank -- really sincerely thank all of the speakers in the Open Public Hearing just now for their time and presentations. We now move to session two discussing the safety, including vector integration. And our next speaker is Dr. Stephen Hughes from the NCI, please.

INVITED SPEAKER PRESENTATION: LENTIVIRAL VECTORS AND INTEGRATION

DR. STEPHEN HUGHES: Thank you. What I'm going to spend most of my time talking about today is the integration of HIV progresses in oncogenes and how that causes both benign clonal expansion of T-cells and in some rare cases can contribute to development of T-cell lymphomas.

And you might ask yourself, if this is really a meeting about gene therapy and the use of retroviral vectors, why I'm going to focus on -- primarily on HIV. And the reason for that is there isn't very much information in the literature. Experience is relatively limited in terms of what happens following lentiviral therapies in either humans or non-human primates.

However, I've listed a few relevant publications here, three that show that there is -- there are known cases in which integration in or near oncogenes can cause clonal expansion in humans and a more troubling case in a non-human primate at the bottom in which the lentiviral vector caused lethal disease. And I'll point out something that I'm going

to come back to at the very end. In this particular case, the problematic cell in the non-human primate actually had nine proviruses in it. And so that's something to try and remember. And as I say, we'll come back to that.

Before I speak about the data on integration, I want to give a very brief introduction on the early stages of HIV replication which are in fact the same as the early stages of infection with a retroviral vector. The first thing that happens during the infection is that there's fusion between the membrane that surrounds the virus and the membrane of the target cell. That fusion is brought about by an interaction between the viral envelope's lack of protein and host receptors on the surface of the cell.

That introduces into the cytoplasm of the infected cell, the virion core, which contains the genetic information of the virus. In the case of retroviruses, that genetic information is reverse transcribed. Reverse transcription, the copying of the RNA genome into DNA, begins in the cytoplasm. We've

recently come to understand that the viral capsid remains intact in the cytoplasm, transits the cytoplasm, and enters the nucleus through the nuclear port. Once inside the nucleus, reverse transcription is completed.

The viral capsid loses its integrity when the reintegration complex comes into contact with host DNA. That allows the DNA to be integrated by the viral protein integrates. And in the rest of the talk we're going to focus on integration and its consequences. Once integrated, the provirus actually in a sense masquerades as a host gene and is copied -- the genetic information is copied by host RNA polymerase. But for the purpose of today's talk I want to point out that the insertion of a provirus is a mutagenic event.

I also want to point out that HIV proviruses, and this is also true of HIV vectors, referentially integrate into highly expressed host genes. More than 80 percent of the integration events are in the bodies of genes. One of the things that I was asked to mention at least briefly was how we go about

determining the integration sites and analyzing the data based on data that we obtained from HIV infected individuals.

As I mentioned a moment ago, HIV proviruses preferentially integrate into the bodies of expressed genes. And this is as a result of the interaction of the viral components, the two host factors, CPSF6 and LEDGF. We also know that in the case of HIV infections the initial distribution of HIV proviruses, that is the integration sites that we find, is affected by both positive and negative selections on the infected cells and, actually, also on the progeny of the infected cells.

Here are some relevant references. This is not nearly a complete set. But the first two listed papers describe the initial experiments -- some done by my colleagues and myself, some done by others -- in which the fact that there is clonal expansion of HIV infected cells, some of which is due to the integration of the provirus in oncogenes. This is the first two papers. For those who have an interest in how the

analysis was done, the next two papers, Sherman, et. al. and Wells, et. al., give slightly different versions of protocols that are used to identify, classify, and analyze integration sites.

And at the very bottom there's an overview review that was written by John Coffin and myself that gives more information about the data that's available and how it was analyzed. So, how do we go about determining integration sites, and how do we know that there are cells that have -- that are clonally expanded after they've been infected by HIV or modified by a vector? DNA is isolated from the cells and the host virus DNA junctions are selectively amplified in a PCR reaction using a Linker-Mediated-PCR protocol.

We -- and not everyone does the experiments quite the same way, but my colleagues and I do the experiments by amplifying both the junctions at the left and right end of the integrated viral DNA, both the five prime and the three prime LTR and their host junctions. And those DNAs in the -- and the ends of those DNAs are then sequenced using Illumina protocols.

We estimate on a good day that we recover approximately -- oh, damn.

MR. MICHAEL KAWCZYNSKI: I think we lost you there, sir, for a second. We'll let you -- did you lose internet or --

DR. STEPHEN HUGHES: I don't know what happened. I'm still on the phone obviously.

MR. MICHAEL KAWCZYNSKI: Sure.

DR. STEPHEN HUGHES: What would you recommend I do? (inaudible).

MR. MICHAEL KAWCZYNSKI: Why don't you try logging in right away?

DR. STEPHEN HUGHES: (inaudible).

MR. MICHAEL KAWCZYNSKI: Log back in again, sir.

DR. STEPHEN HUGHES: I'm going to log out and them I'm going to go back in. I do apologize --

MR. MICHAEL KAWCZYNSKI: All right.

DR. STEPHEN HUGHES: -- to everyone.

MR. MICHAEL KAWCZYNSKI: That's all right. We'll take a 30 second break. We'll just put the --

DR. STEPHEN HUGHES: I hope.

MR. MICHAEL KAWCZYNSKI: That's quite all right.

DR. STEPHEN HUGHES: The connection is not coming up when I -- when I --

MR. MICHAEL KAWCZYNSKI: So you --

DR. STEPHEN HUGHES: -- go back out and --

MR. MICHAEL KAWCZYNSKI: So you may have -- your internet may have blipped or something like that. Sir, while you're still doing that, if you want, you have your -- if you have your slide deck with you, we have you on phone. We can continue to let you present and we'll just move the slides for you.

DR. STEPHEN HUGHES: Yeah. But I don't know which -- I need to look at the slides to know what to say.

MR. MICHAEL KAWCZYNSKI: Oh, no, no. I meant I'll tell you which slide we're on if you have your slide deck with you.

DR. STEPHEN HUGHES: Let me -- if you don't mind, let me take one more --

MR. MICHAEL KAWCZYNSKI: Sure.

DR. STEPHEN HUGHES: -- shot at --

MR. MICHAEL KAWCZYNSKI: No problem.

DR. STEPHEN HUGHES: -- getting back on.

MR. MICHAEL KAWCZYNSKI: It wouldn't have -- it wouldn't have been a public meeting without at least one glitch, sir.

DR. STEPHEN HUGHES: Yeah. But I wish it was someone else.

MR. MICHAEL KAWCZYNSKI: I totally understand.

DR. STEPHEN HUGHES: I can try and do this from a different computer. But if I do that, you're not going to have -- you're not going to see my face. But that may actually be

MR. MICHAEL KAWCZYNSKI: Well --

DR. STEPHEN HUGHES: -- an advantage.

MR. MICHAEL KAWCZYNSKI: Let me ask this and let me ask this to the Chair. Dr. Butterfield, if you don't mind -- or Christina Vert, do you want to possibly go on to the sponsor while we get Dr. Hughes back in and then come back to him?

DR. LISA BUTTERFIELD: I think that might be a good idea. This sounds like it might take a few minutes. So, I'm okay going on to the bluebird bio presentation that would follow.

MR. MICHAEL KAWCZYNSKI: Okay. As long as that's all right. Bluebird, if you're ready I'm going to pull you up. And then I will continue to help you, sir. So I'm going to pull bluebird up.

DR. LISA BUTTERFIELD: All right. Thank you, very much. So again -- so, we're going to pause the presentation from Dr. Hughes from the NCI. And we'll move on to the next presentation from the sponsors of bluebird bio. And I'd like to welcome back Ms. Eggimann and also welcome Dr. Bonner for their presentation. Thank you.

APPLICANT PRESENTATION: INTRODUCTION

MS. ANNE-VIRGINIE EGGIMANN: Thank you, Dr. Butterfield. Good afternoon. I'm Anne-Virginie Eggimann, chief regulatory officer at bluebird bio. In

this session, we will discuss the safety of lentiviral vectors based on our experience across our clinical development programs.

As we discussed this morning, bluebird bio uses lentiviral vectors, or LVVs, to add functional copies of a gene in the DNA of the patient's own blood stem cells. For this purpose, we use two different LVVs to manufacture three distinct gene therapy products. Lenti-D LVV is used to manufacture eli-cel; BB305 LVV is used to manufacture beti-cel -- the two products whose benefit-risk assessment we are discussing today and tomorrow respectively.

In addition, BB305 LVV is used to manufacture a third product, lovotibeglogene autotemcel, or lovo-cel, currently in clinical development for the treatment of sickle cell disease. These LVVs are custom designed to support a specific mechanism of action, and each LVV has a distinct safety profile. This afternoon, we'll review the differences between Lenti-D and BB305 and how they contribute to the unique safety profiles of eli-cel and beti-cel.

As we briefly covered this morning, Lenti-D LVV was designed so that eli-cel can produce functional ALDP in the brain. BB305 LVV was designed so that beti-cel and lovo-cel can produce functional adult hemoglobin in red blood cells. As you can see on this slide, there are several key differences between Lenti-D LVV and BB305 LVV. Of importance is the use of a different promoter which is the on switch that genes use to drive expression. Lenti-D uses a modified viral MNDU3 promoter, and BB305 uses the human beta-globin promoter.

And let me explain why we purposefully used a different promoter for both of these LVVs. For beti-cel and lovo-cel we could use an LVV that restricts production of the desired protein in a specific lineage. Hence, the BB305 LVV was designed with a human beta-globin promoter to drive robust gene expression only in the erythroid cells or red blood cells as indicated on the left on this slide. In contrast, for eli-cel, we used the modified viral MNDU3 promoter to drive high levels of ubiquitous gene

expression in all lineages deriving from blood stem cells.

We made this choice because the exact type of hematopoietic derived cell that is responsible for long-term engraftment in the brain is unknown. Thus, to ensure appropriate expression of the ALD protein in the brain, the ubiquitous promoter, MNDU3 was chosen. As you heard, our two LVVs were designed differently on purpose. So it is not surprising that they would have a different safety profile.

And for each of our products we believe the safety profile of each LVV, along with the risks inherent to the treatment process, must be weighed against the severity of the disease they aim to treat, the availability of other treatments and their own risks, and the probability and magnitude of the lifelong benefit LVV gene therapy could offer to patients and their families.

With that, I'd like to introduce Dr. Melissa Bonner, Head of Research at bluebird bio who will share with you the deep expertise we have accumulated over

the past decade to understand where LVVs integrate in the genome and evaluate the potential impact of these integrations using the state-of-the-art technologies.

Dr. Bonner will be accompanied by Dr. Williams and Dr. Adrian Thrasher, as well as Dr. Coleman Lindsley to respond to questions this afternoon. Dr. Williams and Dr. Thrasher are world renowned experts in the field of gene therapy, and Dr. Lindsley has profound expertise in clonal hematopoiesis and MDS. Dr. Bonner.

APPLICANT PRESENTATION: LENTIVIRAL VECTOR SAFETY (RELEVANT TO BOTH ELI-CEL AND BETI-CEL)

DR. MELISSA BONNER: Hello. My name is Dr. Melissa Bonner. And I will provide an overview of lentiviral vector safety. As you just heard, bluebird has three products in development for the treatment of cerebral adrenoleukodystrophy, beta thalassemia requiring regular red blood cell transfusions and sickle cell disease. They are all ex-vivo autologous lentiviral vector genetically modified hematopoietic

stem and progenitor cell products. And this is where the similarities end.

These three programs use two unique lentiviral vectors with different safety profiles. As discussed this morning, there have been three cases of Lenti-D LVV mediated insertional oncogenesis in CALD patients treated with eli-cel. Separately, across our two unique hemoglobinopathy programs, beti-cel and lovo-cel, using the BB305 LVV with 113 patients treated to date there have been no cases of insertional oncogenesis.

The vector related safety profile of eli-cel differs from that of beti-cel and lovo-cel. In this session, I will provide an overview on retroviral vectors, including safety, benefits and risks, and traceability. I will then discuss vector design elements of the Lenti-D LVV used for manufacture of eli-cel and vector related safety events of insertional oncogenesis in three patients treated with eli-cel. I will then contrast this with vector design elements of the BB305 LVV used for manufacture of both beti-cel and

lovo-cel where insertional oncogenesis has not been seen.

Lentiviral vectors, or LVVs, are part of the retrovirus family along with gamma retroviral vectors, or GRVs. These two distinct classes of retroviral vectors have both been used clinically in gene therapy products. Notably, these have also been used for manufacture of CAR T products, some of which are FDA approved. Retroviruses, including lentiviruses, are RNA viruses that reverse transcribe viral RNA into DNA which can then be integrated into host cell genomic DNA.

Integration is necessary for therapeutic efficacy in proliferating tissues such as hematopoietic stem cells. Retroviral vectors are modified retroviruses that replace the viral genes with a therapeutic trans gene that can be delivered to target cells via a process called transduction and result in expression of the therapeutic gene in appropriate cell types.

Due to the absence of intact viral genes, no

viral genes are expressed in patient cells, and integrated viral vectors, sometimes called proviruses, are incapable of replication and further propagation. Hence, retroviral vectors are replication incompetent. Although both result in permanent integration of transgenes into the patient genome, they have different biases for where they insert. And this is important because it influences the inherent safety profile and risk a vector mediated adverse event.

This is important because GRVs historically have seen vector related safety events. And this has shaped the view of the use of integrating vectors in gene therapy products. Insertional oncogenesis refers to a malignancy that has directly resulted from the integration of an exogenous sequence like a provirus into genomic DNA, which has led to either gene dysregulation, dysfunction, or destruction of key genetic regulatory elements.

Insertional oncogenesis has been observed clinically with the use of GRVs where an expression of the transgene is via promoter and enhancer sequences in

the long terminal repeats, or LTRs. Across four different disease indications treated with gene therapy using GRVs, insertional oncogenesis occurred in 2 to 90 percent of patients. Eighty-four percent of these cancers were seen in the first five years post-treatment.

The severe adverse event of insertional oncogenesis seen clinically following the use of GRVs necessitated the development of a safer vector design. One design element engineered into both GRVs and LVVs is the removal of the viral enhancer and promoter sequences from the LTRs and the addition of an internal promoter, here shown with the orange arrow, to drive expression of the transgene. The removal of the viral enhancer and promoter sequences from the LTRs is a vector design element referred to as self-inactivation or SIN.

Use of an internal promoter allows for more flexible design and more control of transgene expression including restriction of transgene expression to specific cell types. In addition to

incorporating SIN features, LVVs also have inherent features that contribute to their improved safety profile over earlier iterations of GRV. LVVs have an integration profile that is biased away from promoters and transcriptional start sites and tends to be entronic (phonetic), as depicted here.

And importantly, less than 25 percent of the HIV-1 genome is contained in the provirus, and there are no intact HIV-1 genes, further rendering it replication incompetent. These inherent and engineered attributes have led to a new generation of clinical development for severe genetic diseases which have been foundational in our products in development at bluebird bio.

LVVs are ideal for genetic modification of hematopoietic stem cells because transduction results in the stable integration of the therapeutic vector into the host cell genome. Importantly, all daughter cells of a transduced hematopoietic stem cell will contain the therapeutic vector. Expression of the therapeutic transgene is controlled by promoter choice

and not all hematopoietic cells that contain the therapeutic vector will necessarily express the therapeutic transgene.

Since the therapeutic vector is stably incorporated into the genome, the benefit is expected to be lifelong. And innervating vectors have an advantage over other genome modifying technologies in that they are traceable, with high throughput integration site analysis, enabling monitoring of clonal dynamics with regard to the vector insertion as well as investigations into hematological aberrations such as malignancy allowing for either exoneration or attribution of the vector insertion.

It's important to be clear that all vector insertions are mutations. As such, there could be a theoretical unintended impact on an endogenous gene such as knock out of a gene -- so this would likely impact only a single allele -- or an enhancer activity leading to increased gene expression. While LVVs incorporate many safety advantages to mitigate the risk of insertional oncogenesis, the risk is not eliminated.

Therefore, it is key that LVV integrations are traceable as that property allows for robust monitoring of patient's post-treatment for signs of expanding clones.

Each LVV insertion results in a unique mappable insertion site which you can think of as a genetic bar code. The unique and mappable insertion sites can be determined via sequencing the genomic DNA. And a high throughput sequencing method that allows for identification of these unique mappable insertion sites is called integration site analysis, or ISA. ISA allows us to track clonal populations to learn about hematopoietic reconstitution and can shed light on events of clonal expansion or even oncogenesis to help determine any potential role of specific insertion sites.

ISA is routinely performed on post-infusion peripheral blood in our clinical studies. Shown on the left is a standard representation of ISA data for any given patient timepoint. Each colored bar represents a unique mappable insertion site and its relative

frequency amongst all unique mappable insertion sites from that sample analysis. These represent the top 10 most abundant insertion sites. The gray bar is an aggregation of relative frequencies of all other unique mappable insertion sites for that sample.

Quantification of relative frequency of any given insertion site allows for traceability of the clone bearing that insertion site over time. And as mentioned previously, progeny from that cell will contain the same insertion site and can be tracked. Notably, for most patients, thousands of unique mappable insertion sites are observed at any time point.

And the vast majority of patients have top 10 unique insertion sites with relative frequencies less than one percent. And a one percent relative frequency of any insertion site does not equal one percent prevalence of that insertion site containing clone in the peripheral blood as the proportion of LVV containing hematopoietic cells post-treatment is less than 100 percent.

While ISA is a powerful tool, it's important to be clear on what ISA can and cannot do. ISA allows traceability of clonal populations bearing specific insertion sites over time to track clonal dynamics. It can identify insertion sites that could be of interest for further characterization. Insertion sites with similar relative frequencies that track together over time could represent clones with more than one insertion site. ISA can identify oligoclonality to satisfy regulatory guidance and provide contextualization to treating physicians.

ISA, while useful, is importantly not predictive. It cannot predict which, if any, clones will become predominant in a population. It cannot predict if or how oligoclonality will change over time. It cannot predict clinical outcomes or disease onset. Importantly, ISA is only able to detect transduced cells; it cannot predict oligoclonality with respect to unmarked cells.

ISA is a useful tool that allows for traceability of clonal populations, an attribute that

is unique to integrating vector technologies. But it is not predictive. Clinical assessments, including physical exam and complete blood count analyses or CBC, remain the standard for directing patient care.

Let's look at an illustrative example. Here, we have three cell populations seen over time. Each circle is a cell. Each colored vertical bar represents a unique LVV insertion. Therefore, a circle with a colored vertical bar represents a unique transduced clone. Not all cells contain an insertion. This is aligned with what we see post-treatment. Note that this example does not contain cells with more than one insertion site for simplicity. Cells can contain more than one insertion site.

Since ISA analysis can only detect cells that do contain an insertion site, ISA can only see these cells. Of these transduced cells, let's focus on the green clone. ISA analysis calculates a relative frequency or percentage of a given insertion site amongst all detected unique insertion sites. For the green clone, here are the relative frequencies across

the three samples. At bluebird, we define oligoclonality as any insertion site with a relative frequency greater than or equal to 10 percent.

Therefore, for these two highlighted time points where the green clone has exceeded this 10 percent threshold the population is considered oligoclonal with respect to that insertion site. What is the significance of oligoclonality? Oligoclonality is an operational definition. It does not in and of itself imply an outcome in hematopoiesis. Oligoclonality can suggest clonal hematopoiesis with relation to a vector insertion. This could suggest an increased risk of a hematological aberration. However, this can also occur in the absence of a hematological aberration.

The determination of oligoclonality can satisfy regulatory guidance for post-treatment monitoring in the clinical setting. And using the art of science and medicine, oligoclonality could trigger further follow-up out of an abundance of caution because patient safety is a priority. It's important

to recognize that oligoclonality does not equate to malignancy. Oligoclonality does not diagnose or predict a malignancy.

Oligoclonality in this case only refers to clonality with relation to any given insertion site and therefore does not shed light on overall clonality which would include cells that do not contain an insertion site and any endogenous gene variants. We define oligoclonality as any insertion site greater than or equal to 10 percent relative frequency. Of the 176 patients for whom we have ISA data, as of the most recent visit, oligoclonality criteria were met at two or more consecutive visits, i.e. persistent, by five patients treated with eli-cel, two patients treated with beti-cel, and two patients treated with lovo-cel.

An additional two patients treated with eli-cel and one patient treated with beti-cel met the definition of oligoclonality only at the most recent time points and therefore are not considered persistent. The three patients treated with eli-cel that were diagnosed with MDS also met the criteria for

oligoclonality, but due to their allogeneic hematopoietic stem cell transplant are no longer being followed by ISA.

Finally, two additional patients, one treated with eli-cel and one treated with lovo-cel, met the criteria for persistent oligoclonality. But both patients have since had allogeneic hematopoietic stem cell transplant and ISA follow-up was discontinued. Thus, across all three programs, greater than 90 percent of patients currently have a diverse polyclonal LVV integration site profile. For patients treated with a product manufactured with the Lenti-D LVV 84 percent are currently polyclonal. For patients treated with the product manufactured with the BB305 LVV, 95 percent of patients are currently polyclonal.

Let's discuss vector design elements of the Lenti-D LVV used for manufacture of eli-cel and vector related safety events of insertional oncogenesis in three patients treated with eli-cel. The Lenti-D LVV pictured here at the bottom was designed in 2010 to deliver intact copies of the ABCD1 cDNA to autologous

hematopoietic stem cells to enable production of functional ALDP. The ubiquitous MNDU3 promoter and enhancer was a specific design choice for the Lenti-D LVV for multiple reasons.

First, it is unknown what hematopoietic drive cell is responsible for long-term engraftment in the central nervous system. Therefore, to ensure appropriate expression of ALDP to achieve stabilization of disease progression, a promoter that drives gene expression across many cell types, like MNDU3, was necessary. Second, the suitability of the MNDU3 promoter for gene therapy for CALD had been previously demonstrated. And third, non-clinical assessments of the Lenti-D LVV did not suggest any vector related safety events, including oncogenesis, as quantifiable hazard.

Despite these favorable data, insertional oncogenesis has been seen in three patients treated with eli-cel to date. Here is an overview of the three cases of MDS, all determined to likely be Lenti-D LVV mediated insertional oncogenesis in CALD patients

treated with eli-cel. Two patients have persistent cytopenia following treatment with eli-cel. And one developed cytopenia several years after treatment. Thrombocytes were most effective for all three patients.

Oligoclonality was also observed. Patient 104-18 and 104-8 had insertion sites greater than 10 percent at the first ISA analysis, and these insertion sites were persistently oligoclonal. Patient 102-3 had an insertion site that increased to greater than 10 percent 92 months post-treatment. Identified clones contained between two and six unique insertion sites. And at least one of those insertion sites was in a well-known proto-oncogene, either MECOM or PRDM16, which had been previously identified as oncogenesis related GRV insertion sites.

The persistent cytopenias and evidence of expanded clones led to bone marrow evaluations and the observation of dysplasia. Patient 102-3 notably had 15 to 20 percent blasts in their bone marrow. All of these patients were subsequently diagnosed with MDS.

All three cases were determined to be likely Lenti-D LVV mediated insertional oncogenesis using the LVV exoneration criteria seen here on the left.

This criteria was aligned on with key opinion leaders in gene therapy and hematology oncology. If all exoneration criteria are met, the key opinion leaders agreed the totality of evidence would support that the LVV insertion was a non-causative passenger insertion. Two of the patients had no detectable classic driver mutations associated with MDS that could biologically explain the emergence of disease. All three patients had at least one insertion site in a known proto-oncogene.

While MECOM and PRDM16 are common insertion sites found in most patients without clinical sequalae, and therefore by themselves are unlikely signs of clonal expansion or malignancy, in these cases aberrant gene expression was detected and attributed to either enhancer activity of the internal MNDE3 promoter or interference with gene silencing as hematopoietic stem cells differentiate. As you can see, not all of the

LVV exoneration criteria were met.

Because we see gene expression changes in all genes analyzed, including known proto-oncogenes, in the three eli-cel patients diagnosed with MDS and there are no clear alternative driver mutations in two of the patients signifying a mechanism for disease onset, we cannot exonerate the activity of the LVV insertion in these cases. And therefore, we believe these three cases are likely insertional oncogenesis. Vector insertions in proto-oncogenes are common and the vast majority of clones with insertion sites in proto-oncogenes do not expand.

This is true in non-bluebird studies as well. A clinical trial for ADA-SCID using a similar promoter in their GRV found MECOM as the most common insertion site. And there have been no malignancies in that trial with now greater than 10 years of follow-up. Therefore, we believe the root cause of malignancy in these cases is multi-factorial.

Switching gears, now I will talk about the vector design elements of the BB305 LVV, a different

LVV used for manufacture of two unique products, beti-cel and lovo-cel, where insertional oncogenesis has not been seen. There have been no cases of malignancy nor insertional oncogenesis in patients treated with beti-cel. And as you will hear tomorrow, the great majority of patients achieved transfusion independence across all phases of study, all ages, and all genotypes with durable transfusion independence up to seven years post-treatment.

As discussed previously, the SIN LVV design coupled with an erythroid specific internal promoter and enhancer limits the transgene expression to nucleated erythroid lineage cells and therefore limits the potential for aberrant gene dysregulation. Additionally, there is no evidence in the published literature to suggest that beta-thalassemia patients have an elevated risk of hematologic malignancy.

We have observed malignancy but not insertional oncogenesis in two patients treated with an early version of lovo-cel for sickle cell disease. As these two malignancies were not related to the

lentiviral vector, these lentiviral events have no impact on the safety assessments of eli-cel or beti-cel. Importantly, beta-thalassemia and sickle cell disease are very different diseases despite both being beta hemoglobinopathies.

Different disease specific consideration and risks likely impact the observed difference to date in occurrence of malignancy between beti-cel where we have no malignancy and lovo-cel where we have two cases of malignancy. One key difference is that there is evidence of baseline increased risk of hematologic malignancy in patients with sickle cell disease. And in fact, this is a two- to ten-fold increase in risk of hematologic malignancy and specifically of AML. And this is in the absence of a hematopoietic stem cell transplant.

Additionally, disease specific risks necessitated different clinical development paths that likely led to different product specific risks with the early version of lovo-cel. The two sickle cell disease patients that developed malignancy were treated with an

early version of lovo-cel as part of Group A in study HGB 206. These two malignancies were not insertional oncogenesis.

The first case had blasts that did not contain the provirus, and therefore the vector could not have been a driver of blast formation. The blast did have numerous hallmark AML mutations at the time of diagnosis providing a biological explanation for emergence of disease. The second case had similar hallmark AML mutations and a non-causative passenger insertion in a gene called VAMP4 which is not a known proto-oncogene and has no documented activity relevant to cancer.

As with the MDS cases, in the eli-cel treated patients the role of the LVV in driving malignancy was robustly evaluated. After evaluating all established criteria for determining exoneration of LVV involvement in development of the AML, which are summarized on this slide, and the same criteria shown earlier for evaluation of the eli-cel patients, the totality of the evidence supported that the insertion site in VAMP4 is

a non-causative passenger insertion. This work has since been peer reviewed and published in the *New England Journal of Medicine*.

Both of the malignancies in patients treated with the early version of lovo-cel are unrelated to the use of the BB305 lentiviral vector. Therefore, these safety events are unique to the pathophysiology of sickle cell disease and do not impact the safety assessments of beti-cel or eli-cel. To recap, the vector related safety profile of eli-cel differs from that of beti-cel and lovo-cel.

The Lenti-D LVV uses a ubiquitous MNDU3 promoter to drive appropriate expression of ALDP and has led to insertional oncogenesis in three patients treated with eli-cel to date. The BB305 LVV uses a cell type specific promoter to drive appropriate expression of the beta-A T87Q globin in erythroid lineage cells and has not led to insertional oncogenesis across two different programs.

In summary, retroviral design has come a long way since the original GRVs utilized in gene therapy

trials in the 1990s and early 2000s. LVV properties, both naturally occurring and designed, limit the risk of any on insertion to cause gene dysregulation in nearby endogenous genes. Insertion sites can be tracked with a high throughput ISA method that can provide a lot of insight into clonal dynamics, but importantly is not predictive of clinical sequelae. Therefore, we recommend regular CBC analyses for all patients treated with novel one-time therapies.

Oncogenesis is a known hazard for hematopoietic stem cell transplant in the absence of gene therapy and can be exacerbated by underlying disease characteristics. Insertional oncogenesis is an acknowledged hazard associated with gene therapy products and is likely interdependent on the presence of other genetic changes, the properties of the internal transgene promoter and enhancer in the lentiviral vector, the specific insertion site within a proto-oncogene, and the activity of the transgene.

Importantly, eli-cel is distinct from beti-cel with regard to risk for insertional oncogenesis. Today

we are focusing on eli-cel for the treatment of CALD, and tomorrow we will discuss beti-cel for the treatment of beta-thalassemia requiring regular red blood cell transfusions. To preview what you will hear tomorrow, the benefit risk profile of beti-cel is positive. The great majority of patients achieve transfusion independence across all phases of studies, all ages, and all genotypes with durable transfusion independence up to seven years post-treatment.

The safety profile largely reflects known side effects of mobilization and conditioning agents. In the 63 patients treated with beti-cel in clinical trials, to date there have been no malignancies and no insertional oncogenesis. To review what you heard today, the benefit-risk profile of eli-cel remains positive despite insertional oncogenesis in three patients. For boys with CALD who only have a mismatched donor, eli-cel is a lifesaving therapy. Eli-cel is also a meaningful treatment option for boys with a matched unrelated donor.

CALD is aggressive, and it is fatal.

Treatment with eli-cel allows for the possibility of disease stabilization with preservation of physical and intellectual function in the majority of patients. And for boys with CALD without a match sibling donor, eli-cel is more likely to achieve both overall and event free survival compared with allogeneic hematopoietic stem cell transplant. Every CALD family deserves a suitable option for their little boy, and that option simply does not exist for all families.

These safety profiles must be weighed separately. Along with the risks inherent to the treatment process, the possible risk of oncogenesis in each program must be weighed against the severity of the disease, the availability of other treatments and their risks, and the probability and magnitude of lifelong benefit that gene therapy could offer. I thank you for your time.

DR. LISA BUTTERFIELD: All right. Thank you, very much, to the bluebird team. And now, we're going back with solved internet issues to Dr. Hughes -- the remaining of Dr. Hughes presentation. Thank you.

INVITED SPEAKER PRESENTATION: LENTIVIRAL VECTORS AND INTEGRATION (Cont.)

DR. STEPHEN HUGHES: Please accept my apologies on the behalf of my computer. I think this is where we left off. And I apologize for the break in the action.

So, when the internet failed, I was talking about how we actually go about isolating integration sites and defining (inaudible) clonally expanded cells. And actually, having this after the previous talk may simplify things for people. So, when we obtain the cells we want to analyze, we make DNA from them. The DNA is fragmented, and the host virus junctions are selectively amplified using Linker-Mediated PCR. When we do this analysis, we actually attempt to amplify and sequence the junctions from both ends of the integrated provirus. They're selectively amplified and sequenced using Illumina technology.

On a good day, we estimate in samples -- HIV

sample patients where approximately one cell in a thousand is infected, we think we can recover about 10 percent of the provirus in the sample. But it's important to recommend that there's a great deal of material that is not analyzed. We take only a very small sample.

All of the cells in any expanded clone, as you were just told, are descended from one original infected cell. And that means, as you were just told, that all the proviruses in the cells in any given clone are integrated exactly the same spot. And of course, this is how we identify clones. And we can monitor the independent isolation of the same host virus junction in the sample because we sheer the DNA randomly. Now as a consequence, if you share -- if you sheer several different pieces, they'll have different host -- different break points in the host chain.

So, if we repeatedly isolate the same exact host virus junction with different break points in the appended host DNA, we know that that's evidence of clonal expansion. That brings us back to another

question. And this is again relevant to the talk that we just had. And that is why do HIV -- infected T-cells clonally expand in an HIV infected individual? And of course the very first thing is that the majority of the HIV infected cells are T-cells. And T-cells normally clonally expand in response to both antigens and cytokines.

So if uninfected T-cells clonally expand, it's certainly reasonable to expect that there are infected T-cells that will also clonally expand. However, I mentioned -- and you're almost certainly aware of, in the parental T-cell a provirus can be integrated in or near an oncogene in a way that alters the expression of that oncogene and promotes the growth or survival of the infected cell. And so far, we have identified seven genes, all of which are known oncogenes, in which HIV provirus can cause clonal expansion.

I'll point out something that should be obvious. And that is that of course there's lots more than seven oncogenes. So it appears that having an HIV provirus land in just any oncogene is not sufficient.

Although there certainly are some that can affect the growth properties itself. So, how do we recognize which proviruses actually contribute to the growth and persistence of an infected T-cell? In the first case there's an enrichment for the number of proviruses that are integrated in that chain in-vivo, that is in an infected individual, relative to the starting distribution. And I'll explain that in more detail in just a moment.

Secondly, in the case of HIV proviruses, the ones that cause clonal expansion of T-cells in-vivo, all of them are integrated in a host gene, and all of them are oriented in the same direction as the gene. And I would point out based on data from a variety of groups that neither of these last statements are true for all retroviruses, for example, non-lenti retroviruses in animal models.

Finally, HIV proviruses that cause clonal expansion in-vivo -- the ones that are actually involved in the clonal -- in driving or sustaining clonal expansion, they're always integrated in specific

introns. So, here is a specific case. And this is from the Maldarelli paper of the reference of which I gave just a few minutes ago. And this shows that there's a positive selection for T-cells with proviruses in particular introns in the MKL food chain. This is data from an individual we call patient one. And this person was on successful therapy for 10 years when the analysis was done.

And what you see is a diagram of the MKL2 gene which is about 200 kb. And most of the gene is intron. The little vertical bars actually are the coding exons. And what you see in the diagram are little arrow heads, and those represent the integration sites that we obtained in patient one. They're all clustered in a very small part of the gene, and they all point in the same direction as the gene.

And what I want to emphasize is this particular collection of integration sites is clear evidence that there is selection for these integration sites. That is to say that the cells that have them grew better. And we know that because we can compare

the distribution that we see. So there's initial distribution that was obtained by infecting simulated PVMCs with HIV in-vitro. And what you see in the diagram at the top is the distribution of integration sites in freshly infected cells.

And what you see is two important things. The integration sites are scattered throughout the gene, and quite obviously they're not all pointed in the same direction of the gene. It's about 50/50. About half of them are in the same orientation as the gene, and about half of them are in the reverse orientation. We looked more closely at the data from the patients. So when we blow up the little region where the integrations were obtained from the patient are, you see that the integrations are in intron four and six but not in intro five. Again, that's evidence of selection, not specific integration.

Some of the little arrow heads have little black circles around those. Those are the ones in which we are certain based on the data we have that those integration sites come from clonally expanded

cells. I think the integration sites that are not circled also come from clonally expanded cells, but the data we have don't allow me to conclude that definitively.

So, here are the seven genes what we have good evidence that there can be clonal expansion when it's driven by the provirus. And there are a couple of things I want you to focus on. First, if we simply look at the fact that there is an enrichment of proviruses in these genes and people have been infected and on therapy for a long time, that's always true. If you look at the next column over next to the circled column, you'll see that there's also a very strong preference for proviruses that are oriented in the same orientation as the gene.

In the last column all the way over on the right you see that some of the insertions are upstream of the coding region, and some are in between the coding exons. Finally, there's one last thing I want you to take away from this slide. I don't think there's any point in trying to ask you to pay much

attention to the name of the oncogenes that are involved here.

But I do want to point out two things. Although one of the genes that figures very prominently is in these benign non-oncogenic clonal expansions, the STAT5B, neither STAT3 nor LCK are on this list. It'll be clear in just a few minutes why I think that's important. However, although it's clear that there are cases in which clonal expansion is either caused by or sustained by integration of a provirus in an oncogene, that actually turns out to represent only a small fraction of the clonally expanded cells.

In most cases, the clonal expansion of HIV infected T-cells is not caused by a provirus that's integrated in an oncogene, but by the same forces or factors that cause uninfected T-cells to clonally expand and persist. That is antigen stimulation in cytokines. However, there is -- there are two or three percent of the clonally expanded cells in which there is one of the insertions I just described on the last slide. So although these events are at one level

fairly rare, in fact, many patients have these kinds of provirally inserted, provirus driven clonal expansions.

So, I've shown you so far that the insertion of a provirus can cause benign clonal expansion. As far as we know insertion of a provirus in any one of those seven oncogenes doesn't lead, at least so far, to any kind of malignancy. Does that mean there can be no malignancies that are caused by -- no T-cell malignancies that are caused by HIV proviral insertion? Unfortunately, the answer is in fact there are T-cell lymphomas in which HIV proviruses make a direct contribution.

Here's the reference for that. It's a paper that John Mellors and I published last year. And I'll show you a very small amount of data from that paper. And I'll be happy to answer additional questions if people have them. So we looked at a total of 15 different malignancies and at some human control tissue. And what we saw was that if you looked primarily at the T-cell lymphomas that there were in fact five of the 15 samples that we had that had a very

high ratio of HIV DNA to globin DNA. That means there were a lot of proviruses in the malignant tissue sample that we have.

And in fact, there was considerably more than one provirus per cell. And I'll come back to that in a few minutes. I also want to point out that although there are five positive samples, they actually come from three donors. The samples 1A and 1B are from separate lesions from one donor, and 12A and 12B are from separate lesions from the second donor. So we really only have samples from three donors.

We wanted to know if the lymphomas that are -- that we call 1A and 1B, which are both from the same donor, represent cells that had a common origin. And because they're T-cells, we can ask that question by looking at the T-cell receptor. And what you can see here is, if we look at the T-cell receptor in tumor 1A, almost all the material comes from a single cell. It has a particular rearranged T-cell receptor. Tumor 1B has exactly the same rearranged T-cell receptor.

And although it's in the majority of the

cells, it's not as large a fraction as it is in tumor 1A. And when we looked at histological sections, the tumor 1A was almost all tumor. Tumor 1b had some normal tissue in it. So those data make sense. We then looked in all of these samples: 1A, 1B, 12A, 12B and another one called tumor 11. And all of them share the fact that there are -- there is a clonally expanded cell in the population in which there is a provirus sitting in the STAT3 gene.

I do apologize, at the bottom of the slide it says STAT instead of STAT3. That's my fault. It's my error, and I didn't catch it in time. Importantly and interestingly, the three samples at the bottom -- 12A, 12B, and 11 -- not only have a clonally expanded cell with an integration in the STAT3 gene, we have a second clonally expanded integration in the LCK gene. And both STAT3 and LCK are known oncogenes.

I will also point out that the samples we got for tumor 1A and 1B were from frozen tissue which allowed us to do much more extensive and sophisticated analysis, including RNA analysis on those samples. The

rest of the samples were formal and fixed and paraffin embedded. And we were able to do DNA analysis but not much else.

And finally, I want to point out that with the possible exception of tumor 12b, all of the samples we have, in addition to the primary clonally expanded integration site, have lots of other integrations. And what that strongly suggests is that all of these tissues were heavily super infected and that for the most part they were heavily super infected late in the development of the tumor. We'll come back to that too.

So here are diagrams again of the STAT3 gene and the LCK gene. And as before, the long horizontal line represents the extent of the gene. The introns are the skinny parts of the diagram. The exons are the little vertical -- that look like little vertical bars. This diagram is a little bit more complete than the one I showed you before. The coding exons are the taller bars. Non-coding is the shorter bar. So, for example, at the very end of both of the diagrams, there's a little bit of non-coding information.

And what you can see in tumor 1A and 1B, which is what we expected based on the fact that these are descended from a single cell, was that they have an integration in the STAT3 gene in exactly the same place. And also, as expected, the integrations in tumor 11 and 12A and 12B are different from the ones in 1A and 1B.

So let's look a little bit at the provirus that is driving the expression of STAT3 in tumor 1A and 1B. So, it turns out the provirus is highly deleted. The blue arrow with the two arrow heads represents the extent of the deletion. It removes most of the five prime LTR, all of gag, and most of pol. The rest of the viral genome appears to be intact. However, the piece of the five prime LTR that contains the promoter that would normally express the viral genetic information has been lost in this deletion event.

And that suggested to us the possibility that instead of the five prime LTR doing the driving it was three prime LTR. And that turns out to be true. STAT3 is over expressed from the three prime LTR promoter.

Because these were frozen tissues, we were able to isolate the RNA and sequence it in its entirety. That sequenced RNA contains the viral LTR connected to STAT3. The entire STAT3 coding region is expressed. And it's over expressed at about 30 times as high as the normal allele, which is still present.

There's one other quick thing I want to show you. And that is if we look at 12A and 12B, it's not surprising and we weren't surprised to see that the integration in STAT3 was in exactly the same place in both the 12A and 12B tumors. What we found quite surprising when we looked at the integration for the LCK gene 12A and 12B each has an integration in the STAT -- in the LCK gene, but they're about five kb apart.

And what that tells us is that in the development of this tumor, which must have been a multi-step process, one of the first things that happened was the insertion of a provirus in the LCK gene. And as those cells divided, there was subsequent integration independently in two cells in two different

places in the LCK gene. And this provides very strong evidence that the acquisition of the provirus in LCK was an important influencing event in the development of the tumor.

So what did we learn from looking at the proviruses that are present in the tumor tissue? We now know that HIV proviruses in STAT3 and LCK can play an important role in the growth and development of frank T-cell lymphomas. The integration of a provirus in STAT3 and LCK does not directly cause the clonal expansion of the cells in-vivo. This was an astonishing result as far as we're concerned.

STAT3 and LCK are not on the list of the seven oncogenes in which the provirus has caused a benign clonal expansion in-vivo. What it suggests is that the pathway to get the tumor and the pathway to get benign clonal expansion at least as far as we can tell so far are independent. The good news for us is that T-cell lymphomas are rare. And that's true in both normal individuals who are not HIV infected and in HIV infected individuals.

Progression to the lymphomas appears to be a multi-step process. And we know that in part because, although I didn't talk about it, we found a somatic cell mutation in the STAT3 that was LPR driven in lymphomas 1A and 1B. And we know that in 12A, 12B, and 11 LCK is driven by a second HIV provirus.

For LTR promoter driven expression, Tat would be expected to be required. And although again, I didn't show you this -- it's described in the paper -- in the 1A and 1B lymphoma, Tat is actually expressed because it's driven from the STAT3 promoter. The HIV infected T-cell tumors we analyzed were almost all heavily infected -- super infected late in their development.

So let's get back to the important question we began with, and that is how does the information we have about what happens when HIV infects cells in-vivo -- what does that -- how can we use that information to better understand what happens when HIV vectors affect host expression? For example, we know that the LTR promoter has been removed from a self-inactivating

vector. Thus, in the same vectors, there's no LTR promoter that could drive host expression.

However, SIN vectors do not -- do have -- they all have to have some sort of internal promoter. Moreover -- and I think this is very important -- deletions and other changes arise very frequently in HIV and other retroviruses and their vectors. And changes in the structure of the provirus -- and I showed you the deletion for the STAT3 thriving provirus in 1A and 1B -- those kinds of changes can affect the ability of the provirus to alter the expression of host genes.

In our case, the primary targets for HIV infection is CD4+ T-cells. T-cells are quite rare in both those who are infected and not infected. However, animal vitals that are based on non-Lenti retroviruses suggest its susceptibility to tumor genesis is both very dependent on the cell type that's infected and the virus type that's involved and suggest that there may well be substantial differences in terms of what happens with vectors -- actually, in HIV and among

vectors.

And finally, the conversion of the normal cells with -- to a tumor cell, at least for the T-cells and probably for a lot of other things, is a multi-step process. And having multiple proviruses in the infected cells will almost certainly increase the risk. That was true in the case of STAT3 plus LCK and probably in the non-human primate that I referred to at the very beginning.

And I would like very much to thank my colleagues who worked with me on these projects. And of course to the patients who volunteered the samples that allowed us to do the work. I thank you for your patience and attention. And I do apologize for the computer.

DR. LISA BUTTERFIELD: All right. Thank you very much, Dr. Hughes. Appreciate those data. So, what we have next is a very short 10-minute break for everyone. When we come back, we'll continue with an FDA presentation.

[BREAK]

FDA PRESENTATION RISK OF INSERTIONAL ONCOGENESIS WITH ELI-CEL, LOVO-CEL, AND BETI-CEL

MR. MICHAEL KAWCZYNSKI: Hi and welcome back to the 72nd Cellular Tissue and Gene Therapy Advisory Committee meeting. Let's get reconvened for the afternoon session. Dr. Butterfield, if you'd like to take it away.

DR. LISA BUTTERFIELD: Welcome back, everyone. We have a final talk in this second session on safety, and that will be from Dr. Crisafi from the FDA.

DR. LEAH CRISAFI: Thank you, Dr. Butterfield, and good afternoon. My name again is Dr. Leah Crisafi, and I'm a medical officer in OTAT. I will present the risk of insertional oncogenesis with eli-cel and two related bluebird bio products: lovo-cel and beti-cel.

In eli-cel and lovo-cel clinical studies, the development of cancer in five subjects has called into question the safety of these products and has shifted

the benefit/risk assessment. Myelodysplastic syndrome has been diagnosed in 3 out of 67 subjects treated with eli-cel, and there are additional cases of concern from malignancy where eli-cel treated subjects have expanding clones that contain vector integration into a proto-oncogene.

Lovo-cel, a related product developed for the treatment of sickle cell disease, has been administered to 49 subjects; 2 of whom died from acute myeloid leukemia. However, multiple factors confound the determination of causality in these AML cases. At least three additional subjects treated with lovo-cel are of concern for developing malignancy.

The third product, beti-cel, was developed for the treatment of beta-thalassemia. Beti-cel is nearly identical to lovo-cel. Fifty-nine subjects have been treated with beti-cel in clinical studies, and none have been diagnosed with cancer. However, there are concerning instances of prolonged thrombocytopenia of unclear etiology.

In this presentation, I will briefly provide

some background on myelodysplastic syndrome, the potential for insertional oncogenesis, and a comparison of the three related gene therapy products. I will then discuss specific cases of eli-cel and lovo-cel treated subjects. Because I have limited time, I will not mention all subjects where there is a specific concern for the development of malignancy. My goal is for you to understand the cancer cases, how they develop, the data about the vector integration, and why we are concerned that additional malignancies may be identified in the future.

First up is an overview of myelodysplastic syndrome or MDS. MDS is a malignancy of the bone marrow that usually has three components. These are dysplastic stem cells, peripheral cytopenias, and genetic evidence of clonal hematopoiesis.

The figure on the right shows the aspects of the hematopoiesis relevant to MDS with the three components denoted by the red boxes. MDS has no association with pediatric CALD and is rare in the overall pediatric population with an incidence of one

to four cases diagnosed per million children per year.

The prognosis of MDS in children is variable and multifactorial. It is important to note that MDS is life-threatening with a three-year overall survival rate of 35 percent for pediatric MDS patients treated with a hematopoietic stem cell transplant from a matched, unrelated donor. Also, approximately one-third of MDS cases progress to acute myeloid leukemia, which is difficult to treat and has a particularly poor prognosis.

Next, I will provide background on the potential for lentiviral vectors to cause malignancy. Lentiviral vectors are used for gene therapy because they permanently integrate into the host-cell genome allowing long-term expression of the transgenes that they were designed to deliver. Integration sites are random in that they are not targeted to a certain location although lentiviruses are thought to integrate preferentially into areas of active transcription.

Wherever they integrate, they have the potential to alter expression of nearby genes including

genes that may factor in the development of cancer such as proto-oncogenes and tumor suppressor genes. There are several high-level mechanisms for altering gene expression and thereby promoting oncogenesis, including viral activation of host cell gene transcription, altered host cell RNA processing, and tumor suppressor gene inactivation. Viral activation of cellular gene transcription appears to have been a factor in the development of malignancy in the CALD cases, which you will hear more about shortly.

While the cases I'm presenting today are the first cases of malignancy that have been attributed to lentiviral vectors, as we have heard, vectors of another retroviral class, gamma retrovirus, appeared to have caused cancer in a number of other diseases. And because of the risk of hematologic malignancy due to integration of lentiviral vectors, FDA recommends that clinical studies include assays to assess the pattern of vector integration sites. The next slide will demonstrate how the applicant applied this recommendation to their studies.

The applicant incorporated integration site analysis from monitoring patterns of integration sites in peripheral blood cells. The method for performing integration site analysis changed during the study but, since mid-2019, has been S-EPTS/LM-PCR which provides more accurate data than the previously used method. The algorithm for assessment is depicted in the figure on the right, and it has changed several times during the eli-cel studies in response to recognition of the algorithm's limitations with accumulated experience. The values that came from these assessments are defined on the left.

Overall, vector copy number is the number of copies of vector per cell in a mixed group of cells; some of which may not contain any copies of the vector.

Integration site relative frequency is the percent of vector integrations that occur within a specific site based on the S-EPTS/LM-PCR method. Per the algorithm, when the overall vector copy number was greater than 0.3 copies per displayed genome and any relative integration site frequency was greater than 30

percent, confirmatory qPCR was performed to determine integration site-specific vector copy number.

Integration site-specific vector copy number is the number of copies of vector located in a specific integration site in a mixed population of cells. And an integration site-specific vector copy number of greater than 0.5 copies per deployed genome would mean that half of the cells contained that specific integration site. And this was the criterion for a predominant clone and prompted initiation of a clinical workup for malignancy in the bluebird bio studies.

Next, I will compare the three related bluebird bio products: eli-cel, lovo-cel, and beti-cel. The Lenti-D vector RNA is pictured in the top figure. Lenti-D is used to manufacture eli-cel for the treatment of CALD. The BB305 lentiviral vector RNA is pictured on the bottom. It is used to manufacture lovo-cel for the treatment of sickle-cell disease and beti-cel for the treatment of beta-thalassemia.

From left to right, both vectors contain the R and U5 domains, a psi-packaging signal, central

polypurine tract DNA flap, and rev-responsive elements.

Then come the vector-specific components. The Lenti-D vector has an MNDU3 gamma retroviral enhancer/promoter that is continuously active. The MNDU3 enhancer/promoter drives transcription of the ABCD1 transgene. The BB305 Lentiviral vector-specific components include an erythroid lineage-specific beta-globin locus control region and a promotor sequence to promote expression in erythroid cells of the beta AT87Q-globin transgene, which resembles the intron and exon structure of the wild-type, beta-globin gene.

To the right on the figures are the shared polypurine tract, unique three prime region of the long-terminal repeat, and the polyadenylated tail. After integration into the cellular genome, the backbones of the Lenti-D and BB305 vector genomes are identical.

Now that you have heard about the potential for lentiviral-mediated malignancy and the similarities between the vectors that are used in the manufacture of eli-cel, lovo-cel, and beti-cel, I will describe the

individual cancer cases and other cases of concern.

First up are the cases of malignancy after eli-cel. Three subjects with CALD who have been treated with eli-cel have been diagnosed with cancer, and all three cases have been classified by the applicants as likely related to eli-cel. In this table, the three subjects are listed across the top. I will highlight similarities among the subjects in the red box, and then come back to the third subject, 102-03, who is in the far-right column.

Both 104-08 and 104-18 were treated in Study ALD 104. Both developed MDS in the second year after eli-cel administration. Both had primary engraftment failure for platelets. Both also were similar in that they had integration into the proto-oncogene MECOM with a high relative frequency identified at six months. Both had increased expression of EVI1. Both were diagnosed with the same type of MDS, MDS with single lineage dysplasia affecting megakaryocytes.

Now we will look at the integration site data for 104-08 and 104-18. These figures show the

integration site relative frequencies for Subjects 104-08 and 104-18 at the time each subject developed MDS, which was at 22 months for 104-08 and at 14 months for 104-18. In each relative frequency pie chart, the MECOM integration site is colored in blue, and the integration site center also in the MECOM containing clone are in pink. The integration sites that are not located in the clone are white, light gray, and dark gray with the dark gray area representing numerous integration sites with the lowest relative frequencies.

You can see that Subject 104-08 had a single clone with four integration sites, including MECOM, and, at the time he developed MDS, more than 75 percent of the integration sites found in peripheral blood cells were derived from that single clone.

Subject 104-18 had a single clone with two integration sites including MECOM, and those made up less than 50 percent of the integration sites found in the peripheral blood at the time he was diagnosed with MDS. Integration into MECOM in these clones has been determined likely to have caused MDS in these two

subjects.

Now, we will consider the third subject diagnosed with MDS after eli-cel administration. Subject 102-03 was different in many ways from 104-08 and 104-18. He was treated in Study ALD-102 and not 104 and at a much younger age and was diagnosed with MDS much longer after being treated with eli-cel. Rather than having been identified at risk based on integration site analysis, he presented with symptomatic anemia and thrombocytopenia seven and half years after treatment of eli-cel.

Another distinction with this subject is that he had a diagnosis of MDS with excess blasts, not MDS with single lineage dysplasia. Also of note is that he did not have integration into MECOM. He instead had integration into the proto-oncogene PRDM16 and several other genes that likely contributed to his developing cancer. The next slide will include additional details about this case.

Subject 102-03 had an unremarkable integration site analysis at Year 5, which was his last assessment

before he presented with anemia and thrombocytopenia two and half years later. His bone marrow biopsy was interpreted as MDS with excess blasts-2 based on the bone marrow blast percentage following just below the current threshold for leukemia, which is 20 percent.

It is notable that the bone marrow biopsy was interpreted as "worrisome for evolving AML" based on higher percentages of blasts in some foci and that his blast percentage will constitute leukemia after updates to classifications are published in the near future.

He had a clone with six integration sites that represented 92 percent of vector-containing cells when he was diagnosed with cancer. The pie charts show that PRDM16, in blue, was detected as an integration site with a relative frequency of 2.2 percent at Year 5, and that, at Year 7.5, the relative frequency for PRDN16 have increased to 18.2 percent.

In pinks are the five other integration sites that are in the same clone as the PRDM16 integration sites. Based on the protein expression data and known functions of the five other genes, it appears that at

least several integration sites in addition to PRDM16 contributed to this subject's development of cancer.

This figure shows the relative frequencies of the main integration sites for this subject plotted over time. On the right, I have labeled the genes that may have contributed to this case of malignancy. We can see PRDM16's presence at a low relative frequency at 60 months and sharp increase in relative frequency at Year 7.5, likewise, for MIR106A and GAB3.

The purpose of the figure is to show how the integration sites that appear to have led to this case of cancer were not prominent early on, emerged among the top ten integration sites at Year 5, and increased over the next two and a half years until the child was diagnosed with cancer.

Now, we will move on to the four cases of greatest concern for developing malignancy among eli-cel-treated subjects with abnormal findings in these children included on this slide. All have a clone with integrations into MECOM. The two on the left have had gene expression studies performed, and those revealed

increased EVI1 in both cases. EVI1 is a transcript of the MECOM locus but was treated with poor prognosis in MDS and had also been elevated in subjects 104-08 and 104-18 with MDS we just discussed.

Bone marrow biopsies revealed hypocellularity and, in 102-11 and 104-09, megakaryocyte abnormalities. Most recent CBCs for these subjects are mostly normal with the exceptions of a mild thrombocytopenia for 104-09 and 104-22 and mild anemia for Subject 102-31. Next, we will consider the integration site analysis data for each of these subjects.

The pie chart on the left shows the relative frequency for each integration site at Month 30 for Subject 104-09. The colored segments represent the seven integration sites of highest relative frequency, and the gray area represents all the remaining integration sites.

The figure on the right shows integration site relative frequencies but plotted over time. There are several points that I would like to make while looking at these figures.

The first point is that these seven integration sites seem to be divided between two clones. One clone is the blue and yellow clone that appears to be expanding. As shown in the figure on the right, its integration sites LINC00982 and SMG6 increased in combined relative frequency from 18 to 25 percent between Months 24 and 30.

The second point is that there is another clone that I will refer to as the DEFB132 clone. Based on the integration sites that are tracking with the red DEFB132 line in the figure on the right, the clone appears to have multiple integration sites with a combined relative frequency of 15 to 20 percent. Additionally, the DEFB132 clone may include an integration site in MECOM. Both the blue and yellow clone and the DEFB132 clone are worrisome for becoming malignant.

Now that we have looked at the trends in integration site analysis for this subject based on the S-EPTS/LM-PCR, I will provide additional data that add to our concern about these clones.

This table shows the qPCR data from Month 30 for three genes with S-EPTS/LM-PCR results provided in the far-right column for reference. The integration site-specific vector copy number in the middle shows at LINC00982 and SMG6 are present in the same clone that accounts for 59 percent of cells. The table also shows that there is a clone containing a MECOM integration comprising 11 percent of cells in peripheral blood.

Also worrisome with this subject is his vector copy number trend. The vector copy number has been increasing in his peripheral blood and has exceeded the drug product vector copy number, which is yet another signal of clonal expansion.

In summary, despite the subject's early diagnosis of parvovirus that is a cause of cytopenia, now two years post eli-cel, he has persistent thrombocytopenia, hypercellular bone marrow with atypical megakaryocytes, integration into MECOM, and evidence of clonal expansion. And FDA is very concerned about him developing malignancy.

Subject 102-11 is another subject who appears

to be at risk for developing malignancy. He has a clone with integrations in MECOM and two other genes, and the clone has expanded over time to account for 100 percent of the subject's integration sites. In addition, a vector copy number approximating one indicates that this clone comprises nearly all the myeloid progenitor cells.

Also concerning is the increased expression of EVI1 in this subject. His bone marrow findings vector integration data and increased expression of EVI1 are concerning for the development of malignancy.

Subject 102-31 is another subject who appears to be at risk for developing malignancy. The pie chart on the right depicts integration site-relative frequencies in this subject at Month 42 and Month 48. He appears to have two notable clones. In the blues are the relative frequencies of integration sites in MECOM and EVI5 that are located in a clone that appears to be expanding in size and, at Month 48, represented almost 60 percent of integration sites.

The subject also has a second clone

represented in the pie chart by the pinks that appears to be decreasing in size. This subject is concerning because of the expansion of the MECOM-containing clone and increased expression of EVI1 because abnormalities on bone marrow biopsy and CBC are unexplained and could signal impending development of a hematologic malignancy.

The last CALD subject I will briefly present is 104-22. He has integration sites in MECOM and MPL that appear to be expanding. The pie charts show his integration site-relative frequencies at 6, 12, and 18 months for the MPL and MECOM integration sites. The relative frequency for MPL is shown in yellow and has clearly increased between Months 6 and 18. One MECOM integration site was noted at six months and appears to have increased in relative frequency between Months 6 and 18 as well.

Also notable is that there are four additional MECOM integration sites that were noted at 18 months but not at 6 and 12 months. These integration sites are of a comparatively low frequency but notable

because of their location in the MECOM proto-oncogene and because they appear to be increasing in relative frequency as well. The subject deserves close monitoring for further evidence of clonal expansion and for persistence of his unexplained thrombocytopenia.

Five of the six CALD subjects I've described have a MECOM integration site in the problematic clone. I wanted to, therefore, say a few words about MECOM and mention a few other significant proto-oncogenes that are common integration sites in eli-cel-treated subjects. The full name for MECOM is the MDS1 and EVI1 complex locus, and it is a known oncogene involved in myeloid malignancies. The MECOM locus can yield one of several proteins including the oncoprotein EVI1. EVI1 expression was assessed in limited instances in the CALD studies, and, in all of these instances that I am aware of, EVI1 was found to be overexpressed.

My final point about integration into MECOM is that it is nearly universal with eli-cel. Of 54 subjects who had integration site data available by October 2021, 53 had at least one integration site in

MECOM, which means that virtually all subjects may be at increased risk of developing cancer related to integration into the MECOM proto-oncogene.

PRDM16, MPL, and MIR100HG are also proto-oncogenes where the vector seems to have frequently integrated, and the vector's repeated integrations into MECOM and these other proto-oncogenes are very concerning for potentially contributing to additional cases of malignancy.

Now, I will move on to covering malignancy in subjects with sickle cell disease who have been treated with lovo-cel. In contrast to CALD, which does not confer an increased risk of hematologic malignancy, it appears that the risk is increased in patients with sickle cell disease. Twenty-six years of data from the California Cancer Registry renews to evaluate the risk of malignancy in sickle cell disease as compared to the general population. These data demonstrate that the incidence of AML in sickle cell disease is 0.1 percent based on the occurrence of 6 cases in 6,243 sickle cell disease patients.

In contrast, 2 of 49 subjects treated with lovo-cel have developed acute myeloid leukemia. This makes the incidence of AML four percent, which is 40 times higher than the incidence of AML observed in the California Cancer Registry study.

This table includes some details about these two subjects. Subject 206-01 in the middle column was diagnosed with AML five and half years after treatment with lovo-cel. The clone contained a single integration site in the VAMP4 gene. In addition to the VAMP4 integration, the clone had other cytogenetic abnormalities that are listed on this slide.

Subject 206-02 in the right column was diagnosed with MDS and then AML in his fourth year after treatment with lovo-cel. He did not have a predominant clone and did not have any vector integrations in the blast. However, he had several cytogenetic abnormalities that are also listed on this slide.

It is notable that both of these subjects had monosomy 7 and mutations in RUNX1 and PTPN11. The

applicant has called these other mutations the driver mutations which may be reasonable; however, FDA does not agree that the presence of other driver mutations excludes the possibility that lovo-cel contributed to these malignancies. Rather, we find the four percent incidence of AML and the similar cytogenetics suggestive of a common tumorigenesis pathway that could be related to lovo-cel.

In addition to the two subjects who have been diagnosed with AML, there are two subjects who have bone marrow biopsies concerning for MDS. These two subjects are both of the same sickle cell disease genotype and have other similarities that I will highlight.

Starting with Subject 206-27, she has had persistent severe anemia since her treatment with lovo-cel and is transfusion-dependent. Her bone marrow smears demonstrated dyserythropoiesis and a diagnosis of MDS was considered. However, she ultimately was given a diagnosis of stress erythropoiesis secondary to hemolysis and persistent hemoglobinopathy. Cytogenetic

abnormalities included transient trisomy 8 and tetrasomy 8. The subject also has several additional genetic variants that appear to have been present prior to lovo-cel, including a pathogenic ATM variant.

I will now move on to Subject 206-32. He has also had persistent anemia since the treatment with lovo-cel although he is not transfusion-dependent. He does have vitamin B12 deficiency that could be a factor in his anemia. His bone marrow biopsy, like 206-27, demonstrates dyserythropoiesis and was interpreted as likely stress erythropoiesis.

In another parallel to 206-27, Subject 206-32 also has findings of trisomy and tetrasomy 8. We are concerned about the possibility of malignancy in these subjects mainly because of their erythroid dysplasia and because of the trisomy 8, as trisomy 8 is the most common trisomy seen in myeloid malignancies.

Adding to our concern for the risk of malignancy in 206-27 is the pathogenic ATM variant. While the variant is not attributable to lovo-cel, the administration of lovo-cel may contribute to the

development of malignancy in this subject who was already at elevated risk. Adding to our concern for the risk of malignancy in 206-32 is the trending vector copy number which is consistent with expansion of a lovo-cel clone. The vector copy number in his peripheral blood is higher than the administered lovo-cel product vector copy number of three copies per deployed genome, and it appears to be increasing over time.

The applicant has concluded that these cases of persistent anemia and abnormalities on bone marrow biopsy are due to these subjects' specific genotype. However, this has not been proven.

Returning to the concept that myelodysplastic syndrome is characterized by dysplastic stem cells, peripheral cytopenia, and genetic evidence of clonal hematopoiesis, and, given the similarities in these subjects' cytogenetic findings, it seems that the possibility of them developing MDS with a similar tumorigenesis pathway deserves close consideration.

I have one last subject to present. Subject

206-23 was treated with lovo-cel for sickle cell disease, and he appears to have a clone with four integration sites that is expanding and recently surpassed 50 percent for the combined relative frequency of the four integration sites.

These integration sites include two proto-oncogenes involved in myeloid malignancy STAT3 and the arguable proto-oncogene HMGA2. In addition, the subject has a rising peripheral blood vector copy number, although it is below the vector copy number of 5.1 for this subject's lovo-cel products.

Subject 206-23 is ultimately very concerning because of the increasing vector copy number and because of the large clones that contain integrations into at least one proto-oncogene that could drive the development of malignancy.

Returning to the overview of malignancy cases, we have now reviewed the three MDS cases with eli-cel as well as four additional cases of greatest concern for developing malignancy. We've also heard about the two AML cases and three additional cases of greatest

concern in subjects treated with lovo-cel.

Beti-cel is nearly identical to lovo-cel and also has several cases of concern for potential malignancy. However, my focus with regard to beti-cel is to demonstrate the similarity of its integration profile with lovo-cel in the final section of this presentation. And so I will move on to briefly present on the integration site patterns.

As previously mentioned, eli-cel seems to have a propensity for integration into the MECOM proto-oncogene. The problematic clone in five of the six eli-cell-treated subjects that I have presented have an integration into MECOM. Of the 54 eli-cel-treated subjects with integration site data available, 53 or 98 percent had at least one MECOM integration site. Lovo-cel and beti-cel do not have the same propensity for integration into MECOM. However, VAMP4 is an integration site of interest because one of the lovo-cel subjects who developed AML had integration into VAMP4. It is very concerning that VAMP4 is a common integration site for these two products with 71 percent

of lovo-cel-treated subjects and 56 percent of beti-cel-treated subjects having at least one integration site into the VAMP4 gene.

The purpose of this slide is to demonstrate that lovo-cel and beti-cel appear to have relatively similar patterns of integration sites and that eli-cel's integration sites are relatively different. Lovo-cel is in blue, beti-cel in red, and eli-cel in green. Only one gene appears to be a main integration site for all three gene therapy products, and that is the potential proto-oncogene HMGA2.

The red boxes identify genes with similar frequencies of integration from lovo-cel and beti-cel, and the blue box identifies genes that are proto-oncogenes with a high relative frequency of integration for eli-cel. These data suggest similarity in integration site patterns from lovo-cel and beti-cel.

In summary, there is a significant risk of malignancy with eli-cel administration. The current incidence is four percent but is likely to increase. Hematologic malignancy generally takes time to develop

whereas the duration of follow-up from many of the subjects was relatively brief and may have been insufficient for malignancy to have occurred.

I have presented four specific cases of subjects treated with eli-cel where the risk of progressing to malignancy seems high. I have also shared that two of the three cases of malignancy involved integration into the MECOM proto-oncogene, which nearly every eli-cel-treated subject has. The incidence of hematologic malignancy after treatment with the related product lovo-cel is currently four percent greatly exceeding the 0.1 percent incidence in the overall sickle cell disease population.

The two AML cases and the two stress erythropoiesis cases each have parallels that suggest a common tumorigenesis pathway that lovo-cel may contribute to. However, the contribution of lovo-cel to these cases is not clear. It is also not clear how the safety data for eli-cel informs a safety of beti-cel and lovo-cel and vice versa.

I thank you for your attention and look

forward to your discussion of the serious and yet important, not completely characterized risk of insertional oncogenesis.

CLARIFYING QUESTIONS TO PRESENTERS

DR. LISA BUTTERFIELD: Terrific. Well, thank you very much to all three of our speakers. So we have an opportunity now to ask some clarifying questions of our speakers from NCI, FDA, and bluebird bio. And especially I know some of those were cut a little short in the earlier session, so now is the time to ask your MDS and integration-type questions. So let's start with Dr. Coffin then Dr. M. and Dr. Keller.

DR. JOHN COFFIN: I have a bunch of questions of both the last two speakers. In the first place, interpreting these numbers is quite difficult the way they've been given to us. We don't know what the denominator is. How many integration sites were looked at in these studies? I mean, integration, we have data actually. Steve knows. Dr. Hughes knows about this as

well because in collaboration with him and his colleagues in Frederick all the in vivo and in vitro integration from HIV or HIV vectors into CD34 cells. And, in round numbers, it's on the order of 1 in 10,000 integrations ex vivo. In a cell-culture model, is into either MECOM or PRDM16.

So, if you look at 10,000 integrations, you often see one. If you only looked at a hundred integrations and you see one, it's quite meaningful. If you look at 10 to 100,000 integrations and you see one, it's more. There's fewer than you would expect. So this denominator here is really important, and, if somebody could help me with that, that would be very nice.

I have a bunch of other questions too. I can go through them all if you want, or we can come back.

DR. LISA BUTTERFIELD: Why don't we go one by one.

DR. JOHN COFFIN: Okay. All right then.

DR. LISA BUTTERFIELD: Dr. Bonner, do you want to start?

DR. MELISSA BONNER: Yes. Thank you. So you are correct, right. The denominator is really important here. In most of our patients when we analyzed a single peripheral blood sample at each time point, we will get thousands of unique insertion sites and unique genes. And the numbers that you are hearing -- so, for example, I can tell you right now that, in our CALD program, 98 percent of patients treated with eli-cel have at least 1 insertion in PRDM16.

That is amongst the hundreds of thousands that have been detected over the entire time span that we have been conducting integration site analysis. The vast majority of those integration sites are at relative frequencies that are substantially less than one percent, and they do not typically hit the top ten integration sites.

DR. JOHN COFFIN: Yeah, I more accurate number would be nice, I have to say. You know, what the denominator actually is in each specific case would be quite meaningful. And you apparently are not prepared with sharing this right now.

Another question, as Dr. Hughes pointed out, it's very clear in the cases where you do get insertional activation -- activation's a bad word, but it's one that's commonly used -- disruption of gene expression. The proviruses tend to all be in the same orientation and tend to all be in a common location or at least in one or a few neighboring introns, and this is what we see over and over again in this. And we saw nothing about the location of these.

I'd feel very differently about integrations in all those different patients if they were all in the same intron and all pointed in the same direction than if they were scattered across the gene.

DR. MELISSA BONNER: Yep, can I have Slide 2 up, please? This is a snapshot of what we see when we look across the genome. The vast majority of our insertions are intronic followed by intergenic and then there are handfuls that are exonic. And, as you can see on the right-hand side, this is a representative gene and going from left to right annotated on the bottom are the exons, and then obviously in between

those are the introns. And on the row above that, each triangle is an insertion site that has been identified within that gene. So you can see that they again fall typically entronicly, and they are not enriched for any one particular position within a gene. I can show you this for other genes if you would like.

DR. JOHN COFFIN: Show it to me from MECOM?

DR. MELISSA BONNER: I can. Slide 1 up, please. So this is what the MECOM locus looks like, and, as you can see, it is a common insertion site.

DR. JOHN COFFIN: Okay.

DR. MELISSA BONNER: We see MECOM insertions in all patients, and it is across the locus. There is no specificity in terms of where it inserts other than it being intronic. There's no preference for the directionality and if I could actually Slide 2 up, please. And then we're not the only ones to see this.

The MECOM is a common insertion site for lentiviral vectors and for hematopoietic stem cell oncogene therapy.

DR. JOHN COFFIN: It's not in our data set. I

mean, it's an okay integration site, but it's not one of the biggies.

DR. MELISSA BONNER: Well, this is an ex vivo genetically modified hematopoietic stem cell with a lentiviral vector that is very different from HIV.

DR. JOHN COFFIN: That makes very little difference to integration. The structure that integrates, for all practical purposes, is the same, I think, as Dr. Hughes pointed out.

DR. MELISSA BONNER: Yes, HIV -- the target cell for HIV is a T cell, and HSCs are actually highly refractory to HIV infection. And that is actually why LVVs had to be redesigned in order to actually achieve transaction efficiency in hematopoietic stem cells, for example, changing our fusion routine.

DR. JOHN COFFIN: Well, yeah. But part of that -- it's mostly the change in the envelope protein so that it -- because these aren't (inaudible) positive. But I'm still not entirely clear. That distribution does look like it's everywhere. You don't show the orientation there. The three colored

triangles you have are the three patients with MDS? Is that correct?

DR. MELISSA BONNER: Two of them. Can we actually get that slide back, please? Slide 1 up, please? So two of these patients, Patient 104-18 and 104-08, which are the arrows that happen to be pointing to the left, are patients that have been diagnosed with MDS. Patient 102-11 has a clonal expansion that appears to be stable, and that patient has not been diagnosed with MDS and does not appear to have any clinical signs of MDS.

DR. JOHN COFFIN: Okay. One more -- well, a couple more questions. Have you looked at transcripts at all in these patients? The understanding of what's going on, a lot of that could be helped and so on. But again, as you can see from Dr. Hughes' presentation, it could be informed by looking at transcription patterns of these of Hughes' genes. Do you have any data like that?

DR. MELISSA BONNER: Yes, so we can conduct the transcriptional analysis. I want to make it very

clear for everyone that the polyclonality of our patients actually prohibits a useful RNA sequencing analysis in the absence of a clonal expansion.

DR. JOHN COFFIN: It makes RNA seq difficult --

DR. MELISSA BONNER: Yep.

DR. JOHN COFFIN: -- but it would not prohibit a focused PCR analysis for the primer near the -- in the vector. And another one in --

DR. MELISSA BONNER: No, sorry. I would like to clarify. What I meant is that the population is so diverse that seeing any sort of transcriptional change that could be associated with an insertion is difficult because any given clone containing that insertion is generally low in that population. So, unless you were looking at a clonal population, it's exceedingly difficult due to the limitations of the heterogeneous sample.

There is a great example I can show you of our VAMP4 analysis in our AML patient from our lovo-cel program in sickle cell disease from February of 2021

where we did do a very robust RNA sequencing analysis to look at whether or not the transgene was active in the blast-enriched population and to see if there was any impact on the surrounding genes. And I would be happy to walk through that if that would be helpful.

DR. JOHN COFFIN: Well, what I'm more interested in is with MECOM cases where the clones are quite large. There's a pretty large fraction of -- a lot of your transfused cells have that one integration site. And a prediction would be that there is -- that you're starting transcripts from the homologous within your construct, and, if that's the case, that could be satisfied by a focused PCR analysis. You don't need to go through -- RNA seq can be difficult to interpret, and I'll grant you that. But then I'm not talking about overall RNA seq; I'm talking about more focus analysis and test-specific hypothesis about how the transcription might be current.

DR. MELISSA BONNER: So we have done those focus analyses on the MECOM insertion sites -- sorry, on the patients who have been treated with eli-cel who

have a clone within insertion in MECOM that have gone to develop MDS, and we do see perturbed gene expression, i.e. increased expression in the MECOM locus in those cases.

DR. JOHN COFFIN: Last one. One more question but perhaps when we come back if not.

DR. LISA BUTTERFIELD: Yeah, one more short question, please, and then we'll move on to the other's questions.

DR. JOHN COFFIN: Okay. Here's a simple question. Have you or do you plan to look at the cell sites that are sharing these clonal integrations? I would expect that you would have some lymphocytes there that it would transfuse (inaudible) all the hematopoietic stem cells were it, right. And I would expect some of those lymphocytes would have been clonally expanded in response to antigen. Have you looked at the cell types that have some of these other clonally-expanded genes that are at the moment not expanded?

DR. MELISSA BONNER: Sorry, I want to make

sure I'm understanding your question. So, as we're doing an ex-vivo transduction of enriched CD34 positive hematopoietic stem and progenitor cells, there are exceedingly low T cell impurities within that product. There are T cells that are resulting from the transduced hematopoietic stem cells that engraft.

DR. JOHN COFFIN: That's fine. Thank you. That's what I'm asking about.

DR. MELISSA BONNER: Yes, okay. So post-treatment, we do a peripheral blood analyses that is typically done on whole peripheral blood samples, and we do not routinely look at lineage distribution unless we are concerned that there might be an emergence of a clone for example. So there were a few cases where we have done this.

DR. JOHN COFFIN: Don't you think it would be helpful to show this? I would expect that you would see some of those in lymphocytes and that those lymphocytes would likely to be expanding just as a part of normal lymphocyte biology.

DR. MELISSA BONNER: Yes, so we do see those

sites also in lymphocytes, but they are much lower in prevalence than compared to the myeloid population in particular because likely MECOM is a myeloid gene.

DR. LISA BUTTERFIELD: Thank you very much. Moving onto Dr. M. and then doctors Ott, Keller, and Ahsan.

DR. JAROSLAW MACIEJEWSKI: Can you guys hear me?

DR. LISA BUTTERFIELD: Yes.

DR. JAROSLAW MACIEJEWSKI: Oh, thank you. Thank you for the presentation. I agree with a couple of questions previously. I think, you know, if you find lymphocytes scarring, you take them. But then it would indicate that the dominant clone comes from a stem cell as supposedly (inaudible) of a committed progenitor. And you know, either way, it could be that the virus hit the progenitor and it's small, it produces a different effect.

But you guys probably have a hypothesis and why is it that you have this enrichment for MECOM as an integration site? And obviously the fact that it

should passenger and marker for actually something else that happened genetically or whether this is sincerely (inaudible) link indicates that there is something autogenically [sic] going on.

And the reason I'm asking is because obviously as you know, EVI1 or MECOM is a very common and good, but not bad prognostic factor gene affected noting myelodysplastic syndrome. This would be highly unusual because these are highly progressive, and usually we diagnose them as a stage of AML affecting the WHO classification. This is an extra category with several permutation, expression, and so on.

So, if it would be any other gene that this nonrandomly occurring across the spectrum of patients, this would be sort of, okay, right, particularly at the integration site as seen two different direction and (audio skip). But here we have EVI1 or MECOM being very important but imminent oncogene that is activated through inversion in acute leukemias. MDS would be very, very rare with this because usually they are at the stage of AML.

The other thing is that the nominators that -- so this is the first question. What is your thought about it? But the second is of course, that the nominator of three cases of MDS -- again, you know, it's almost AML to me because of the nature of the oncogene. But there are four other cases, and four have the same MECOM again. So it's like really makes it sort of frustratingly uncomfortable about this particularly that these cases that are starting the classification, if it would be any other mutation, we would say, three of these patients have a chip and one of the patients or two or maybe two patient have chip and two have something that we would describe as sequels because they have single lineage cytopenia which is a clonal hematopoiesis with a single lineage cytopenia.

So consider the sort of the increased risk for development of later malignancy with the same mutation in it (inaudible) on it. I would like to hear your thought about these two questions.

I think I just wanted to point out that the

cases in the lovo-cel were that there's no integration. It looked like the leukemic clone should displaced -- since it doesn't have integrated virus of any sort, it would have displaced the (inaudible), the clones that these cells use. So in any event, the leukemia would sort of take over the result of our therapy transaction because it would squeeze out the vitally used normal cells. Go ahead.

DR. MELISSA BONNER: So to clarify then your opinion --

DR. JAROSLAW MACIEJEWSKI: To summarize, what is your thoughts why MECOM is so common and why -- if you reduce the frequency and now you have seven cases of clonal hematopoiesis that is suspicious of progression either imminent or already occurring, and the frequency would be not 4.1 percent but almost 10 percent, right, of this particular event. What is your thought pathogenically what's happening because this would, of course, instruct your method to monitor it?

DR. MELISSA BONNER: So it's a great question of what is exactly causing MECOM to show up so

frequently as a common insertion site. I don't know that I have a great answer. We see MECOM insertion sites commonly in our eli-cel trial and across all of our trials, and, in fact, most gene therapy trials that are using an integrating retroviral vector for hemopoietic stem cell gene therapy see MECOM as a common insertion site.

Likely, it does have something to do with the biology of the particular spot that the insertion is within the MECOM locus. The orientation, the number of other potential genetic abnormalities that could be present already in that particular cell, the disease, specific attributes of the vector, and the expression of the transgene. So we do think that it is likely multifactorial, but we don't have a distinct mechanism for why this is the case.

I would like to remind everyone though that, again, being a common insertion site means that it is found in different patient samples. It doesn't mean that it is prevalent in distribution samples.

DR. JAROSLAW MACIEJEWSKI: Sure.

DR. MELISSA BONNER: So we don't actually -- there is no meaning necessarily to it being a common integration site other than that we can detect it with our integration site analysis method. And so it is uniquely traceable, and we can monitor clonal dynamics over time.

I would add though that in the case of an emergent malignancy -- so, for example, going back to our experience with our sickle subject who developed AML, the insertion site was not clearly predominant within the population until the time of the blast formation in the blast crisis for that patient. So frequent monitoring is helpful for looking at clonal dynamics. It's probably substantially more helpful for the patient to have routine clinical care and routine monitoring.

DR. LISA BUTTERFIELD: We should move I think although these are important questions to really dig in on in detail obviously central to our discussion. Dr. Ott and then Dr. Keller next. Thank you.

DR. MELANIE OTT: Hi. Just wanted to focus

the attention on the MNDU3 promoter in your lentiviral vector. This is not just any ubiquitous promoter, expressing promoter. This is actually a promoter from a myeloproliferative sarcoma virus that has been shown to have effect on neighboring genes either on the same gene expression plasmid or on neighboring host genes.

So I am just wondering why this promoter with known potential myeloproliferative capacities have been chosen and why has it been kept and what are the plans to exchange it? That's my first question. I have a few more.

DR. MELISSA BONNER: Yeah. So there are different reasons -- okay. I'll start with the first one. So we have a couple of different reasons that we chose the MNDU3 promotor for the Lenti-D/lentiviral vector. If I could have Slide 1 up, please. So as stated previously, we don't actually know what hematopoietic cell is responsible for crossing the blood/brain barrier and long-term engrafting in the central nervous system to have the therapeutic effect that is necessary for stopping disease progression for

CALD.

CALD is not a hematologic disease, so, in order for us to ensure that the appropriate cell was expressing the ALDP protein in the CNS where it actually matters the most, we needed to use a promoter that would allow for expression across multiple cell types that hematopoietic stem cells are responsible for producing. And the MNDU3 promoter is an appropriate promoter from that perspective.

In addition, a similar construct that used that MNDU3 promoter and enhancer had already been tested for a gene therapy for a CALD, and it was demonstrated to be suitable. And notably there have been no cases of MDS in that trial.

And thirdly, we did do many nonclinical assessments utilizing the Lenti-D/lentiviral vector both in vitro and in vivo in accepted models of hematopoietic stem cell research. And, in the gene therapy field, for example, the in vitro immortalization assay and in all of our nonclinical assessments, there was no quantifiable hazard

associated with the use of the Lenti-D/lentiviral vector. And this includes no quantifiable risk of oncogenesis.

So it passed all of the tests, and, because it passed all of the tests, it also tells us that the tests are probably not appropriate. So I, unfortunately, think that if we were to, today, have a different promoter that we test through all of these tests, we could generate data to say, oh, maybe it would perform better than the MNDU3 promoter from a risk perspective. But, because the MNDU3 performed well, I don't actually know that we have any leg to stand on there.

And so I don't know that we could decrease the risk and maintain the efficacy that we do see and that is where the challenge lies. I mean, I think the other thing to keep in mind is this was designed in 2010. It's been over a decade to get to this point where we actually are seeing these risks start to emerge. So I don't think that making a change today could necessarily allow us to predict a future product that

could potentially have a safer safety profile but maintains that efficacy. And without suitable nonclinical assays, I think it's going to be exceedingly difficult.

DR. MELANIE OTT: Yeah, I would certainly encourage you to look into this because I would not keep a myeloproliferative virus promoter in a construct that is causing MDS.

I think I also would like to point out that EVI1 only come as a frequent integration site for retroviruses as you have pointed out. It actually is very frequently causing myeloproliferative diseases. It does the defining insertion in a mouse model that has myeloproliferative diseases. So I think the combination of it -- the MNDU3 promoter and a MECOM integration site -- might not be very favorable here.

My second question is --

DR. LISA BUTTERFIELD: Let's keep the discussion part for the discussion and really focus on questions and answers briefly. Thank you.

DR. MELANIE OTT: Okay. Next question is what

is your MOI that you're using in your transcription protocol, and are you aiming for multiple integration sites per cell? And is the multiple integration sites per cell that we have seen for all these MECOM clones and other clones in any way predictive or special for these people that develop oligoclonality or MDS?

DR. MELISSA BONNER: I'm going to ask Dr. Ilya Shestopalov to comment on our germ product manufacture. While he's walking up here, I do want to add that the mouse data they referred to, if I'm remembering correctly, is from a syngeneic transplant and not a xenotransplant.

DR. MELANIE OTT: Yes. It's syngeneic. Yeah.

DR. MELISSA BONNER: And so that is very different, right, when we're doing our nonclinical assays to test the relevant product. We're using a xenotransplant to test human CD34 cells. Dr. Shestopalov.

DR. ILYA SHESTOPALOV: Thank you, Melissa. Again, I'm Dr. Shestopalov. I'm the head of analytics at bluebird bio. So, to the question of MOI, that is

proprietary, but I'd like to remind folks that haven't worked with CD34 cells that they are notoriously difficult to transduce lentiviral vectors. In fact, when I went into this field, some folks thought they are untransducable and you need to generate CD34 cells from IPF cells.

So we do use a high MOI to get enough vector copies to have efficacy. Now, can I have the slide on efficacy and vector copy number? I am -- as we're waiting for the slide to come up. Because I think to your question of what range of vector copy numbers we're aiming to get. We're just waiting for a slide to come up.

DR. LISA BUTTERFIELD: If you can keep talking, we have three more questions.

DR. ILYA SHESTOPALOV: All right. Slide 2 up, please. Sorry about that. All right. So --

DR. MELANIE OTT: Do you see multiple integration sites in every cell or just in these clonal expanded cells?

DR. ILYA SHESTOPALOV: Yes, so with vector

copy number, as you can see in the slide in the graph on the left, we have -- the mean is about 1.4, right? And we know that the two patients that progressed are now below what we were proposing as our lower specification limit. They're below 0.7.

So what does 1.4 mean? It's a distribution, right? So 1.4 is an average. There's zeros, there's ones, and there's typically a long tail of cells, and that's why it's not perhaps surprising that we had a patient where the clone that grew out actually had four integrations, whereas the drug product that went in had a vector copy number of 1.5. So that's the difficulty of looking at drug product vector copy number, and, as you can see our numbers are quite reasonable for the vector copy numbers that we're achieving with our MOI. Very rare clones could have multiple integration sites.

DR. MELANIE OTT: Thank you. My very quick last question is myeloablation absolutely critical for the success of your protocol, or can you do without bone marrow population of your lentivirally transduced cells?

DR. MELISSA BONNER: Myeloablation is critical for all gene-modified hematopoietic stem cell protocols.

DR. MELANIE OTT: Okay. Thank you.

DR. LISA BUTTERFIELD: Thank you. Let's move to Dr. Keller, and then hopefully we'll get to Dr. Ahsan and Dr. DiPersio.

DR. STEPHANIE KELLER: Hi. I just have a few questions, but mine are short so. My first one would be better for Dr. Raymond (phonetic) or Dr. Eichler. In the boys that developed the MDS in regards to the MDS and the stem cell transplant, did either of those seem to affect their Loes score or their NFS?

DR. MELISSA BONNER: Dr. Eichler.

DR. FLORIAN EICHLER: Yeah, we don't see any direct relationship between MDS and neurologic function. The one boy who is longest out and was found to have MDS has progressed in his Loes score, but the other two have not.

DR. STEPHANIE KELLER: Okay. And then my second question was -- and I think somebody tried to

allude to it earlier but -- in the boys that have the MDS and the boys that are suspected of developing that, there a little more cases of the 104 group. And they certainly felt it much quicker than the boys who were in the 102 group. Do you have any idea why they might be developing that more quickly?

And I guess my question is just related to, if we have a shorter follow-up period for the 104 group, so if we had extrapolated that out, you would think there would eventually be more cases than the 104 group than the 102? So would that make you decide to use more of the protocol for the 102 versus 104?

DR. MELISSA BONNER: I'm going to ask Dr. Laura Demopoulos to address your question.

DR. LAURA DEMOPOULOS: Thank you and you're right; I did briefly reference before that we've done many analyses looking to see if there was something about the conduct of the 104 study versus the 102 study that might have led to some different manifestation of MDS in its timing at least. And frankly, we were not able to identify anything, so I don't have an answer

for that.

What I can tell you -- it is somewhat speculative -- is that the two boys who presented in the 104 study, who presented early, presented in a very distinct way; they both had delayed platelet engraftment and very early abnormalities in their ISA studies.

No other subject in the 104 study has a presentation like that at all, so, if that serves as some bases of predicting what might happen to the rest of the boys in that study with respect to a development of MDS in that timeframe, we don't see any other cases. And all the boys in that study have passed the follow-up periods that allow us to be certain that they don't have that same phenotype.

DR. STEPHANIE KELLER: Okay. And, again, does that make you want to do more of the 102 group versus the 104, or it's just not known yet?

DR. MELISSA BONNER: I'm sorry. Can you repeat the question?

DR. STEPHANIE KELLER: Sorry. Does that make

you want to use the 102 protocol versus the 104 if this is eventually proved?

DR. MELISSA BONNER: Dr. Demopoulos.

DR. LAURA DEMOPOULOS: Hi. No, because, frankly, we really couldn't find anything that would bias us towards using one approach versus another. It would with any convincing evidence. So no, I think everything that we foresee for post-marketing treatment where there were variations between the two protocols -- and they were relatively minor -- is going to be at the discretion of the investigator or treating physician.

DR. STEPHANIE KELLER: Okay.

DR. LISA BUTTERFIELD: Okay. We're going to move to our last two questioners, and I'm hoping they have perhaps one burning question to propose -- Dr. Ahsan -- before we move to the group discussion.

DR. TABASSUM AHSAN: Hi. Thanks. I will try to keep this short. I know we're short on time.

In looking at the official site frequency, you looked across the programs and you set that at greater

than ten percent. I noticed that the FDA set monitoring at greater than 30 percent. So can you talk about -- because I know we're getting into the insertion site, and that's an important conversation, but I kind of want to look at a little bit higher level, which is, if you tune that value differently, do you see different correlations as you are trying to put programmatically across the three products?

DR. MELISSA BONNER: Yeah, it's a great question. I'm glad you asked this because I was hoping to clarify some of our integration site analysis algorithm details.

So, if I could have Slide 2 up, please. So it gets a little complicated. So we have an integration site analysis algorithm that the FDA had in their presentation, and this algorithm, we are still using per our clinical study protocol. However, we are also in the process of currently aligning on a new algorithm with the Agency because we have decided in agreement with the Agency that we want to have a more conservative threshold for triggering a notification to

the Agency and notification to treating physicians that they can contextualization for any sort of potential clinical abnormalities that may or may not exist.

So our current protocol that we are operating on under our clinical study protocol is what was detailed by the FDA which is to look at a 30 percent relative frequency threshold. However, we have already implemented the reporting on our ten percent relative frequency threshold, and we have chosen to define oligoclonality as this ten percent relative frequency threshold. So we are --

DR. TABASSUM AHSAN: Sorry, not to interrupt only because I know we're short on time, and I appreciate what you're saying. I would love to see the analysis though because those are really justifiable values; they're just a little bit arbitrarily chosen. So taking that ten, chipping it down to five -- 7.5, 10, 12.5 et cetera -- kind of creating a gradient and seeing your results in terms of how they fall out with MDS is I think very important.

You made that a central argument in your case

as to why this oligoclonality is not associated with MDS across these programs. And so it would be really important to set the criteria by which you selected the data. And so I think that that's a really important point, so if you have that as a metric, that would be great.

And then my second question is in the eli-cel, it's a broad spectrum of phenotypes that express, right? Did I hear correctly that you made this one comment that, in these patients with MDS, that the silencing differentiation was not seen? Is that what you said?

DR. MELISSA BONNER: No, sorry. I said that the MNDU3 promoter was likely leading to either overexpression as like a novel overexpression mechanism or the fact that MECOM and EVI1 are active in very early progenitor cells, so the promoter might just be preventing the silencing of that gene as the stem cells differentiate.

DR. TABASSUM AHSAN: Okay. Thank you for that clarity.

DR. MELISSA BONNER: You're welcome. So to address your question about the choice of the ten percent, the integration site analysis assay that we utilize at our third-party vendor has a dynamic range of 5 to 70 percent. The lower limit of quantification is 5 percent with a coefficient of variation of 20 percent, and, therefore, we thought 10 percent was going to allow for a sensitive measure that was still reliably quantifiable.

DR. LISA BUTTERFIELD: Thank you. And so a single final clarifying question from Dr. DiPersio and, then we'll move to the discussion.

DR. JOHN DIPERSIO: Thank you. So I want to know is there any comparator group that has been treated the same way without gene therapy, meaning exposing either sickle cell patients or these kinds of patients with high dose busulfan without gene therapy and what the result of that would be as far as clonal evolution and MDS and things like that?

DR. MELISSA BONNER: So you're referring to an allogeneic comparator group?

DR. JOHN DIPERSIO: No, what I'm saying is that we just don't have a good comparator group in which patients are just treated with therapy without -- so one of the issues here is whether this MECOM is an innocent bystander or driver of the disease? In other words, it's occurring in a very small subclone that's already developed a mutation.

We know that mutations are present in many stem cells even in children. Even in cord blood, there's a few. And so the question is whether this is really driving the disease or whether this is just landing in the correct soil at the right time and sort of aiding things along. That's all I say.

So that's just a comment to suggest that we don't know what the background rate of MDS and AML is in people that get high-dose busulfan without gene therapy because we don't even use busulfan outside of an allo setting. And an allo setting's not appropriate because all the donor cells are completely normal, and all the host cells are eliminated, not so much from the busulfan but from the T cells that you infuse. That's

all I'll say still.

DR. MELISSA BONNER: Yeah, so I do think there is some data that could I think serve as a reasonable comparator for some of these studies. I mean, I agree with you; we do not condition people and then not provide them a transplant or provide them an autologous transplant without genetically modified cells as they clearly would not have any benefit of therapy. So it'd be -- there's a clear ethical line there. You know, we -- allogeneic transplant is obviously --

DR. JOHN DIPERSIO: I just want to add one more thing that the rates of MDS in Hodgkin's disease or non-Hodgkin's lymphoma is, at 5 years, is 4 percent and 10 percent, and, at 20 years, it's 10 percent and 20 percent. And we don't use busulfan, and we use sort of drugs that aren't really strong (inaudible). It's just an observation that it would be great to have a control group that we could actually compare those to.

DR. MELISSA BONNER: If I could have Slide 1 up, please. So I think this study actually is a fairly reasonable comparator specifically for sickle cell

disease. So this is looking across many different clinical studies evaluating different donor sources for allogeneic hemopoietic stem cell transplantation for the treatment of sickle cell disease.

What you can see is that there are instances of MDS on the third row, and you can see that the proportion of MDS and AML that develop in these situations are actually fairly comparable to what we have seen in our trial evaluating lovo-cel. And they are also typically associated with the decline of donor cells essentially failure of the therapy, which I think is very much akin to what we see in our sickle patients who are treated with the early version of lovo-cel where they had limited therapeutic benefit.

DR. JOHN DIPERSIO: Thank you.

DR. LISA BUTTERFIELD: Okay. Well, thank you very much, everyone. I think we had a lot of important questions to get to. So now we're going to move to the discussion of the specific questions put to us from the FDA.

QUESTIONS TO THE COMMITTEE/COMMITTEE DISCUSSION/VOTING/MEMBER REMARKS

DR. LISA BUTTERFIELD: Now we're going to move to the discussion of the specific questions put to us from the FDA. So, I'll read each question, and then we'll have a first and second discussant who will weigh in on these. And then we'll have opportunity for discussion from the rest of the Committee members. We'll go through those three questions and then move at the end to the votes. We have about an hour and a half left for this.

So, the eli-cel efficacy data are difficult to interpret due to problems with the benchmark calculation, issues of comparability between populations, potential bias, concerns regarding imputation methods, few events during a limited duration of follow-up, and limited sample size for treatment and control populations.

So, this is the rest of Question One. Please discuss the limitations of the primary and secondary

efficacy endpoint data and whether the data support the presence of the clinically meaningful benefit of eli-cel. And discuss the populations, e.g., children without a matched willing sibling donor, children without a matched donor, in which the efficacy data are or are not supportive of a clinically meaningful benefit.

So, for Question One our first discussant is Dr. Keller. So, we'll please have Dr. Keller and then Dr. Dueck weigh in on Question One.

MR. MICHAEL KAWCZYNSKI: Sorry, can you go by their first name, please, so they can raise their hand? It'll make it much easier.

DR. LISA BUTTERFIELD: All right. I'll ask everyone to raise their hand. Dr. Stephanie Keller.

MR. MICHAEL KAWCZYNSKI: There we go.

DR. LISA BUTTERFIELD: Dr. Amylou Dueck.

MR. MICHAEL KAWCZYNSKI: There we go. Thank you.

DR. STEPHANIE KELLER: So, for this one I think that it does -- that there are limitations,

obviously, with this, and there may be bias. But I think a lot of it is just rarity of this (audio skip) and the limitations and the ability to collect data and have other control populations and things like that for such a small group of people that you're testing.

But I think it does support the presence of a clinically beneficial effect from the eli-cel, especially for the mismatch unrelated donor group with the eli-cel. Even based on the FDA's recalculation, eli-cel had 91 percent, the major functional ability at 24 months, and it was similar for the matched LID (phonetic) at 90 percent. And then the mismatch unrelated was 42.9 percent. So that was certainly a significant benefit there for those patients.

And then (audio skip) population in which the efficacy data are not supported by clinically meaningful benefit. I think in this population if you were looking at a cancer risk in any other disease, it would certainly be that -- not that it's not an issue, but it would certainly be much more important in -- or much more relevant in another population where there

were other potential treatments or that you could actually live with the disease or be managed in some other way.

But this is such a devastating disorder, without good treatments or ways to even live with this disease without a treatment, that I think the risk of cancer and seizures and other things that were (audio skip) I think are tolerable, in some ways, and certainly hearing from the families I think these are things that they're willing to risk in order to have a potential benefit for their children to be able to live and be functional.

I think this treatment is (audio skip) and hopefully there is a cure one day. But it at least gives these boys time that hopefully one day we can come up with something better for them. But without a treatment then they don't have the time. They don't have the potential to wait for anything else. So, I think, even with the problems that exist for this treatment, I think it certainly shows a significant benefit that boys right now can't wait on a better more

perfect treatment to (audio skip).

DR. LISA BUTTERFIELD: Okay. Anything to add about specific populations, or were you conveying that any of those three that are listed -- or the two listed in the question you see that you answered the relative benefit for both of those?

DR. STEPHANIE KELLER: I think there's relative benefit for both of those because the one for the matched unrelated patient is very similar to the eli-cel at 90 percent. Again, I think that's up to the families if they want to risk the graft versus host or potential cancer with this treatment. And then, again, for the patients that have mismatched unrelated, I think that's such a significant benefit there, definitely one that should be considered for this treatment.

DR. LISA BUTTERFIELD: Thank you. Appreciate that additional detail. Dr. Dueck, what are your thoughts on Question One, please?

DR. AMYLOU DUECK: Hi. So, I'm going to sound pretty similar to Stephanie. So, starting at the

primary analysis, we can agree that the lower limit of the 95 percent confidence interval for eli-cel exceeded the 50 percent benchmark. But based on the gross lack of comparability in the disease characteristics between the eli-cel cohort and the observation cohort, I somewhat disregarded that particular comparison and focused more on the comparisons with the transplant group.

And then, specifically, in the primary comparison between eli-cel and the no-matched sibling donors' comparisons that showed benefit, I did share the FDA reviewer concerns about inclusion of second transplant as an event in the major functional disabilities free survival endpoint. I felt that the sensitivities analyses were conducted in which all second transplants were excluded and then the MDS cases were included as events may have been a slight overcorrection, but nonetheless, these show that the clinical event is less dramatic after you exclude this subsequent transplant in the stem cell transplant cohort.

But all-in-all, I do think the most compelling of the exploratory analyses were the comparisons when you look at the subsets of HLA matched and the HLA unmatched cohorts, which suggests there were predominantly the most clinical benefit of eli-cel within HLA unmatched donors' group. And really that showed that both were major functional disability-free and overall survival there was consistent benefit for eli-cel primarily driven by the early test (phonetic) line related toxicity in the HLA unmatched donor group.

So, in terms of issues of comparability and bias, I did think the propensity score adjustment methods that were used I thought adequately controlled for the included co-variants. And I wasn't surprised that the results were actually fairly consistent between the propensity score message and the unadjusted message, mostly because the cohorts actually were only mildly imbalanced, in my opinion.

Another issue was raised in term of limited follow-up. I thought that this was actually kind of lesser concern, particularly in the HLA unmatched

comparison, but then the vast majority of those events were in the first six months and represented toxicity of the stem cell transplant population. Of course, I'm not taking into consideration the MDS risk which would be kind of a different calculation in terms of risks and benefits, and I'm just strictly considering kind of clinical benefit here.

I also had lesser concerns as raised by the FDA reviewers in terms of evaluating major functional disabilities, again, because the primary comparison that I felt was the most compelling in terms of the HLA unmatched group because, again, it was -- the primary, I think, benefit was more based on transplant toxicity which I think is less biased in terms of blinded comparisons.

So finally, in summary, again I think the most compelling clinical benefit was supported in the unmatched donor group. Okay. I'll stop there.

DR. LISA BUTTERFIELD: Terrific. Thank you very much. All right. So to continue the discussion of Question One, I'll watch for hands. So, we're still

on Question One, and so, Dr. Ahsan, what would you like to add to our discussion for Question One, please?

DR. TABASSUM AHSAN: Yeah, I think that in considering the sponsor's data which has stratified in a more favorable way, but even if you look at the FDA presentation of the data, I think if we think about the different populations, they would be unmatched. I think it's very clear that there's some benefit. With the matched, right, there looks like in terms of survival there wasn't a marked difference, but if we think about the graft versus host disease versus the risk of insertional mutagenesis, that seems to be unbalanced.

I do want to point out that there was that public comment -- it was a very small point, but I think an important point -- where one of the parents said something about, they -- someone had said if their child had had cancer instead, that would've been at least something that they could treat, that the graft versus host disease is really a very nefarious side effect.

And so, I think -- thinking about that, I think the paradigm of allowing the clinician to select what is best for the matched non-relation -- the non-sibling -- is, I think, a nice paradigm that allows us to have the flexibility of doing what's in the best interest of the patient. It also allows us to -- the other benefit is -- to treat early is such a huge benefit in this case that it allows you to not have to wait for the matching process which can be extensive.

DR. LISA BUTTERFIELD: Great. Thank you for raising those points. Next, I see a hand from Dr. Roberts.

DR. DONNA ROBERTS: Yes. Yes, I just wanted to mention one minor concern. I agree with everything the other speakers said, but just one minor concern is that one of the promises that this is for unmatched donors and a large percent of unmatched donors are going to -- are -- patients that have unmatched donors are going to be minority populations. And if you look at the race breakdown in 102 and 104, there were, for example, three African Americans, one Asian, and 36

white.

So, I think there's not a lot of data on those minority populations for which this would have a benefit. But again, that's a minor comment, and I completely agree with what the other speakers said.

DR. LISA BUTTERFIELD: Thank you. I appreciate that. Okay. So we have a little time for more discussion of Question One. Are there other viewpoints to add or echo to what's been presented so far? Dr. Lee?

DR. JEANNETTE LEE: Yeah, so I think one question I have -- and this is maybe a question for the FDA -- if, in fact, an approval for a BLA is issued for eli-cel for this group, what is the process of monitoring, for example, for MDS and some of the other issues and also the concern, I think, that some have raised regarding the follow-up and effect that the primary endpoint was based on 24 months?

Can somebody FDA maybe describe a little bit about, briefly, what that process would be, because there are -- obviously, this is a rare disease so your

ability to really start is not there, but there are obviously significant concerns. And I don't know if somebody in FDA could respond to that.

DR. LISA BUTTERFIELD: Dr. Bryan, is there someone on your team that you would like to call on?

DR. WILSON BRYAN: Yes. Well, so, we're particularly interested in this Committee's recommendations with regards to monitoring, particularly along the lines of monitoring for the possibly of related, which is a foremost concern. We have a variety of mechanisms for monitoring and trying to ensure the safety post-marketing, and we'll consider those. But the question of what we should do, at the moment, is one we really want this Committee's input on in the subsequent questions.

DR. JEANNETTE LEE: Okay. Thank you.

DR. LISA BUTTERFIELD: Thank you. So, I see two more hands up for discussion of question one. Dr. Crombez, please. And then -- can't hear you yet, Dr. Crombez.

MR. MICHAEL KAWCZYNSKI: You must have --

DR. ERIC CROMBEZ: Sorry about that.

MR. MICHAEL KAWCZYNSKI: Yep, check your phone. There you go.

DR. ERIC CROMBEZ: Yep, thank you. Just wanted to agree with the overall positive benefit risk profile here. I do think this was a very well-thought-out clinical development plan, and just wanted to comment and remind everyone of the challenges in conducting these types of trials for these very rare diseases.

Yeah, so same regulations apply, but it can be very difficult when you're dealing with these small patient populations needing to design and enroll in the global trials trying to identify as many patients as possible. Challenges on endpoint development, obviously, there's not a lot of clinical regulatory precedent to follow here, so I think it's a very good job in this endpoint development.

And we talk a lot about the use of non-concurrent control groups and the challenges they have, and obviously there is some precedent in rare disease.

But I think here it is appropriate. I think it was well done, and the fact that the company conducted their own trials as opposed to use something done in an academic environment or just published is great. And then again, with the duration of follow-up with these types of diseases that can be slowly evolving can be a challenge, and I think the 24 month time point is appropriate with obviously the very good results.

DR. LISA BUTTERFIELD: Thank you. So, we'll go to Ms. Anspach and then finish with Dr. M. for Question One.

MS. SYLVIA ANSPACH: Hi, so I'm Sylvia, and I'm one of the patient representatives. So, I'm coming from the standpoint of a mother of a son who is now 24 years old and was diagnosed in 2005, so way before a lot of this was available. He is alive and doing well post allogeneic transplant but has multiple disabilities, and as I listen to this it's very academic and very predictive in nature, like we're looking at what is the future.

But when you look at the endpoints that they

gave you at two years, that seems very appropriate to me because what we know is once they have gadolinium enhancement, that's a predictor to more rapid progression and death. And so, my experience in taking with other parents and watching children as they go through transplant is once that enhancement hit, your -- time is brain, and you're immediately starting to lose function. So, life expectancy is short, and if they live longer, there's disabilities. So that seemed very appropriate to me.

Early transplant is definitely a benefit, so when they were talking about there may be bias associated with lower Loes scores in the kids that were on the bluebird trial, I feel like that was not so much a bias but a benefit because we know that when kids are transplanted with a lower Loes score they'll come out with less dysfunction.

Again, I echo that donors are hard to come by, not just because that it's difficult to find donors in a diverse population, but we're talking about people with genetic disorders. So our other children are

impacted. There's a 50 percent chance that any other child will be impacted, so that even decreases the donor pool more. Yes, there is a risk of MDS and malignancy. And my background, I'm nurse practitioner who's spent my life in hematology oncology, so I understand the risks of those. However, the kids that are being identified have already outlived their life expectancy.

And so, as a parent, I understand that, and I think that they made the comment that time -- Dr. Keller made the comment that time gives you the potential to look at other options. And as somebody who's lived their life in the unknown world of ALD for the last 20 years, that's where we live. We don't know what the future is going to hold, and so the opportunity to have time is essential. Thank you.

DR. LISA BUTTERFIELD: Thank you. All right. I no longer see Dr. M.'s hand up so --

DR. JAROSLAW MACIEJEWSKI: No, no, I'm here. I am here.

DR. LISA BUTTERFIELD: Sorry.

DR. JAROSLAW MACIEJEWSKI: So, totally agree with the families who would with this treatment have an option, particularly if they have to weigh this against mismatched or unrelated transplant that is of higher risk. I think what should be, however, happening -- that having the choice is always good, but I think that in addition to post-market surveillance, what has to be done on the other side, the company is obliged to for those who selected the other option and not the product here on commercial grounds -- that the results of bone marrow transplantation in these settings are just relevant is being updated too because there is a lot of progress in this.

The mortality decreases. There are other ways of conditions. There is a lot of progress going on, and it's important that's presented as a choice. Look we have this product versus this, and this has so many disadvantages that current data and not historical data presented. In other words, the update has to have not only on what happens to the people who receive this product but also what happens in terms of the

improvement of a standard bone marrow transplantation.

DR. LISA BUTTERFIELD: Thank you. Dr. Ott, did you want to make a final comment on Question One before I summarize and we move to Question Two? I see Dr. Melanie Ott's hand up.

DR. MELANIE OTT: Yes, good. I actually have more question for the clinical colleagues at the FDA or the sponsor. What is the prognosis of the kids with MSD (sic) currently in terms of after their allotransplant? What is -- I know it's early and we don't really know. But what is expected in terms of the transgene expression in the brain, the continuation of this, and also the curing of the disease -- the syndrome?

DR. LISA BUTTERFIELD: So, I know we're not usually including the sponsors any longer in this part of the meeting.

DR. MELANIE OTT: Okay. Maybe one of the clinical colleagues could comment on this what they expect. Are they expecting a full recovery? Is this going to be a 50/50 chance? What is the survival

expectations of these kids with MSD (sic) after their allotransplant now?

DR. LISA BUTTERFIELD: Dr. Bryan, do you want to make a comment about this, please?

DR. WILSON BRYAN: Let me call upon Dr. Elenburg from our group to comment, if we could.

DR. LISA BUTTERFIELD: Terrific. Thank you.

MR. MICHAEL KAWCZYNSKI: I'm sorry, who did you want to call on?

DR. WILSON BRYAN: Shelby Elenburg.

DR. SHELBY ELENBURG: Hello. So, I actually was primarily involved in the efficacy review, so I'm not sure how much I can answer about this. But I know Dr. Crisafi was the primary safety reviewer. I don't know that we have that information either. We are getting frequent clinical updates about the subjects who have MDS, but I'm not sure that we have that specific update on their prognosis or -- especially because it happened recently, we don't necessarily have the efficacy data after their transplant either.

DR. WILSON BRYAN: Dr. Butterfield, maybe we

could check with one of the clinicians from the sponsor's team.

DR. LISA BUTTERFIELD: Okay. Thank you. bluebird bio, would you like to have one of your clinical representatives address this? I have bluebird bio's hand up. Thank you.

DR. JAKOB SEIKER: Yes. Can you hear us?

DR. LISA BUTTERFIELD: Yes.

DR. JAKOB SEIKER: I'm going to ask Dr. Lindsley, who's an expert in MDS, to discuss the outcome of MDS in these patient population.

DR. COLEMAN LINDSLEY: Good day. I'm Dr. Coleman Lindsley, and I'm the director of clinical genomics and hematologic malignancies at Dana-Farber Cancer Institute and co-director of the Edward P. Evans Center for MDS at Dana-Farber. In pediatric patients with MDS, the long-term overall survival is quite good, and it is, to provide context here, older adults with MDS the five-year survival is less than 50 percent. And the ten-year survival is more like 10 to 15 percent. However, in children and young adults that

survival is much better. And we can pull up slide one.

In a large registry-level study, we can see that the survival in MDS patients after transplantation is much better in children and young adults at the top ranging from about 70 percent. And then if we pull up slide two, particularly those patients with primary MDS and, again, lacking adverse mutations like P53, their survival in the long term is approaching 80 percent overall.

DR. LISA BUTTERFIELD: Terrific. Thank you very much for sharing those data.

DR. MELANIE OTT: Thank you.

DR. LISA BUTTERFIELD: Okay. So what I've heard in the discussion for Question One is that the Committee members certainly agree with the number of the issues raised by FDA and the concerns in the different ways of calculating some of these outcomes. But despite that, given the preponderance of the data, the way the numbers come out from either bluebird or FDA analyses, that the members of the committee have spoken up so far find that there is still evidence for

efficacy for eli-cel in the proposed patient populations without a matched willing sibling donor, without an unmatched unrelated donor.

There are other comments about that the two-year end point for now is deemed reasonable, that continued comparisons with transplants that exist now are compelling and that going forward, given that there is progress in the transplant field, that there should be ongoing analysis of current transplant data in a post-market analysis. And then a note that the race breakdown for patients who are unlikely to have matched donors will be more diverse in the population treated so far and that will be something important to look at.

So, that's what I heard. I'll look for a quick hand. If not, otherwise, we'll go on and discuss Question Two and then Question Three and our vote. All right --

MR. MICHAEL KAWCZYNSKI: So, Dr. Butterfield, as a reminder just to those who are answering questions, if at any time you are there for support, raise your hand. It'll help us identify you faster so

we can answer those support questions. So, there you go. Take it away.

DR. LISA BUTTERFIELD: Thank you. So, Question Two, "Three eli-cel treated subjects have developed myelodysplastic syndrome, MDS. Subjects with sickle cell disease treated with a related product, lovo-cel, have been diagnosed as myeloid malignancies. Please discuss the extent to which the myeloid malignancies associated with lovo-cel raise concerns regarding risk for hematologic malignancy with eli-cel."

So, we have two discussants. First, Dr. M. and then Dr. DiPersio to get us started for Question Two.

DR. JAROSLAW MACIEJEWSKI: Yes, thank you. Can you guys hear me?

DR. LISA BUTTERFIELD: Yes. Thank you.

DR. JAROSLAW MACIEJEWSKI: Hello, again. As mentioned before, there's three patients who developed this unusual form of myelodysplastic syndrome, which the co-currents with EV1 and the other cases of clonal

hematopoiesis are indeed concerning that it has something to do with this particular gene. It's not an MDS. Typical MDS, it's very unusual for MDS to get this particular variant. Usually it's typical to find it in very advanced MDS ones and in leukemia because these particular genetic hits are very sweeping in terms of the clonal architecture of the leukemia.

So, the question is how are the other cases using the other product affect our worrying? And I think that they are different because they don't have these typical L7, and they are not typical myelodysplastic syndrome or treatment-related neoplasm that are seen in relatively high frequency in auto transplant for malignant conditions first mentioned by John. The conditioning there is different, and it may be that patients are treated or heavily treated for the original malignancy.

But autologous transplant has increased rate of treatment related secondary malignant, and these seem to me in the other cases -- seem more like typical treatment related neoplasm. The previous studies have

shown that in people that the usage of hydroxyurea is not associated as high risk, but one cannot help believing that if I go through cases that I know use of hydroxyurea is sort of concerning, particularly in younger patients who receive it for years.

So, this might be contributing factor that the conditioning itself, and I don't know that we don't need to invoke the concerns with this other product, with lovo-cel, in order to be concerned about the EV1-related clonal evolution. I would separate them from each other.

So, this has to be weighted, of course, against the overall risk of the disease which is such overwhelming that it occurs that the benefit ratio has to be the right of the patient. Then, of course, if this treatment does not get approved, they will have not this benefit. So, the imperative would be to give more understanding to the mechanism of this EV1 that it's hard to oversee given the fact that it's genes so intricately involved in the particular prognosis subset of AML.

And so, as explained by somebody here as because it frequently integrates, it would frequently occur in the clonal context, but then one would have involved there is other superseded ancestral event. And this would be only a passenger event and sort of given the nature of the gene hard to believe.

DR. LISA BUTTERFIELD: Thank you. Thank you for those perspectives. So, Dr. DiPresio, do you want to address question two, please?

DR. JOHN DIPRESIO: Yeah. So, I agree with Jarek (phonetic). Really, he answered both Questions Two and Three, I think, and I think I agree with him regarding both responses. Number one, as I think the malignancies that have occurred in the lovo-cel setting are more consistent with a treatment-related MDS or AML -- secondary AML with sort of classic kinetics of presentation and classic cytogenetic abnormalities and mutations.

But yes, one of these cases was associated with integration of the lentiviral genome. I think it may be true, true unrelated, as Jarek said, that you

integrate that lentivirus and lots of stem cells and there is one stem cell in millions that has two other mutations and they are at very low vats and persist but then expand over time, they may be driving the disease in the context of this MDS or AML. And it's not the lentivirus per se. It may do something, but -- and also in the sickle cell patients, they have a very stressed hematopoiesis. It's an inflammatory disease.

The patients are constantly in the hospital with fever, vaso-occlusive crises. This is the kind of setting that induces ROS inflammation, and everyone knows that this probably puts patients at risk for generating these malignancies. Their marrows are under great stress, and so I think -- and also, we know that the incidents of heme malignancies in these patients is ten times the normal population. And the incidence of heme malignancies in this trial was about 20 to 30 times higher than the baseline sickle cell population.

So, I just want to say one other thing, and that is clonal hematopoiesis is never seen in a mouse. But -- because the mice don't live long enough, but if

you stress a mouse by doing a transplant, you can get clonal hematopoiesis to occur in mice. And if you do sequential transplants in mice, there are clones that expand over time. So, it's stress -- hematopoietic stress may be one of the contributing factors for the lovo-cel.

For the other product, there is really kind of a smoking gun here, it seems. I still am not convinced that this is true, true unrelated. That is that this may not be the driver, and there may be just other incidental drivers. I'd like to know more about some of the other mutations that occur. And again, the conditioning regimen for these patients is a conditioning regimen for which we have no control group, and all we have is patients that have gotten autologous transplant with less toxic drug than Busulfan. Less. And those patients have MDS rates of four to ten percent at five years, so not out of control compared to what we're seeing here.

The final issue is that Jarek raised the issue of toxicity of transplant and how we're getting better

at that. And that's true. We are able to do mismatched transplants and haploidentical transplants and mismatched unrelated donor transplants, and I've been transplanting patients for 40 years. And one of the things that even with haplos and even with modern therapy, that the rates of acute and chronic graft - chronic is a little bit lower, but the rate of acute GvHD is as high as a matched unrelated donor transplant.

And so, these patients -- and even though kids have it a little easier time than adults, these patients do have really persistent overwhelming problems, and that's what I was mentioning earlier. When you're really looking at outcomes and you look at the outcome of an autologous transplant recipient who gets one treatment and then is gone forever and feels well forever versus an allotransplant patient which is in your office every week getting adjustments so their immunosuppression, multiple infections, steroid related complications -- everything you can imagine.

But the endpoint should be not whether their

disease is worse or whether their GvHD is worse but a composite endpoint. What's their quality of life related to GvHD and to their underlying disease? And I think that that was not really brought forward by the FDA, and my guess is that there's nothing better than the quality of life of an autologous transplant patent. And there often is nothing worse than the quality of life for an allotransplant recipient who's successfully transplanted.

So, all of those things suggest to me that even though there are substantial risk for this population, I'm convinced by what I saw and by what everybody said that this is probably a worthwhile endeavor for these high-risk patients.

DR. LISA BUTTERFIELD: Thank you very much for those perspectives. I see three hands to further discuss Question Two. Dr. Ott, Dr. Hawkins, and Dr. Ashan. So, please, Dr. Ott.

DR. MELANIE OTT: Yes, thank you. I wanted to just report both speakers' opinions. Also, from the virology side, I would say that these two treatments

are quite different from the vector perspective. One is really a very strong ubiquitous promotor that is likely causing larger problems. The other one is a cell type specific promotor that is more physiological, and I think for that reason I would also separate these two and not consider them the same entity here.

I think the key is really to find out what is happening in the eli-cel vector and whether it is a strong connection with the vector. And I just encourage the company to further investigate and develop that vector.

DR. LISA BUTTERFIELD: Thank you. Dr. Hawkins.

DR. RANDY HAWKINS: Thank you. So, the FDA is asking (audio skip) suggestions about monitoring for these patients. I'm an adult physician. I'm an internist and pulmonary physician (audio skip) for adults. My approach is somewhat simplistic because I don't understand as much of the science as I would like to, although, I've certainly learned a lot. Despite what we know about the situation moving forward,

there's a lot that we don't know, and we've spoken about the small numbers.

I think it would be a mistake to miss the opportunity to continue to provide this tool to these patients and people because they have the opportunity to learn potentially more about what's going on. And by that I mean that where there's a risk we're all aware of shared decision making, we can actually learn more about these entities we don't know quite enough.

And with the oversight FDA provides, (audio skip) and generally we want for patient care and improve quality of life, we need to continue to study to understand information. And if we determine that this risk is too great five years from now, then we say this is not something we can do if the risk-benefit ratio moves us towards doing this rather than assume based on the data we have now that it's too dangerous. And I agree with Dr. Butterfield's summary of Question One.

DR. LISA BUTTERFIELD: Thank you. All right, Dr. Ahsan, and then we'll finish Question Two with Dr.

Coffin, afterwards.

DR. TABASSUM AHSAN: Thanks. I just want to reiterate a couple points. Right, so for Question Two it's really looking at whether lovo-cel and the observations related to lovo-cel have any implications as related to eli-cel. That's the question that we're focused on at the moment, and I agree with -- I leave it to the clinicians -- and I'm not one of them -- to discuss the differences in the treatment paradigms and how that may affect the observation. And so I think they articulated that nicely that there's a difference.

And I want to echo what Dr. Ott said, which is that the product definition of what is going into these patients is actually quite different, and so I don't think that there is necessarily a correlation between one and the other. I will raise the issue that I don't think that they did a very good job in terms of tracking how oligoclonality can be related to MDS. I think that they can dig deeper into that, and they can actually present the data in a more clean fashion that makes it easier to actually look at the relationship

between those activities.

But I don't think, that based on the product definition in a way the vectors are defined, that there is necessarily an increased concern about eli-cel based on the observations of lovo-cel. The other thing that I did not really -- I wish that the sponsor would expand on a little bit more is that relationship between VCN and the percent (audio skip) and efficiency. They presented them independently. They didn't actually make a bivariant plot of those which really gives you some good information.

But again, I think, regardless of some flaws and how they could've presented the data more cleanly, I don't think that there is necessarily an increased risk to eli-cel based on the observations of lovo-cel based on the product definition.

DR. LISA BUTTERFIELD: Thank you. And finally, on Question Two, Dr. Coffin.

MR. MICHAEL KAWCZYNSKI: Dr. Coffin?

DR. LISA BUTTERFIELD: We can't hear you yet, Dr. Coffin.

MR. MICHAEL KAWCZYNSKI: There we go. There we go. Let's see if we got you now. Let's see. There, you back now? Go ahead, sir.

DR. JOHN COFFIN: Can you hear me now?

MR. MICHAEL KAWCZYNSKI: Yup, go ahead.

DR. JOHN COFFIN: Now you can hear me. Okay. Yeah, I was really just going to weigh in pretty much agreement with everything that was said so far in regards to this question just to put a second virological vote into it -- not really a vote, but a second virological point of discussion. I think there is not much of a smoking gun in the lovo-cel as far as there being a virological emerging of the diseases which has come up. And I'm glad to hear from the other -- from the people who know better than I that this is probably not unexpected in the case of sickle cell patients who've been transplanted, although the numbers may be different and so on and so forth.

And also, I would point out that I think the comparison with lovo-cel and beti-cel with eli-cel actually gives some optimism that a much better vector

could be found for this, one that focuses the promotor to the cell site that's really important for the disease. And I think there's a lesson there that for bluebird and for others interested in developing these kinds of things that ten specific promotors are not a good thing to use in this context.

And although we don't know for sure, the others -- what the outcome will be ten years from now, it certainly looks promising that in the other cases we're not getting at least anywhere near the level of these kinds of problems that we're concerned with in this particular context. But that's all I've got to say for this.

DR. LISA BUTTERFIELD: Great. Thank you very much. So, if I can summarize the discussion of question two, what I heard is that regarding the extent to which the lovo-cel observations impinge on the eli-cel concerns, the panelists who spoke said that these are really different settings. They are different viral vectors, different promotors, different treatment settings and that they don't -- that any lovo-cel

observations are not directly concerning. For eli-cel, that there's certainly need to continue to examine the mechanisms of viral integration to understand all these sites of integration. The lovo-cel malignancies that have been seen are more of a classic form; the eli-cel are more of a not typical setting -- again, pointing to key differences -- and that there might be opportunity to think about improve next generation vectors and other learnings by examining these mechanisms and differences between the two vectors and the two diseases and the two treatment settings, where sickle cell has a very stressed hematopoietic setting.

So that's what I heard. Not seeing any hands shoot up, so let's move to discuss our final -- our third question, and that is that "Eli-cel has a risk of heme malignancy, which is a potentially fatal adverse event. The number of cases of malignancies, currently 3 out of 67, or about 4 percent, which seems likely to increase over time. In addition to the three recognized cases of MDS, there are least four other subjects with concern from pending MDS. Although the

clinical significance is unclear, 98 percent of subjects in the eli-cel study population have vector integration sites that include MECOM, a proto-oncogene.

"Please discuss the risk of insertional oncogenesis in patients with early active childhood ALD treated with eli-cel." So, we'll start with Dr. Shah. Thank you.

DR. NIRALI SHAH: Thank you. Can you hear me okay?

DR. LISA BUTTERFIELD: Yes.

DR. NIRALI SHAH: Perfect. So, I feel confident about the potential benefit of this therapy for children with ALD given the natural course of the disease without transplant and eli-cel and agree with the points that have been raised in the first two discussion questions. I think that one of the primary indications for eli-cel specifically to avoid transplant toxicity, particularly GvHD in the mismatched unrelated donor setting and to avoid transplant.

So, we're given that transplant is the only

curative therapy for MDS. The question that I end up being left with is what is the threshold at which the MDS incident is what can be considered non-acceptable and if whether the data we have on file is sufficient to feel confident that the benefit continues to outweigh the risk, particularly, as we know that transplant supportive care is improving.

I think the other point that I wanted to make is that, while there is historical data on pediatric MDS and what the outcomes may be, I don't know how much we can rely on that data to determine the outcomes of gene therapy-induced MDS due to insertional oncogenesis.

Although, it's promising that two of the three patients who are accessible for remission status are currently doing well and in remission. While the median follow up time on all patients is longer, but for the ALD-104 the median follow up is only six months and the concerns that have been raised have only relatively recently arisen.

On the other hand, I think that we all

appreciate that if the children are able to live long enough to develop this toxicity which seems to be occurring at about as early -- the earliest time I think to be about two years -- that we're halting the progression of their disease, and that this is leading to both improved event free survival without progression of CALD is clinically meaningful.

So, I think that the concern from MDS is of concern, but I think that the question I'm really left with is what will we do to implement, if this is approved, the safety to monitor both the ongoing incidence of MDS as well as the outcomes for this treatment of MDS should the children develop it.

The other thing that I want to also be mindful of is that assuming that the indication is for those who do not have a matched related donor -- it's really for the mismatched unrelated donor -- that that same population is also going to have the same donor selection availability for even their MDS, and so we'll have to be mindful of monitoring what those outcomes are. But I think given where we're at right now, it

remains a concern, but I still think the benefit to eli-cel is important and outweighs the risk at present moment.

DR. LISA BUTTERFIELD: Thank you very much, Dr. Shah. Dr. DiPersio.

DR. JOHN DIPERSIO: Thank you. So, I agree completely with Nirali. I think that the benefit outweighs the risk in this particular situation, and I understand what the risk could be in the future. The risk could be based on the appearance of a smoking gun here is that over the next four or five years we'll find that the frequency of evolution to MDS is much higher than we expected. I can just tell you that this is not the usual MECOM kind of mutation or rearrangement or clinical scenario.

There are really two kinds of MECOM related defects we see in adults with acute leukemia, and that's one with a classic EVI1 rearrangement. And those patients have overexpression of EVI1, but they almost always have a very fulminate acute leukemia which is really unable to be treated with anything.

And then there are a very small population of patients with MDS associated MECOM rearrangements or EVI1 rearrangements, and they actually have a different clinical course. And their course is tremendously impacted by other mutations, though, in particular RUNX1, which was present in one of these patients, and TP53 mutations. And so we know a lot about some of the things that modify the progression of the disease.

The most important observation in this group of patients that might develop MDS associated with MECOM-1 is that early identification of disease, which is at a lower stage IPI, a low risk, results in a much better outcome with transplant, and that's in the adult setting. But when it's actually developed into acute leukemia, then the chance of cure is very low.

So the issue of monitoring and surveillance becomes incredibly paramount, and so I think that our suggestions or the FDA's suggestions would be to develop a very rigorous approach in these patients to really follow all of the things, including variant allele frequencies using error corrective sequencing,

maybe even RTPCR -- whatever it takes to really -- frequent bone marrow biopsies -- whatever it takes to intervene early in the potential allogeneic transplant of patients that look like they're progressing because they're the only ones that seem to be cured with the MECOM-1 rearrangement. That's all I have to say.

DR. LISA BUTTERFIELD: Thank you very much. All right. I see three additional comments from the Committee for Question Three. Dr. Ott, Dr. Coffin, and then Dr. Shah. Dr. Ott, please.

DR. MELANIE OTT: Yes. Yeah, I think they're all very valuable insights into our perspective. I want to come back to the question that the FDA asked us before about what would be valuable in terms of monitoring and what could be done. I really want to also come back to what John said before that this is maybe a lesson to be learned in terms of the promotor change in that vector that might make a difference if there's effort to find out what cell type is actually relevant in the brain implant of these HFCs as I think that would be enormously reducing the risk if we could

tailor the promotor to that cell type.

I also think that the gene expression of MECOM, and potentially PRDM16 and others that have been identified, could really be used more effectively in predicting whether clonal expansion is going to occur to see whether there's really a gene expression dysfunction in use by the integration of the vector close to it.

And I also think that the perspective that this is not really a typical MECOM malignancy clinically I think is also very valid because I think it comes back to the point that it's going to be a multi-hit pathogenesis here, and I would say that these multiple integration sites that we see and these expanded clones should be better used to predict and potentially correlate with MDS development. Thank you.

DR. LISA BUTTERFIELD: Thank you. Dr. Coffin.

DR. JOHN COFFIN: To the extent to which all of the additional MECOM mutations or insertions that are seen is a smoking gun for future problems, I couldn't get a handle on, and I didn't get very good

answers, I'm afraid, from the sponsor. It really comes down to what quantitative issues, what are the frequency of these insertions relative to what you started with when you put the cells into the patient. And they could have and should have, in my opinion, taken a small sample of some of the patients before they started and done the integration site analysis on them. If they did that, they certainly didn't share it with us.

But that would have been -- then the frequency of the integrations that you saw in the patients would've been much more meaningful, the frequency of which you saw integrations in MECOM, particularly if they were focused in the same intron which is unfortunately rather large and about half the genes as far as I can tell from the map she showed. But if their frequency and the same intron and the same orientation were coming up with a lot of frequency, then you'd feel quite differently about it then if things were just scattered mutations all over the gene at those orientations.

There were a lot of scattered integrations that she showed, but the diagram she showed was really nowhere near clear enough to tell whether there was a subpopulation that actually looked like it was clonal expanding and that looked like it was oriented and in a position to cause the same kinds of effects. That said, I am not worrying about this, but I think -- at the moment I think we have to agree that the risks of this will outweigh the benefits at least in the unmatched allotransplant population.

But very close monitoring -- I think there should be two things. One is very close monitoring of these patients, as tight as FDA can insist on really, and also, I think it's very important to do meaningful mechanistic studies of what's going on. We have to understand what the relationship of the integrated provirus and promotor and so on is to the actual pathophysiology of the disease that's seen. And what is the role that additional mutations are possibly -- that may be additional hits by integration, or they may be just other mutations by other means.

All of this needs to be watched very closely in post approval, assuming that it is approved.

DR. LISA BUTTERFIELD: All right. Thank you very much, Dr. Coffin. Dr. Shah.

DR. NIRALI SHAH: It goes back -- I think we're hearing the same things from the other presenters. But again, I think we just need to reiterate that we don't know a lot about this particular form of MDS, and I think that the natural history of being able to treat insertional oncogenesis potentially related MDS is unknown. So I think that will have to be very closely characterized.

And I think that it should be clear that if at present moment we're assessing the risk based on the three cases, but that we do think about what level we're willing to accept overall knowing that, again, that patient population that is most likely to come to eli-cel is going to be the same population that does not have good, related donor options which is why they're choosing this in the first place. The long-term monitoring is going to be critical to the next

step.

DR. LISA BUTTERFIELD: Thank you. So, my cameras have frozen. Can you still see and hear me well enough?

MR. MICHAEL KAWCZYNSKI: Yeah, we can hear you. Let me just give it a shot here.

DR. LISA BUTTERFIELD: Okay. So I don't see any additional hands up to weigh in on Question Three, so I can summarize. And then I'll ask our FDA colleagues if they have additional questions for the Committee. So --

MR. MICHAEL KAWCZYNSKI: I think you had one more.

DR. LISA BUTTERFIELD: Do we have one more?

MR. MICHAEL KAWCZYNSKI: Yup. Just in case you had -- Dr. Ahsan do you have your hand up? Dr. Ahsan, make sure you unmute yourself, please. Dr. Ahsan, please unmute yourself. Hold on a second here. She's muted, so take it away, Dr. Butterfield.

DR. LISA BUTTERFIELD: Okay. So, I'll summarize what I heard for Question Three about MDS,

which is certainly seen by the Committee as a real concern, certainly seen as something that the Committee thinks is likely to increase in frequency given the current data.

But the risks of GvHD toxicity versus the risks of the CALD disease are nonetheless currently seen as favorable. The future is not yet clear to what extent will there be additional MDS cases in a higher frequency, and notably the eli-cel patients who lack autologous donors -- unmatched donors would also then be in a less favorable transplant situation for treatment of MDS if that's required.

So there's really an agreed need for a detailed surveillance, sequencing biopsies to be able to, one, intervene early in the MDS to have the best opportunity for treatment, but also, again, to understand the mechanism of action with this vector in the eli-cel product and to collect baseline product sequence integration data and other data to shed light of the mechanism of the MDS.

Should I sign out and sign back in because my

screen's not come back to life yet?

MR. MICHAEL KAWCZYNSKI: Yup, go ahead, and you can do that. And we'll hand it over to Christina while you're doing that. Just stay on the phone.

DR. LISA BUTTERFIELD: I will stay on the phone and will ask Dr. Bryan if FDA has other questions for the Committee before we move forward.

DR. WILSON BRYAN: Thank you. No other questions at this time. We'll look forward to the voting questions and particularly the explanations from the individual members on how they voted.

DR. LISA BUTTERFIELD: Thank you. Okay. I hope I've signed back in again. Okay, Christina.

DR. CHRISTINA VERT: Dr. Butterfield.

DR. LISA BUTTERFIELD: Handing it back to you for the vote.

DR. CHRISTINA VERT: Oh, okay. I'll go ahead and get started. Only our six regular members and nine temporary voting members, a total of 15, will be voting in today's meeting. And with regards to the voting process, Dr. Butterfield will read the final voting

question for the record, and afterwards all regular voting members and temporary voting members will cast their vote by selecting one of the voting options, which include yes, no, or abstain.

You'll have one minute to cast your vote after the question is read, and please note that once you cast your vote you may change your vote within the one-minute timeframe. However, once the poll has closed, all votes will be considered final, and once all the votes have been placed, we will broadcast the results and read the individual votes out loud for the public record.

Does anyone have any questions related to the voting process before we begin? And also if you feel you need more than one minute to cast your vote, let me know if you need more time. We can increase the voting time to two minutes, and also if I need more time, I will extend the time as well.

DR. LISA BUTTERFIELD: Thank you.

DR. CHRISTIAN VERT: Mm-hmm.

MR. MICHAEL KAWCZYNSKI: We have a question

from -- we have one question here.

DR. JOHN DIPERSIO: I just want to make sure that if the voting thing comes up on the screen here, where do I find it? I missed the beginning so.

MR. MICHAEL KAWCZYNSKI: Yeah, so it'll come up on the screen. We haven't pulled it up yet, sir.

DR. JOHN DIPERSIO: Okay. All right. That's all, sorry. I'm good.

DR. CHRISTINA VERT: And please wait. I'll tell you when to star the voting. Okay. So, yes, another question from Dr. Lee?

DR. JEANNETTE LEE: Yeah, this is Jeannette Lee. Is there more than one question we're going to answer today?

DR. CHRISTINA VERT: Yes.

DR. JEANETTE LEE: Okay.

DR. CHRISTINA VERT: There's two questions.

DR. JEANETTE LEE: Okay. Thank you.

DR. CHRISTINA VERT: We'll show them. They'll be a slide.

DR. LISA BUTTERFIELD: Okay.

DR. CHRISTINA VERT: I don't see any more questions, so we'll go ahead and get started. Dr. Butterfield, please read the voting question.

DR. LISA BUTTERFIELD: All right. Voting Question One, everyone. "Are the lovo-cel safety data relevant to the safety assessment of eli-cel?" And hopefully your --

DR. CHRISTINA VERT: Okay. At this time, you can go ahead and vote. Select your voting choice. I'm going to extend the time a little bit because I'm going through the votes.

DR. LISA BUTTERFIELD: Do we not have all the votes yet?

DR. CHRISTINA VERT: I am checking right now. Okay. Let's go ahead -- I'm going to end the vote. And we can broadcast the vote results. Okay. All right. Let's see what we have here. Hold on. Okay. Okay. All right. There are a total of 15 voting members for today's meeting, and as you can see, we have one yes vote, 13 no votes, and one abstain. Okay. And so, the vote does not pass for that particular

question.

I will now read the voting responses of each voting member for the record. Okay. Randy Hawkins, yes; Amylou Dueck, no; John Coffin, no; John DiPersio, no; Sylvia Anspach, no; Bernard Fox, no; Steven Shapero, no; Melanie Ott, no; Nirali Shah, no; Jaroslaw Maciejewski, no; Jeannette Lee, no; Taby Ahsan, no; Lisa Butterfield, no; Stephanie Keller, no; Donna Roberts, abstain. And that concludes my reading the voting responses of each member for the record.

And now we can go to the second voting question.

DR. LISA BUTTERFIELD: All right. Voting question number two, "Do the benefits of eli-cel outweigh the risks for the treatment of any subpopulation of children with early active cerebral adrenoleukodystrophy, (CALD)?"

DR. CHRISTINA VERT: Okay. Let's start voting. Looking one more time. Almost done here. Okay. Okay. We can close the poll. All right. Okay. Okay. So, you can broadcast the vote results. Okay.

Again, we have 15 total voting members for today's meeting, and we have a unanimous vote of 15 out of 15 yes votes. The voting question passes unanimously. I will read the voting responses of each voting member for the record. Okay.

Amylou Dueck, yes; John Coffin, yes; John DiPersio, yes; Sylvia Anspach, yes; Bernard Fox, yes; Steven Shapero, yes; Melanie Ott, yes; Randy Hawkins, yes; Nirali Shah, yes; Donna Roberts, yes; Jaroslaw Maciejewski, yes; Jeannette Lee, yes; Taby Ashan, yes; Lisa Butterfield, yes; Stephanie Keller, yes. And that concludes my reading responses of each voting member for the record, and I will now hand the meeting back over to Dr. Butterfield to ask the Committee for their voting explanation. Thank you.

DR. LISA BUTTERFIELD: Thank you. Well, thanks everyone for voting. What we need to do now is to go around and you can see after the voting questions we're asked to explain our vote. For those of us who voted yes to -- and just to clarify, we're only discussing our vote to the final Question Two about

risk benefit and not the first question about the lovo-cel safety data. Is that correct?

DR. WILSON BRYAN: Yes, that's correct. Thank you and let me ask that part of the explanation is about risk mitigation and monitoring. We ask the Committee to be as specific as possible in your recommendations regarding the population and any monitoring that you think would be appropriate.

DR. LISA BUTTERFIELD: Thank you, Dr. Bryan. Yes, so it's up there on the screen, and so all of us did vote yes -- all 15. So when we go around what we need to each weigh in on are the subpopulations of children for whom we believe there's a favorable benefit-risk profile, any additional information we would consider necessary to support a favorable benefit-risk profile in any other subpopulation, and then any recommendations for risk monitoring and mitigation in who receives eli-cel. So those are the three things for us to touch on as we go around and so let's see. I'm going to go back to the email I received that does list the voting members.

And so, I will go top to bottom which -- the voting members and then the temporary voting members, I'll just go down this list. My name is first as chair, and my yes vote was the subpopulation who I believe there's a favorable risk-benefit profile is those without a matched donor for hematopoietic stem cell transplants.

I did not have any specific additional information I would consider necessary to support a favorable profile in other subpopulations. Perhaps our clinical colleagues will have more suggestions there. And then my recommendations for risk monitoring and mitigation is to continue in-depth molecular analysis including integration site sequencing and clinical monitoring to catch any MDS early when it's easier to treat.

With that, I move down the list to Dr. Fox. After that it will be Dr. Lee, Ott, Shah, and Ahsan, and then I'll move to the non-voting members. Dr. Fox.

DR. BERNARD FOX: So, I thought that this is absolutely -- for the mismatched patients it's

absolutely necessary, but I think that even for with an unrelated matched donor that those patients should be -- - the mismatched unrelated donor -- or matched unrelated donor should also be an option for the decision and discussion, so I felt very strongly that listening to Dr. DiPresio talk about his 40 year experience and the issues of GvHD in that population that destroys the necessary -- I think to have that be an option for physicians.

I think, two, the question about the monitoring -- the issue, given where we are today and that the technology that's available, I think that some of the points that were brought up about RNHC and I would think -- I don't know the role for things like single cell, but I would be very aggressive in looking at the mechanism of action for why you're getting myelodysplastic syndrome in these patients. And I think there's probably lots of tolls -- I'm not an expert in that area, but I can't imagine our great tools to really dissect that and be looking at that.

And then the regular -- I'm not sure what the

timepoints are for the blood draws -- CDC's or potential bone marrows -- but I think the clinical people will be on that. I would support an aggressive monitoring of these children, these boys.

DR. LISA BUTTERFIELD: Thank you. Dr. Lee.

DR. JEANNETTE LEE: I agree with the subset of those who don't have a matched donor as a subpopulation of who would benefit the most. I don't have any specific additional information needed to support a favorable benefit-risk profile. Again, I do endorse aggressive monitoring, not only for MDS but I think follow-up in general. So, I think it's an opportunity to see how these children do with the (audio skip). Thank you.

DR. LISA BUTTERFIELD: Thank you. Dr. Ott.

DR. MELANIE OTT: Yes, I also support the application to patients with no HLA matched donors, for number one. For number two, I think it would be good to have a better matched data to make a decision about the matched unrelated donors that were also mentioned and also by some favored here. But I felt that here

the information and potentially the discrepancy between the study groups that the FDA has pointed out might make a difference and to revisit this and clean this out would be beneficial.

And my third recommendation is also very close monitoring for the MDS but also to look early into before transplant into prevention and to see what we can do there to identify either by integration sequencing, expression, profiling -- those at risk that develop years later so that we can actually by the time for transplant potentially decide whether that transplant should not be made.

So, I think there's an opportunity here in this early phase after the transduction, before and after the transduction of the hematopoietic stem cells to really include some more steps that could potentially lead to prevention of the MDS.

DR. LISA BUTTERFIELD: Thank you. Dr. Shah.

DR. NIRALI SHAH: Thanks. So, for the subpopulation, I agree with everybody else. It should be for those without HLA matched donor or those who

have a mismatched donor. For additional information for other subpopulations, I would recommend that they conduct an ongoing assessment for the role of transplant. In particular, haploidentical transplant in patients to conduct a contemporary analysis that is parallel to the approval to evaluated the efficacy of transplant.

In particular, be mindful that whatever forward-facing analysis that they do addresses the issues that the FDA raised as it related to the benchmark calculation and comparability, and I think that this becomes even more important, particularly as newborn screening increases and patients are going to be referred for treatment earlier when they're less severely affected. So, I think knowing that will be important.

In terms of recommendations, I think that I would agree with the recommendations, continue the integration site analysis that they have planned. I would like to see the incidence of MDS and AML developed in the population at least in every six

months basis, and I would like to make sure that the outcomes for the treatment of MDS and AML are captured.

DR. LISA BUTTERFIELD: Thank you very much. And final voting member, Dr. Ahsan.

DR. TABASSUM AHSAN: Yeah, I think I'll echo what others have said about the subpopulation. I think that those without a matched donor are a good patient population for this, for the eli-cel. I think those that do have potential for a matched donor, we should leave that option open to the clinicians to do it on a case-by-case basis. I think Dr. Shah very nice articulated some things that they should consider about making that evaluation.

In terms of what might support a more favorable benefit-risk profile, I think that we need the sponsor to continue to track very closely the onset of MDS but also evaluating the quality of life through various tools after the onset of MDS. Do the same for those with graft versus host disease, track when the onset is, the quality of life afterwards. I think that that's just the real question about this is not about

the efficacy which might be similar, but the benefit is really in terms of the onset of MDS versus the onset of graft versus host disease.

So, tracking those I think is really important to really deeper understand the benefit-risk profile. Also, in terms of risk monitoring, I think what they've been doing needs to be augmented a little bit. I think about things in a couple of different ways. I do think that they need to look at the drug substance and the drug product attributes. I'd like to see tighter tracks over time for the different lots, BCN, and percent production in the drug product and then, of course, tracking in the patient as well in insertional site frequency, et cetera, to really have a deeper understanding of how this oligoclonality might be related to MDS.

DR. LISA BUTTERFIELD: Terrific. Thank you. So, let's move to the temporary voting members. Drs. Dueck, Roberts, Dr. M., DiPersio, Coffin, Hawkins, Keller, Shapero, and Anspach. Dr. Dueck, please.

DR. AMYLOU DUECK: All right. So, I will

agree with all the previous folks and agree with the HLA unmatched donors group. I didn't think any further information is needed to support favorable benefit-risk in other subpopulations. In terms of recommendations for risk monitoring and mitigation, I agree with continued monitoring and reporting of MDS, AML for early diagnosis and treatment.

I also think it's important to report the subsequent outcomes of those diagnosed with MDS and AML so we understand what those ultimate outcomes are. And that's it.

DR. LISA BUTTERFIELD: Thank you. Dr. Roberts.

DR. DONNA ROBERTS: Yes. I didn't feel like I had the genetic expertise to comment on the first question, but on the second question I felt that this product was indicated for non-matched donors. I also think that there's a use in non-related donors that could be left up to the clinician and patients' discretion. As far as additional information that's needed for other populations, I think that we need more

data understanding the risk and benefits of this treatment versus stem cell transplant.

I like that the sponsor has already stated that they're planning on doing post-marketing monitoring and also offering the treatment in a limited number of sites with the expertise to carry it out. Some information that I think would be good to have too is more information on racial and ethnic subpopulations and how they respond to this treatment. One of the things that there was a discrepancy between the neurologic functions score and the MRI findings in that the Loes scores increase whereas the neurologic findings didn't, and I'd like to understand that better in patients treated with this. And so, I think maybe looking at something like lesion volume on MRI scans and other findings on MRI scans might give more information about that.

And we discussed some malignancy issue, but another issue that has the potential to be serious was the incident of seizures in these patients. The sponsor mentioned that they were limited, but I saw

that some of the patients had repeated seizures. And so I think that would be another important issue to follow up on. But overall, I think this is a very important product to have on the market.

DR. LISA BUTTERFIELD: Thank you very much. Dr. M.

DR. JAROSLAW MACIEJEWSKI: Well, I voted -- this Question One, right?

DR. LISA BUTTERFIELD: Yes. So, this is Question Two about efficacy, and we're looking at the -- since we all voted yes, we're looking at those three subquestions at the top of the screen.

DR. JAROSLAW MACIEJEWSKI: Yeah. Yeah, I see only A and B. I see only two sub question. Are we talking about going to A?

DR. LISA BUTTERFIELD: We're all on A because we all voted yes.

DR. JAROSLAW MACIEJEWSKI: Yeah. I think the monitoring is important for both. For ongoing results of a competitor procedure memory allogenic bone marrow transplant, particularly, why we need it to salvage

those patients who develop malignancy. Two patients got transplant already, and if the rate will continue, then I think that it's important to see what the outcomes of the allogenic transplant without this would be to be able to share with patient, pros and cons.

The post-market monitoring should include the results and monitoring for the presence of -- for the outcomes and the risk-benefit but also for alternative procedures. That's good to have them for the patient and family assessment of the options available.

DR. LISA BUTTERFIELD: Thank you. Anything else?

DR. JAROSLAW MARCIEJEWITZ: No.

DR. LISA BUTTERFIELD: Okay. Dr. DiPersio.

DR. JOHN DIPERSIO: Yeah. So, I agree the primary population should be mismatched donors, but I'm inclined to include the matched unrelated donors as well. It should be left up to the discretion of the physician and the family and the patient. I think that I would actually ask them to do sort of an analysis with the CIDMTR (sic) to look at patient related

outcomes after matched unrelated donor transplants compared to the patients in their study.

As far as other issues relating to things like GvHD and disease related progression -- the patients that have GvHD-free and disease-free progression -- that's the most important category. And then do some post-marketing issues with patient related outcomes, too. I think that would show a dramatic difference between the groups. And then recommendations regarding monitoring, I don't think I have anything to add to what everyone else is said. I think that there are -- there's lots of biology and lots of important work that needs to be done and wasn't done. I was really struck by the lack of analysis of the sub-clonal architecture of these MDS patients.

What were the driving underlying mutations, and how were they progressing over time? So those are the kinds of things that I would want to know, and I think you have to do this by not just regular panel sequencing but by corrective sequencing to really get very sensitive measurements of progression of these

clones and see if some of these other genes outside of the integration events are associated with driving the disease forward.

DR. LISA BUTTERFIELD: Perfect. Thank you. Dr. Coffin.

DR. JOHN COFFIN: Yeah, I agree with everybody else that the mismatched subpopulation is the one to recommend it's certainly for. Regarding the second question, I agree with the sponsor's approach and that several others have also, that this would be up to the physician in consult with the family and patient, of course. One of the things I would recommend in this case, though, would be some intensive survey to assess the quality-of-life issues that are involved in this decision. We heard a lot of questions about that.

We didn't hear anything that was really real data, just lots of parents had real problems, but the ones that didn't have problems we didn't hear from. And so we don't really know what the numbers of are as far as being able to weigh these issues in the quality of life. I would strongly recommend some surveys on

that by well-established outcomes type clinical researchers.

And again, as I said before for number three, I think the patients should be monitored very intensively both for risk assessment for progression and for mechanistic issues that might well inform further development, by bluebird or by others wanting to get into this field or in this field. For example, some ideas about whether change in promotors would be something worth doing for example. And lots of mechanistic issues have also been raised by others -- additional mutations, RNA analysis to understand how these genes are being driven and so on and so forth.

And one other point is that I would also -- the issue was raised that many of the patients who are in this group will be ones who are there because they did not have a good match to begin with, particularly minorities of various kinds, and one of the issues there is that in the case where you have the CLD, you're really under the gun for the transplant. The time is very short as far as I understand it before you

get irreversible damage.

I would guess that the time could be much longer when you have to do -- if you have to do a transplant later on because of MDS, you might have a much longer window, and it might be worth researching the availability of transplants as soon as you begin to suspect that something -- that some adverse event like MDS is on the horizon even though you don't know it for sure. It would never to be too late, or too soon rather, to try to begin to discuss with the donor pool to see if probably somewhat broader window assigned to do it before it's too late.

DR. LISA BUTTERFIELD: Thank you. Dr. Hawkins.

DR. RANDY HAWKINS: Thank you. Yes, thank you. So, what was stated before, I'm not going to repeat it. I would like to say this is a perfect opportunity, I believe, to elevate the need for potential donors in addition to reaching out to all potential donors -- all citizens, particularly to reach out to those groups that have difficulty with matches -

- Asians, African Americans, and Hispanics to deepen the pool of potential donors so whenever there's something that comes out -- and we have to see what FDA says, this is the time when people -- you have to capture people's minds, ears, and eyes and ask them consider being a donor. Go into the pool so we know who you are to see what's possible in the future.

DR. LISA BUTTERFIELD: Thank you. Dr. Keller.

DR. STEPHANIE KELLER: I think I agree with everything everybody's already said. I think for the populations I agree with everyone for both the mismatched unrelated as well as the matched unrelated groups. I really like the idea of the quality-of-life measures, and I think that might help if there's any potential difference between the eli-cel group and the matched unrelated transplant group.

Then for the last group, I think the observational studies concede for the treated patients in the MDS group. I think they had mentioned CBC every six months especially focusing on the patients that have the low platelet levels at 100 days because they

seem to be at higher risk.

DR. LISA BUTTERFIELD: Thank you. And then our two patient representatives. Mr. Shapero.

DR. STEVEN SHAPERO: Yeah, echoing everyone else, subpopulation definitely would be unmatched donors, but also make it available to the unrelated matched donors, at least to the clinicians so they can have it as they need it based on the particular situation. Additional information, I don't really have any additional information I can offer. Risk monitoring and mitigation, mandatory ongoing monitoring for MDS, of course AML, and any other negative outcomes or any negative effects such as anemia or seizures that they notice they should be keeping an eye out for and be tracking it.

So basically, keep doing that if they've already started but do it as intensively as possible.

DR. LISA BUTTERFIELD: Thank you. And Ms. Anspach.

MS. SYLVIA ANSPACH: Hi. So, I also agree. I feel mismatched donors and matched unrelated donors are

important people to include. I think having the physicians and the family able to make the decision when there's a matched unrelated donor is important. I don't have any additional information to add. In terms of the recommendations for risk monitoring, I agree that limiting the number of sites is important because -- and already have somewhat done that, but when people are not transplanted in sites that are familiar with ALD, it usually does not go particularly well, and quality of life extended over time is important.

I think that as newborn screening comes on, we're going to have a lot more information available, and so having these options available for people as they encounter ALD is super important. So, I thank the Committee really for considering this and approving it as a possibility.

DR. LISA BUTTERFIELD: Thank you. That concludes the vote explanation period.

CLOSING REMARKS

DR. LISA BUTTERFIELD: So now for closing remarks, I call on our FDA colleagues, and I'm not sure if that's Dr. Bryan or Dr. Marks. Dr. Bryan.

DR. WILSON BRYAN: Yes. I just want to thank the Committee. This is a challenging area for us, very difficult clinical data for analysis and obviously the science behind this insertional mutagenesis is complex, and we really appreciate the deliberations of this Committee. And the votes, I think, as well as the deliberations will be very helpful to us in going forward.

And, as always, I wanted to also thank the participants in the open public hearing. It's very important to hear the patient and advocacy voice. And thank, once again, the review team and the folks from the Advisory Committee staff. This meeting really has been very helpful to us.

DR. LISA BUTTERFIELD: Excellent. Thank you, Dr. Bryan. I then turn it over to Christina.

DR. CHRISTINA VERT: So, thank you, everyone. Thank you, everyone, today. It was a great meeting,

and I would like to formally adjourn the meeting.

[MEETING ADJOURNED FOR THE DAY]

DAY 2

OPENING REMARKS: CALL TO ORDER AND WELCOME

MR. MICHAEL KAWCZYNSKI: Good morning and welcome to the 72nd meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee meeting. I'm Mike Kawczynski, and I will be helping get this meeting kicked off and running. Please note that this is a live meeting. We also do have international participants, so if we do have any technical issues at any time, like we just did, I'll take care of that right off the bat and keep this show rolling. That being said, I'm going to hand it off to our chair, Dr. Lisa Butterfield. Dr. Lisa Butterfield, are you ready to kick this off?

DR. LISA BUTTERFIELD: Good morning, thank you, Michael. Good morning, everyone. I'm Lisa Butterfield. I'll be chairing today, and I'd like to welcome all of the voting members, temporary voting members, all of the participants across the U.S., as well as the public who will be viewing remotely to

today's meeting.

A bit of housekeeping, I'd like to remind people who are participating that when you have questions, please use that Raise Hand function. That's what I'll be looking at in order to call on you. With that, I call the meeting to order, and I'd like to introduce our designated federal officer for today, Ms. Christina Vert.

ADMINISTRATIVE REMARKS, ROLL CALL, INTRODUCTION OF COMMITTEE, CONFLICT OF INTEREST STATEMENT

MS. CHRISTINA VERT: Thank you, Dr. Butterfield. Good morning, everyone. This is Christina Vert, and it is my great honor to serve as the Designated Federal Officer, DFO, for today's second day of the 72nd Cellular, Tissue, and Gene Therapies Advisory Committee Meeting. On behalf of the FDA, the Center for Biologics Evaluation and Research, and the Committee, I am happy to welcome everyone for today's virtual meeting. Today the Committee will meet in open

session to discuss the biologic licensing application BLA 125717 from bluebird bio. Today's meeting and the topic were announced in the Federal Register published on April 14, 2022.

I would now like to introduce and acknowledge the excellent contributions of the staff in the Division of Scientific Advisors and Consultants, including our Director, Dr. Prabha Atreya, who is my backup and co-DFO for this meeting. Other staff are Dr. Sussan Paydar, Ms. Tonica Burke, Ms. Joanne Lipkind, and Ms. Karen Thomas, who have provided excellent administrative support in preparing for this meeting. I would also like to thank Mr. Mike Kawczynski in facilitating the meeting today.

Also, our sincere gratitude goes out to the many CBER and FDA staff working hard behind the scenes trying to ensure that today's virtual meeting will also be a successful one. Please direct any press media questions for today's meeting to the FDA's Office of Media Affairs at fdaoma@fda.hhs.gov. The transcriptionist for today's meeting is Ms. Ora Giles.

We will begin today's meeting by taking a formal roll call for the Committee members and temporary voting members. When it is your turn, please make sure your video camera is on and you are unmuted, and state your first and last name, organization, expertise or role, and when finished, you can turn your camera off so we can proceed to the next person. Please see the member roster slides in which we'll begin with the chair, Dr. Butterfield. Please go ahead, Dr. Butterfield.

DR. LISA BUTTERFIELD: All right, good morning again. My name is Lisa Butterfield. I'm the vice president of Research and Development at the Parker Institution for Cancer Immunotherapy, and an adjunct professor of microbiology and immunology at University of California, San Francisco. My expertise is in cancer immunotherapy, cancer vaccines, cell therapies, and biomarkers.

MS. CHRISTINA VERT: Thank you. Dr. Ahsan.

DR. TABASSUM AHSAN: Good morning, my name's Taby Ahsan. I'm vice president of cell and gene

therapy operations at City of Hope. My research and technical expertise for the last 25 years or so has been in tissue engineering, stem cells, regenerative medicine. My more recent focus has been on immunotherapy for oncology.

MS. CHRISTINA VERT: Thank you. Dr. Fox.

DR. BERNARD FOX: I'm Bernard Fox. I'm the Harder Family Chair for Cancer Research at the Earle A. Chiles Research Institution, which is a division of the Providence Cancer Institute. My area is in cancer immunotherapy, primarily translational research and cancer vaccines adoptive immunotherapy and biomarkers. And I'm wearing white because it's Finish Cancer White Day today. Thank you, FDA, for all the immunotherapy work you've approved.

MS. CHRISTINA VERT: Oh great. Thank you. Dr. Lee.

DR. JEANNETTE LEE: Good morning, my name is Jeannette Lee. I'm a professor of biostatistics and a member of the Winthrop P. Rockefeller Cancer Institute at the University of Arkansas for Medical Sciences in

Little Rock.

MS. CHRISTINA VERT: Thank you. Dr. Ott.

DR. MELANIE OTT: Good morning. I'm Melanie Ott, the director of the Gladstone Institute in San Francisco. I'm also a professor of medicine at the University of California, San Francisco. My expertise is in molecular virology, HIV transcriptional regulation, and antiviral vectors. Thank you.

MS. CHRISTINA VERT: Thank you. Dr. Shah.

DR. NIRALI SHAH: Hi, I'm Nirali Shah. I lead the Hematologic Malignancies Section in the Pediatric Oncology Branch. My expertise is in CAR T cell therapy specifically for children, adolescents, and young adults focused on hematologic malignancies.

MS. CHRISTINA VERT: Thank you. Dr. Coffin.

DR. JOHN COFFIN: I'm John Coffin, professor of molecular biology and microbiology at Tufts University in Boston, Massachusetts. My expertise is in basic retrovirology with particular focus currently on integration of HIV and other retroviruses with regards to mechanism specificity and consequences.

MS. CHRISTINA VERT: Thank you. Dr. Crombez.

DR. ERIC CROMBEZ: Good morning, I'm Eric Crombez. I'm the chief medical officer for our Gene Therapy and Inborn Error of Metabolism program at Ultragenyx. I've been working in the field of gene therapy for the past eight years and serving as the industry representative today.

MS. CHRISTINA VERT: Thank you. Dr. DiPersio.

DR. JOHN DIPERSIO: Good morning. I'm John DiPersio, and I'm the chief of the Division Of Oncology and deputy director of the Siteman Cancer Center at Washington University in St. Louis. My areas of interest include transplantation immunology, hemopoietic niche and cancer genomics and cancer-targeted therapy using gene therapy.

MS. CHRISTINA VERT: Thank you. Dr. Gordeuk.

DR. VICTOR GORDEUK: Good morning. I'm Victor Gordeuk, director of the Sickle Cell Center at the University of Illinois at Chicago, professor of medicine, research interest in sickle cell disease and other benign hematologic conditions, as well as

disorders of iron metabolism.

MS. CHRISTINA VERT: Thank you. Dr. Hawkins.

DR. RANDY HAWKINS: Good morning. I'm Randy Hawkins. I'm in private practice internal medicine and pulmonary critical care, Charles Drew University in Los Angeles, and I'm the alternative consumer representative. Good morning again.

MS. CHRISTINA VERT: Thank you. Dr. Maciejewski.

DR. JAROSLAW MACIEJEWSKI: I am attending physician at the Taussig Cancer Center. I specialize in hematology, bone marrow failure, and myeloid neoplasia. I run also Department of Experimental Hematology and Oncology at Case Western Reserve University.

MS. CHRISTINA VERT: Thank you. Dr. Singh.

DR. NAVDEEP SINGH: Hello, my name is Navdeep Singh. I am an assistant professor at the University of Toledo. My research interest is in racial disparities with African Americans in cancer pain. I have beta-thalassemia diagnosed at nine months old, so

I'm the patient representative today.

MS. CHRISTINA VERT: Thank you. Dr. Trieu.

DR. JANELLE TRIEU: Hello, I'm Janelle Trieu. I'm a clinical pharmacist and center operations manager in specialty home infusion. And I am the patient representative with transfusion-dependent thalassemia.

MS. CHRISTINA VERT: Thank you. Thank you for your introductions. We have a total of 14 participants, 13 voting and 1 non-voting member.

I would also like to acknowledge CBER leadership, including Dr. Marks and Dr. Bryan.

Now I will proceed with reading of the Conflicts of Interest statement for the public record. Thank you.

The Food and Drug Administration is convening virtually today, June 10, 2022, the 72nd Meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee, CTGTAC, under the authority of the Federal Advisory Committee Act, FACA, of 1972. Dr. Lisa Butterfield is serving as the chair for today's meeting.

Today on June 10, 2022, the Committee will meet in open session to discuss the biologic licensing application BLA 125717 from bluebird bio and company for betibeglogene autotemcel (autologous CD34 positive stem cells genetically modified with the lentiviral vector to contain a gene encoding functional beta-globin). The applicant has requested an indication for the treatment of patients with beta-thalassemia who require regular red blood cell transfusions.

This topic is determined to be a particular matter involving specific parties. With the exception of the industry representative member, outstanding and temporary voting members of the CTGTAC are appointed special government employees, SGEs, or regular government employees, RGEs, from other agencies, and are subject to Federal 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 including, but not limited to, 18 U.S.C. Section 208 is being provided to

participants in today's meeting and to the public. Related to the discussions at this meeting, all members, RGE and SGE consultants of this Committee have been screened for potential financial conflict of interests of their own; as well as those imputed to them, including those of their spouse or minor children; and, for the purposes of 18 U.S. Code 208, their employer.

These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and development agreements, CRADAs, teaching, speaking, writing, patents, and royalties, and primary employment. These may include interests that are current or under negotiation. FDA has determined that all members of this Advisory Committee, both regular and temporary members, 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 government employees who have

financial conflicts of interest when it is determined that the Agencies need for a special government employee's service outweighs the potential for a conflict of interest created by the financial interests involved, or when the interest of a regular government employee is not so substantial as to be deemed likely to effect the integrity of the services which the government may expect from the employee.

Based on today's agenda and all financial interests reported by Committee members and consultants, there have been no conflicts of interest waivers issued under 18 U.S. Code 208 in connection with this meeting.

We have the following consultants serving as temporary voting members, Dr. John Coffin, Dr. John DiPersio, Dr. Victor Gordeuk, Dr. Jaroslaw Maciejewski, Dr. Navdeep Singh, and Dr. Janelle Trieu are serving as voting patient representatives. Dr. Eric Crombez of Ultragenyx Gene Therapy will serve as the alternate temporary industry representative for today's meeting. Industry representatives are not appointed as special

government employees and serve only as non-voting members of the Committee.

Industry representatives act on behalf of all regulated industry and bring general industry perspective to the Committee. Dr. Randy Hawkins is serving as the alternate temporary consumer representative for this Committee meeting. Consumer representatives are appointed special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the Committee.

Disclosure of Conflicts of Interest for speakers and guest speakers follows applicable federal laws and regulations and FDA guidance. FDA encourages all meeting participants, including open public hearing speakers, to advise the Committee of any financial relationships that they may have with any affected firms, its products, and if known, its direct competitors.

We would like to remind standing 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 that participants need to inform the DFO and exclude themselves from the discussion and the exclusion will be noted for the record.

This concludes my reading of the Conflict of Interest statement for the public record. At this time, I would like to hand over the meeting to our chair, Dr. Butterfield. Thank you.

FDA OPENING REMARKS

DR. LISA BUTTERFIELD: Thank you very much, Christina. With that, I'd like to introduce Dr. Wilson Bryan, Director of OTAT, for the FDA opening remarks. Dr. Bryan.

DR. WILSON BRYAN: Good morning. On behalf of the FDA, the Center for Biologics Evaluation and Research, and the Office of Tissues and Advanced Therapies, welcome back.

Today, we ask this Committee to consider

bluebird bio's BLA for beti-cel, a gene therapy for the treatment of beta-thalassemia. Yesterday, we heard about the risk of hematologic malignancy associated with beti-cel and related products. Today, we will hear about the efficacy and safety of beti-cel to the treatment of transfusion-dependent beta-thalassemia.

We will ask this Committee to balance benefits and risks of beti-cel in the setting of a treatable disease. As with yesterday's discussion, we are asking this Committee to focus on clinical issues regarding safety and effectiveness. I would like to reiterate that there are also CMC issues with these two applications. The FDA is working with bluebird bio to address those manufacturing concerns.

We are grateful to bluebird bio and the scientists and other professionals who have brought this product to this stage of development. We are also grateful to the patients and their caregivers who participated in the clinical trials discussed yesterday and today.

The FDA thanks the participants in today's

open public hearing. To the patients and patient advocates, your voice is always important to us. And we particularly want to hear your thoughts on the benefits and risks associated with this product. Many individuals are not able to participate today, and we appreciate and will carefully consider the written comments that we received regarding beti-cel.

We want to thank all the members of this Committee who have given their time to participate in the discussions yesterday and today. Once again, I want to thank the members of the FDA review team and the Advisory Committee staff who have worked tirelessly to prepare for today's meeting. I now turn to Dr. Butterfield to continue with the agenda.

SESSION 4: BETA-THALASSEMIA EFFICACY AND SAFETY

APPLICANT PRESENTATION: INTRODUCTION

DR. LISA BUTTERFIELD: Thank you so much, Dr. Bryan. In this two-day meeting, we move to Session 4 on beta-thalassemia efficacy and safety. And so I'd

like to now introduce the applicant presentations from bluebird bio, starting with Ms. Eggimann.

MS. ANNE-VIRGINIA EGGIMANN: Thank you, Dr. Bryan. Thank you, Dr. Butterfield. Good morning. I'm Anne-Virginia Eggimann, Chief Regulatory Officer at bluebird bio. I would like to thank the FDA, the Panelists, and the CLD patient community for an information and positive meeting yesterday. We're excited to be here today. I look forward to discussing the development of betibeglogene autotemcel, or beti-cel. Thank you to the Agency, the Panelists, and the patients who participated in our beti-cel trials, as well as their families for making our meeting today possible.

The proposed indication for beti-cel is for the treatment of patients with beta-thalassemia who require regular red blood cell transfusions. Beta-thalassemia is a life-shortening disease. It is a rare genetic blood disease caused by mutations in the beta-globin gene. These mutations cause anemia due to reduced or absent production of adult hemoglobin. For

patients with severe anemia, lifelong, regular red blood cell transfusions as often as every two to three weeks are required for survival and are burdensome.

These transfusions lead to inevitable chronic accumulation of iron causing end-organ damage and ultimately leading to a shortened lifespan.

Beti-cel is a first-in-class, single-administration, lentiviral vector, or LVV, gene therapy that addresses the underlying cause of beta-thalassemia and has the potential to cure patients with this lifelong disease.

Beti-cel consists of a patient's own blood stem cells that have been genetically modified ex vivo with a BB305 LVV. In vivo, the transduced cells differentiate into red blood cells with sufficient functional beti-cel-derived hemoglobin to eliminate the need for transfusions in most patients. This process is briefly depicted on the next slide.

After cell collection, BB305 LVV adds functional copies of the beta A-T87Q-globin gene into the patient's cells. These cells are then infused in

the patient after manipulative conditioning. After engraftment, the genetically modified cells differentiate into red blood cells containing adult hemoglobin with two beta-globin chains derived from beti-cel. We refer to this functional adult hemoglobin as HbA-T87Q. Of note, the T87Q modification allows us to measure directly in the blood of patients how much hemoglobin is produced by beti-cel, which is very helpful as this directly correlates with clinical benefit.

Over the past decade, we learned a lot about beti-cel. We learned how to improve beti-cel and optimize clinical outcomes. Specifically in our Phase 1/2 studies, we learned that increasing transduction efficiency, i.e., increasing the percentage of cells in the drug product with integrated copies of the beta-A-T87Q-globin gene, was necessary to successfully treat patients with all genotypes. As a result, we improved the manufacturing process before initiating our Phase 3 studies in which we treated 41 patients.

We are committed to the long-term follow-up of

patients for 15 years post-treatment in our LTF-303 Study and post-approval in our REG-501 Registry. In total, we treated 63 patients with beti-cel with up to seven years of follow-up.

Our data support a positive benefit/risk for the proposed beti-cel indication. There is consensus that beti-cel provides a clinically meaningful benefit. In our Phase 3 studies, we demonstrated a high rate of durable transfusion independence as well as trends of improvement in iron overload and erythropoiesis.

Beti-cel's safety profile largely reflects known side effects of mobilization and conditioning agents. Importantly, during beti-cel clinical development, there was no deaths, no malignancy, and no BB305 LVV-mediated safety event.

This is our agenda for today. Bluebird bio speakers, as well as external experts, will share robust evidence supporting beti-cel benefit/risk assessment, as well as our plans for post-marketing safety surveillance. Additional key experts will be available to answer questions. I will now turn the

presentation over to Dr. Sheth, who will speak to the significant unmet medical need in patients with beta-thalassemia who require regular red blood cell transfusions.

APPLICANT PRESENTATION: UNMET MEDICAL NEED

DR. SUJIT SHETH: Thank you very much, Dr. [sic] Eggimann. Good morning. I'm Sujit Sheth and professor of pediatrics at Weill Cornell Medicine in New York City. I received honoraria from bluebird bio for being with you today. However, I do not have any financial interest in the outcome of today's meeting, and, after 30 years of treating patients with beta-thalassemia, I have a personal and powerful interest in being here today to support the availability of new options for the treatment of my patients.

Beta-thalassemia is a life-long, inherited condition with a high burden of disease and complications over the entire life of the patient. The most severe form requires life-long, regular

transfusions initiated early in life, which are very cumbersome and hospital time-intense. The overall treatment and monitoring regimen requires a lot of medical visits, which progressively increase over time as complications develop, and have a significant negative impact on survival and quality of life.

While treatment has greatly improved, there remains a huge unmet need for curative options available to all patients. Nearly 350 mutations have been identified that may cause beta-thalassemia. These mutations may be beta-zero mutations where no functional beta-globin is produced; beta-plus, where there is a reduction in beta-globin production but is not completely absent; and beta-E mutations, which result in the production of beta-E-globin.

Patients with beta-thalassemia mutations in both beta-globin genes, therefore inheritance is autosomal recessive, and may be broadly classified as having beta-zero beta-thalassemia with no production of hemoglobin A, or non-beta-zero beta-zero thalassemia where there's some but decreased production of

hemoglobin A.

The spectrum of clinical severity of beta-thalassemia is quite wide, ranging from asymptomatic individuals with a trait to the most severe form requiring regular transfusions, called Cooley's Anemia or Thalassemia Major.

Clinically we've moved towards classifying beta-thalassemia disease into two broad categories: non-transfusion-dependent thalassemia, or NTDT, which includes patients with what used to be called, or is still called sometimes, Thalassemia Intermedia; and transfusion-dependent thalassemia, or TDT, which was called Thalassemia Major or Cooley's Anemia.

It is important to keep in mind that patients may transition from NTDT to TDT over time as complications develop or as the total hemoglobin levels drop.

Treatment options for TDT patients are limited. Transfusion and iron chelation are the chronic treatment with recent availability of luspatercept as an adjunct in adult patients.

Allogeneic transplantation is the only potentially curative option currently available primarily offered to children and young adolescents with TDT.

Overall, thalassemia-free survival after allogeneic transplant is around 90 percent with the best outcomes being in pediatric patients with matched donor availability. Results are best when this is done early in life before complications like alloimmunization and iron-related organ damage have occurred.

A successful transplant is transformative. Individuals become transfusion-independent and after appeared of either chelation or phlebotomy to get rid of the previously accumulated iron. They're free of chelation as well.

They are left with normal or near-normal bone marrow activity and no progression of complications of ineffective erythropoiesis or iron overload. Most importantly, their quality of life after the first year or so is almost normal. Visits to the hospital are limited to quarterly or semi-annual follow-up visits

with some monitoring required for complications which may have already occurred before the treatment.

Potential risks are significant and include development of graft versus host disease, graft failure or rejection, and a small risk of mortality all more so in mismatched or unrelated donors.

Despite these complications, given the high burden of disease, its complications, and its enormous impact on quality of life, allogeneic stem cell transplantation has become accepted practice for a subset of patients with TDT, namely young children with matched related donors. Unfortunately, only approximately 25 percent of patients have a matched related donor. Therefore, in my opinion, limited access to potentially curative transplant based on donor availability underscores the need for a more widely available curative option.

This slide shows the journey for patients with TDT who are not able to be transplanted. Staring at a young age of regular transfusions, addition of chelation, starting regular monitoring, all of which

intensifies over time. Seeing a healthcare professional more often than you see your family or friends is not a good thing.

The lower part of the slide shows the evolution of complications related to iron overload. Complications include delayed growth in the first decade of life, delayed puberty, diabetes, and other endocrinopathies as well as heart failure in the second decade of life. And then in adults, there's secondary amenorrhea in females, infertility in both males and females, osteoporosis and fractures, and liver disease.

Beta-thalassemia is a complex disease in which ineffective erythropoiesis as a result of the alpha-to-beta-globin imbalance is central to the path of physiology. There are myriad complications in beta-thalassemia, which can be disease-related, as seen on the left of the slide, mostly in NTDT patients; and treatment-related, mostly related to complications of the regular transfusions, as seen on the right in TDT patients.

Disease-related complications are due to

ineffective erythropoiesis, which leads to chronic anemia, extramedullary hemopoiesis, and bone disease; vascular disease, leading to cerebral infarcts and the development of pulmonary hypertension; and iron overload from increased absorption of iron from the gut. Transfusion complications include reactions; blood-born infections; and those related to iron overload, including endocrinopathy, liver and heart disease, as well as issues related to chelator toxicity. There's also significant impairment in quality of life, and mental health issues in both patients with TDT and NDTD.

The leading cause of mortality in beta-thalassemia remains iron overload-related cardiac disease though the rate has declined over the years because of more effective chelation regimens. Other causes of death include liver disease, infection, and vascular events. Hepatocellular carcinoma linked to iron overload and potentially complicated by viral hepatitis is the most common malignancy in this population. Data from the Cooley's Anemia Foundation

showed that the median age of death among patients in their database over the last decade was just 37 years, which is half that of the average American.

The potential for developing complications (inaudible) patients of comprehensive, lifelong monitoring, as noted here at frequencies varying from every 3, 6, 12 to 24 months. Ongoing regular assessments of quality of life and mental health issues are important as well.

The impact of the disease and its management of the lives of these patients cannot be minimized. The typical patient receives 15 to 25 transfusions a year, two or three units at each visit, which typically lasts the entire day, longer if they're allantiasis or if they have a reaction.

While they may feel relatively able to cope with and adapt to day-to-day life, the burden of disease is tremendous. In addition to organ complications, anxiety and depression are not uncommon. There is a major financial impact as well with high healthcare costs associated with significant out-of-

pocket expenses and lost workdays.

In summary, beta-thalassemia is a lifelong disease with a very heavy burden for patients and an enormous impact on quality of life. Regular transfusion and more effective iron chelation have played a central role in extending life expectancies for these patients.

Allogeneic stem cell transplants, available only to a limited number of patients, is a potentially curative option. However, these treatments and their potential complications continue to have a significant impact on the lives of patients and their families, thus underscoring the huge need for a more widely available curative treatment. Thank you. I will now pass it over to Dr. Colvin.

APPLICANT PRESENTATION: EFFICACY

DR. RICHARD COLVIN: Thank you, Dr. Sheth. Good morning. I am Richard Colvin, Chief Medical Officer of bluebird bio. I will show you data that

demonstrates that approximately 90 percent of patients with beta-thalassemia became durably transfusion-independent after treatment with beti-cel. Beti-cel outcomes in Phase 3 studies were similar in adults and pediatric patients and in patients with all major categories of beta-thalassemia genotype studied.

First, we'll review the clinical development of beti-cel. Clinical development of beti-cel began with the Phase 1/2 Studies HGB-205 and HGB-204. The Phase 3 studies included adults, adolescents, and children under 12, as well as patients with beta-zero and non-beta-zero genotypes. The HGB-207 Study enrolled and treated adults first to establish the safety and benefit before proceeding into pediatric patients.

The Phase 1/2 and Phase 3 studies followed patients for two years after which patients continued in the long-term follow-up study LTF-303 for 13 additional years. All 51 eligible patients have enrolled in LTF-303. Let's now review the details of the Phase 3 studies.

Although the beta-globin genotypes of patients enrolled in the two Phase 3 studies differed, both studies included patients who received greater than 100 milliliters per kilogram per year of packed red blood cells in the two years prior to enrollment. Patients were less than 50 years old and included children under the age of 12.

The key difference between Studies 207 and 212 is that 207 included patients with non-beta-zero genotypes while 212 included patients with beta-zero genotypes and patients with the IVS-I-110 genotype, which is a severe non-beta-zero genotype. Patients with familial cancer syndromes were excluded. Baseline screening for somatic or germline mutations was not done as part of this screening.

The primary endpoint of both studies was the proportion of patients who achieved transfusion independence. Other than beta-globin genotype, the characteristics of the patients in HGB-207 and 212 were similar. HGB-207 enrolled patients with non-beta-zero genotypes and included six patients with an HB-E

genotype. Patients with this genotype are usually considered to have a slightly less severe form of transfusion-dependent thalassemia but still require a regular transfusion regimen.

Twelve of 18 patients in HGB-212 had beta-zero genotypes, and 6 of 18 had an IVS-I-110 genotype. Both studies included patients from about age 4 to about 34. Adult patients, adolescent patients, and pediatric patients less than 12 years of age were well-represented in both studies.

Median iron burden at enrollment was relatively low for patients with transfusion-dependent thalassemia in both studies. This is likely because the patients were well-managed with chelation prior to enrollment and that most patients were adolescents or younger. However, several patients with elevated liver and/or cardiac iron burden were treated in 207 and 212.

Seventeen percent of the patients in each study had a splenectomy prior to treatment. Therefore, 83 percent of the patients in these studies retained their spleens.

Pre-treatment packed red blood cell transfusion volume per year was similar for patients in both studies.

Next, we'll turn our attention to the primary efficacy endpoint data from Studies 207 and 212. Overall, 32 of 36 patients treated with beti-cel in the Phase 3 studies who had enough follow-up time to evaluate for transfusion independence achieved transfusion independence. There were 22 pediatric patients in these studies, and 20 of these patients achieved transfusion independence.

Note that these results include patients with beta-zero and non-beta-zero genotypes. With these results, both studies met the pre-specified success criteria for the primary efficacy endpoint of the proportion of patients achieving transfusion independence. During transfusion independence, the median weighted average hemoglobin was 11.5 grams per deciliter, which is in the normal range for most patients in the study. Transfusion independence is durable and ongoing in all patients that achieved TI.

The median duration of ongoing TI is 25 months and ranges from 12 and a half to 39.4 months.

Let's look at the data for individual patients. Overall, almost 90 percent of evaluable patients in the transplant population across both studies became transfusion-independent. In this chart the X-axis represents time. Each bar represents a patient that achieved transfusion independence. Red dots represent transfusions that patients received. You can see at baseline prior to treatment, which occurred at Month 0 on the X-axis, patients received a median of 17 transfusions per year.

Following hemopoietic recovery, 32 patients became transfusion independent. Notice that all these patients have remained transfusion-independent through last follow-up, which amounts to up to 48 months after treatment. You may notice the one red dot at approximately Month 22, this patient had a transfusion for an acute bleed that occurred during orthopedic surgery and has not received any additional transfusions. Four patients did not become transfusion

independent.

The four bars in the shaded area represent the patients who did not achieve transfusion independence. These patients continued to receive transfusions after treatment with beti-cel. The drug products that these patients received had relatively low percentages of transduced cells, which resulted in inadequate HBA-T-87Q production to achieve high enough total hemoglobin level in order to completely discontinue transfusions.

Additionally, five patients did not have enough time of follow-up to be evaluable for TI at the time of the BLA data cut. The five bars highlighted in green at the bottom of the plot represent these five patients. None of these patients are currently receiving transfusions, and, as of last week, all five of these patients have become evaluable and are transfusion-independent, meaning that 37 of 41, or 90 percent of the patients treated in the Phase 3 studies have become transfusion-independent.

This figure shows that the unsupported total hemoglobin in patients treated with beti-cel who

achieved TI remain stable over time. The blue line represents the total hemoglobin in patients in HGB-207. The red line represents the total hemoglobin in patients in HGB-212. Total hemoglobin is stable after about Month 3 and out to the last follow-up at Month 42.

The purple and green lines represent total hemoglobin from patients in Studies HGB-204 and 205. Importantly, total hemoglobin for patients in Studies HGB-204 and 205 is stable out to seven years without any sign of decline.

These results demonstrate that transfusion independence and total hemoglobin are stable following beti-cel treatment. Stable transfusion independence and near-normal hemoglobin levels reduce the complications of thalassemia.

In addition to achieving transfusion independence, the post-beti-cel treatment course was consistent with that of allogeneic transplant with respect to iron burden. The results are improved erythropoiesis and decreased iron storage is that over

time patients were able to discontinue iron reduction therapies.

It is important to acknowledge that iron management was not prespecified in the protocols and was left to physician and patient discretion. However, within this context, iron was reduced enough so that most patients were able to stop iron chelators following beti-cel treatment.

Additionally, 11 patients had phlebotomies to reduce iron overload. These are patients with thalassemia who received packed red blood cell transfusions for most of their lives. Following beti-cel treatments, they produce enough hemoglobin to be able to have blood taken from them in order to remove excess iron.

To simply summarize, beti-cel treatment transforms the lives of patients with beta-thalassemia. Transfusion independence is durable and expected to be lifelong for adults and pediatric patients with beta-thalassemia of all genotypes. Approximately 90 percent of patients treated with beti-cel achieved near-normal

or normal levels of hemoglobin without transfusions.

Transfusion independence is evidence of a meaningful, therapeutic effect. It eliminates the risk associated with chronic blood transfusion, removes the need for time-consuming frequent transfusions in the hospital, results in improved erythropoiesis, and allows patients to stop iron chelation with normal iron burden thereby reducing the risk of organ damage. The total hemoglobin levels these patients achieve are expected to reduce or eliminate the complications of beta-thalassemia. These data demonstrates that the benefits of beti-cel treatment for patients with beta-thalassemia are profound.

Thank you for this time. My colleague, Dr. Ajay Singh will now present the safety outcomes in the studies of beti-cel.

APPLICANT PRESENTATION: SAFETY

DR. AJAY SINGH: Thank you, Dr. Colvin, and good morning. My name is Ajay Singh, and I'll be

providing an overview of the safety of the beti-cel program which is derived from the 63 patients who received the drug product and therefore constituted a safety cohort.

Of these, 51 are currently in the long-term extension study. As of the BLA, the median follow-up was approximately three years, and the total exposure is 221 patient-years. Currently, the median follow-up is greater than four years.

In terms of the forthcoming content, in an effort to highlight the key issues likely to be of interest to the panel, I will briefly describe the overall safety profile and then focus the rest of the presentation on five main topics: platelet engraftment, bone marrow findings, recapitulation of vector safety, issues raised in the FDA briefing document which relate to patients in the lovo-cel program utilizing the same vector, and our plans to ensure rigorous oversight to the FDA-approved beti-cel.

In terms of the safety profile, overall survival remains 100 percent. There have been no cases

of acute or chronic GVHD, not surprising given the tolerant nature of the treatment.

The adverse event profile on the regimen as a whole was predominantly reflective of myeloablation and localization. Events deemed specifically related to beti-cel by the investigators typically fell into one of two categories: cytopenias and infusion-reaction, which were generally mild and transient. We've had no cases of hematologic malignancy to date. Safety was similar across genotype and age with one notable exception, younger patients had longer engraftment.

In terms of engraftment, all patients achieved successful engraftment. As shown on the left, the median time to neutrophil engraftment applying standard definitions was 23 days. Time to platelet engraftment was slower, median time of 45 days. Contextualization of these times has been limited by the fact that the only meaningful information in literature is in patients who have received allografts. Data from which are provided in the next slide.

Engraftment times noted in four such papers

are juxtaposed to the beti-cel data. Neutro engraftment is on the left, platelet engraftment is on the right. Overall, engraftment times are long with beti-cel. This is particularly true when looking at platelet engraftment with a median time of 45 days, this compared to 12 to 30 days noted with allogeneic counterparts.

As part of a risk assessment, we interrogated our database to determine if any intrinsic or extrinsic factors correlated with time to platelet engraftment. The most consistent and dominant factor was the spleen status of the patient. This is shown graphically here. The ordinate shows cumulative incidence of successful platelet engraftment. The abscissa shows time in days. Patient with the spleen shown in teal had a median time of 49 days compared to 33 days for patient without a spleen, shown in orange. As noted, this difference was highly statistically significant.

Further recover of platelets beyond the engraftment threshold of 20,000 to 100,000 and to lower limit or normal was also impacted by the spleen.

Patient without a spleen had a more brisk recovery. For example, in regards to recovery to lower limit of normal, the splenectomized patients, shown on the left, all recovered to lower limit of normal, median time of 60 days. By contrast, patient with a spleen recovered with a median time of 199 days, and 11 out of 47 patients did not recover at this threshold. However, it is noteworthy that some of these patients had counts below the lower limit of normal prior to therapy.

There is at least one publication with allo transplantation which corroborates the impact of the spleen on platelet engraftment. Matthews et al. reported the mean time to platelet engraftment was 10 days longer if they had a spleen or, in this case, no splenectomy in this table. They hypothesized that (inaudible) sequestration, including potentially stem cell sequestration may have contributed to this phenomenon.

However, it is noteworthy that platelet engraftment times were still longer with beti-cel in each of the two cohorts, splenectomy and no

splenectomy. What remains unclear is while these engraftment times are reflective of those expected with autologous transplantation or gene therapy in general, but the longer time is probably unique for beti-cel. Therefore, as a conservative measure, we have noted delayed platelet engraftment to be an identified risk.

To summarize, time to platelet engraftment is prolonged compared to allogeneic transplantation. Mechanism is not fully elucidated. However, the spleen plays a key role. As noted in previous presentations, TB34 enriched cells are cryopreserved after transception. There is literature to suggest that cryopreservation may result in longer engraftment times; however, the contribution of cryopreservation with the observations today remain punitive. Though platelet recovery was sluggish, it was steady.

You may have seen an analysis noting that greater than 50 percent of patients were unable to sustain a platelet count greater than 100,000. We would like to emphasize that this was the result of an analysis that had limited clinical value. As of the

BLA cutoff, 90 percent of patients have reached a stable count of 100,000. Though not discussed here, but as presented in the briefing book, the clinical consequences were limited. There was one serious case of epistaxis in context with delayed platelet engraftment.

We did examine the evolution of erythroid and metatartaric morphologic changes in context of time to platelet engraftment. With the caveat that these are qualitative assessments, we found no evidence that longer engraftment times were associated with higher frequencies of these morphologic changes. As Dr. Colvin noted, bone marrow assessments are routinely performed and up to Phase 3 studies.

Study 207 and 212 samples are collected at baseline Month 12 and Month 24. Not surprisingly, the baseline evaluation were critical in assessing the evolution of the various findings. As it turns out, the dataset of approximately 40 patients represents one of the most exhaustive sampling available in patients with TDT given that bone marrow examination is not

routinely done. However, the ineffective erythropoiesis has been well-demonstrated, which is manifested by increase in, turnover of, and apoptosis of the erythroid precursors.

The effects of these were evident in the baseline samples from the Phase 3 studies. These demonstrated variable amounts of erythroid hyperplasia with M:E ratios typically in the 0.3 to 0.7 range, erythroid precursors with dysplastic features, cytoplasmic inclusions, ring sideroblasts, and dysmegakaryopoiesis.

In terms of evolution post-gene therapy, there was improvement in the erythroid hyperplasia, as evident by the improvement in the M:E ratio and near complete disappearance of the cytoplasmic inclusions. However, the morphologic abnormalities were noted both at baseline and post-treatment. We hypothesized that one of the reasons for the persistence of the morphologic abnormalities is the fact that not all stem cells are transduced. Resulting in some degree of stress erythropoiesis within the marrow of these

patients.

To summarize, the pathology was consistent with stress erythropoiesis and the attendant erythroid hyperplasia improved over time. There was evidence of erythroid dysplasia, dysmegakaryopoiesis at baseline and follow-up, but none of these findings were suggestive of MDS or emerging MDS.

Moving on to vector safety, 61 patients had testing for replication-competent lentivirus, all negative. All 63 patients have had at least one ISA. Fifty have shown polyclonal reconstitution. One patient was noted to have oligoclonality at the last visit, and the insertion site is not a known oncogene. Two other patients had oligoclonality confirmed on a subsequent ISA, hence these patients met the criteria for persistent oligoclonality.

The details are presented here. Please note, all the patients have greater than five years of follow-up. The pictures represent relative frequencies of the different insertion sites. The dotted line represents ten percent. The clonal dynamics show

stable oligoclonality. Both patients had prolonged platelet engraftment times, 91 and 191 days, but both have an intact spleen. The patient on the left never had a bone marrow, whilst the patient on the right did have one four years ago, which was normal. All the patients are clinically stable.

To date, we've had no cases of LVV-mediated insertional oncogenesis. Before closing, I would like to address an issue that was raised in the Agency's briefing book regarding two cases in the sickle cell program treated with lovo-cel. In addition to sickle cell disease, both patients had two alpha gene deletions. These are the only two patients in the program with such deletions. Both presented with anemia. The second patient also had neutropenia.

Bone marrow examination demonstrated morphologic abnormalities in the erythroid line, which raised the concern for MDS. Both patients had transient gain of chromosome eight by FISH, a normal karyotype, and no driver mutation are noted on next-generation sequencing. Given the possibility of MDS,

we had the pathology reviewed by Dr. Hasserjian, who is an expert in the MDS pathology. And we reviewed the picture with clinical experts in the field as well.

The consensus amongst our consultants was that the clinical pathological picture was not suggestive of MDS given the following facts. Number one, there was no clonal process. The ISA showed highly polyclonal reconstitution, and the NGS was unremarkable. Dr. Hasserjian's assessment was that the pathology was consistent with stress erythropoiesis. And, number three, the overall picture was very similar to alpha/beta-globin imbalance given patients' hemoglobinopathies.

Returning back to beti-cel and review of the safety issues, delayed platelet engraftment is categorized as an identified risk and the presence of a spleen had a clear impact, which we believe is reflective of hypersplenism, commonly seen in patients with TDT. Similarly, given the clear evidence of bone marrow abnormalities at baseline, the morphological changes were consistent with underlying TDT and the

associated erythropoietic stress.

There have been no case of hematologic malignancies and no cases of insertional oncogenesis in the 63 patients in the beti-cel program or the 113 patients treated with drug product made with BB305 LVV. All but three patients had polyclonal reconstitution. There were insertion sites that were frequently noted. These included MECOM and VAMP4. The latter you heard yesterday is not an identified proto-oncogene. Their relative frequencies were less than 0.25 percent, and there was no correlation with VAMP4 insertion and platelet engraftment times.

In terms of risk mitigation, we are proposing clear communication for a prolonged time to platelet engraftment while labeling and education of the qualified treatment centers. The three patients who are currently oligoclonal will continue to have enhanced surveillance. Bluebird will facilitate ISA as clinically indicated in the post-marketing setting. Regarding insertional oncogenesis, we acknowledge that this and other potential long-term risks require

careful and rigorous surveillance, which we are committed to through our long-term pharmacovigilance plans.

All patients in the clinical trials will be enrolling in a long-term extension study for an additional 13 years. And key adverse events, including malignancy, will be collected. These adverse events will also be collected in the post-marketing registry, which has a target enrollment of 150 patients. This registry will be made available at all initial qualified treatment centers, which will serve as the only sites of treatment.

So, to close, the safety profile of beti-cel supports a favorable benefit/risk. Bluebird remains fully committed to ensuring transparent communication of emerging safety issues throughout PV activities, which will support the prescribers, their regulators, and the industry as a whole in gaining valuable long-term safety data.

Thank you, and I'd like to request Dr. Thompson to provide a perspective on the overall

benefit/risk.

APPLICANT PRESENTATION: BENEFIT-RISK

DR. ALEXIS THOMPSON: Thank you, Dr. Singh. Good morning. I'm Dr. Alexis Thompson. I'm the chief of the Division of Hematology at the Children's Hospital of Philadelphia. I received an honorarium from bluebird bio for being with you today, and both my institution and I have received compensation for support of clinical investigations. I do not, however, have any financial interest in the outcome of today's meeting, but certainly, as a long-time treater of patients with thalassemia and sickle cell, I have a powerful personal and professional interest in being here today to support the availability of a new option for patients.

As you've heard today, there is an unmet need for a potentially curative option for all patients with beta-thalassemia who rely on regular transfusions. A potentially curative option should allow patients to

stop transfusions with a normal or near-normal hemoglobin. It should prevent the life-shortening complications of beta-thalassemia, and it should reduce the need for life-long thalassemia-specific and/or transfusion-related monitoring procedures.

Why beti-cel? As a reminder, most thalassemia patients will not have a suitable donor for an allogeneic transplant and with beti-cel, the patient is his or her own donor. Patients treated with beti-cel can achieve transfusion-independent, have reduced iron burden, and improved quality of life. Since beti-cel utilizes autologous stem cells, there is no risk for GVHD, and treatment with beti-cel does not require depletion of the cellular product or post-transplant immune suppression.

Beti-cel has not been associated with graft failure or graft rejection, and these are both known risks of allo transplants for thalassemia. Thus, beti-cel could provide a potentially curative treatment option for a broader population irrespective of age or donor availability with a positive benefit/risk

profile. The clear and clinically meaningful benefit of beti-cel for TDT has been demonstrated in the great majority of patients across all clinical program phases, all ages, and all genotypes.

Nearly 90 percent of patients in the Phase 3 trials are transfusion-independent with a median weighted average hemoglobin of 11.5 grams per deciliter and durable transfusion independence with an overall follow-up of out to seven years. These trials have demonstrated improvement in erythropoiesis, reflected by the normalization in their myeloid to erythroid ratios; improvement in bone marrow morphology; and also improvement in markers of diserythropoiesis.

Nearly all patients with thalassemia undergoing gene therapy or allogeneic transplant will require some form of iron control to address transfusional iron overload. Some patients have undergone phlebotomy; others have had iron chelation performed post-beti-cel infusion. Many have now been able to subsequently stop iron control measures without iron re-accumulation.

The safety profile of beti-cel is based on all 63 treated patients across the four clinical trials who have been followed for as little as four months, but out beyond seven years, providing an overall post-beti-cel exposure of 221 patient-years. With few exceptions, the overall safety profile is consistent with known toxicities associated with mobilization with plerixafor and G-CSF, and conditioning with busulfan.

Immunologic complications that might otherwise be seen with allogeneic stem cell transplant have not occurred with beti-cel. And there have been no vector-derived replication component lentivirus or lentiviral vector-mediated insertional events observed in patients thus far.

When I have conversations with my patients and their families, we discuss a number of considerations. We talk about the benefits of achieving life-long transfusion independence with a normal or a near-normal hemoglobin following beti-cel therapy. Based on the overall experience to date, I can confidently tell families that they should be able to discontinue

chelation therapy. It's also important to review risks, such as insertional oncogenesis and malignancy, as well as infertility due to myeloablative conditioning.

Delayed platelet engraftment without serious bleeding has been observed and will be discussed. Long-term follow-up will be encouraged through the drug product registry, which will allow us to modify our conversation and considerations for families over time.

I want to share with you two examples from my own patient cohort who have undergone beti-cel therapy. Starting with my very first patient, who, as a high school senior turning 18 years of age, elected to participate in this clinical trial. She started transfusions somewhat later after developing growth delay and early bony changes.

She had siblings but did not have a suitable HLA match for an allogeneic transplant. Her parents certainly had the expectation that she would be frail and dependent, not only on the healthcare system but also dependent upon them. My patient, however, really

wanted the freedom to make choices as to where she attended school and control of her future. She has now been transfusion-independent for over seven years. She's been able to attend the college of her choice out of state and is currently completing a PhD in biomedical engineering.

I think most gratifying for her and her parents was now being able to travel internationally, including, for the first time, to visit her parents' home country.

Another example of the benefits is one of my Phase 3 trial patients, who was a four-year-old with homozygous beta-zero-beta-zero or the most severe form, who was diagnosed by newborn screening, and who began chronic transfusions in a planned manner.

Having been diagnosed by newborn screening, which I would argue is the way most children who are born with this condition in the United States should be diagnosed, his parents almost immediately inquired about curative options and went forward with pre-implantation genetic diagnosis with in vitro

fertilization to hopefully achieve a potential donor match for their son. This ultimately led to the conception of his now healthy sibling, who unfortunately was not an HLA match.

This little boy underwent beti-cel therapy and received his last red cell transfusion about 30 days following beti-cel infusion. He continues to do quite well. At six months, his hemoglobin was 10.5, 9.5 of which was hemoglobin AT87Q. His most recent values at Month 12 are a total hemoglobin of 11.4 grams per deciliter, of which 10.4 is hemoglobin T87Q. He has now completed kindergarten via Zoom, which he thought was quite odd, but apparently is enjoying the first grade in person. Clearly, his family could not ask for, at least in the near term, a more gratifying and hopeful outcome for beti-cel treatment.

So, in summary, I believe that the presentations today are persuasive in that beti-cel can potentially cure patients with beta-thalassemia who require regular transfusions. And that beti-cel has the potential to cure patients across a broad range of

ages, genotypes, genders, race, and ethnicities.

This can be achieved by increasing a functional hemoglobin-A and achieving a total hemoglobin that is normal or near normal eliminating the dependence on chronic transfusions for nearly all patients. The risks and benefits to efficacy are clear with an acceptable safety profile for patients with beta-thalassemia.

Thank you. I will now return to Dr. Colvin. Dr. Butterfield, I apologize. I think I'm handing the mic off to you.

FDA PRESENTATION: BETIBEGLOGENE AUTOTEMCEL (BETI-CEL): BLA 125717 CLINICAL CONSIDERATIONS FOR EFFICACY AND SPECIFIC SAFETY IN TRANSFUSION-DEPENDENT B-THALASSEMIA

DR. LISA BUTTERFIELD: Yes, thank you very much. All right, really appreciate all of the information shared by all of the bluebird bio speakers. And so now we'll move to the FDA presentation. And we'll have a Q&A session after the FDA presentation for

everyone. I'd like to introduce Dr. Karl Kasamon from OTAT.

DR. KARL KASAMON: I'm sorry, Mike. I was expecting that the notes would be also available to the right of the screen.

MR. MICHAEL KAWCZYNSKI: Sure, here you go. There you go. Let me just make sure, Karl. You should have it. Yep, you have advanced rights. I'll do it again.

DR. KARL KASAMON: It's blank.

MR. MICHAEL KAWCZYNSKI: Yes, because you don't have any notes on that slide, sir. If you want me to load another slide deck in, but, go ahead, sir. This slide deck doesn't have any notes in it.

DR. KARL KASAMON: Okay.

MR. MICHAEL KAWCZYNSKI: I can reload another one, but that one that we have doesn't have any in it.

DR. KARL KASAMON: I'm sorry about this. Let me try to read off my other screen with the notes. I apologize for this.

Good morning. I'm Karl Kasamon. I'm a

hematologist and a clinical reviewer at the Office of Tissues and Advanced Therapies within CBER at the FDA.

On behalf of CBER, as well as the AC planning working group, I'll be presenting information from BLA 125717 regarding efficacy and safety of betibeglogene autotemcel, or beti-cel, for the proposed indication, which is treatment of patients with beta-thalassemia who require regular red blood cell transfusions.

I'd like to start with some basic information about the disease for which beti-cel's being proposed, then to describe studies which were reviewed in support of the effectiveness and safety of the product and summarize study results. Finally, I will close with uncertainties that emerged from the FDA's review. My overall goal is to describe our safety concerns and seek input regarding benefit/risk analysis.

Beti-cel is being developed for the treatment of beta-thalassemia. This is a group of rare hemoglobinopathies caused by beta-globin gene mutations which impair production of beta-globin. And in the severe phenotypes, it is characterized by severe anemia

with life-long transfusion-dependence leading to iron overload and causing life-threatening morbidities such as endocrinopathies, cirrhosis, and cardiomyopathy.

These morbidities lead to decreased survival. The phenotype of transfusion-dependent thalassemia, or TDT, is the most severe form. And without red cell transfusions, mortality may be as high as 80 percent by age five.

Currently, the treatment for TDT, or transfusion-dependent thalassemia, remains supportive and consists of regular red cell transfusions and chronic iron chelation. Luspatercept is a red cell maturation agent and has been approved in adults and may help to reduce transfusion burden.

Allogeneic hemopoietic stem cell transplantation may be considered a standard of care for some of the young cohort and may lead to over 85 percent of disease-free survival in children and about 65 percent in adults. Unfortunately, fewer than a quarter of patients have the human leucocyte antigen, or HLA-matched sibling donor available. Therefore, the

transfusion-dependent thalassemia treatment constitutes an unmet medical need.

Now I'd like to briefly tell you about the product, beti-cel. Beti-cel is comprised of autologous hemopoietic stem cells that have been transfused with a BB305 lentiviral vector, encoding the beta A-T87Q-globin. And because it is a variant beta-globin, beta A-T87Q binds to alpha-globin chains and can reconstitute production of stable functional adult hemoglobin and red cells. The ultimate goal of the therapy is to enhance the production of erythrocytes and potentially lead to transfusion independence.

Next, I'd like to give you an overview of the studies from which the beti-cel data were obtained. The FDA analysis included supportive safety data from Study HGB-204, an early Phase 1/2 study, that was a single-arm, open-label study. And it was completed in 2018. It enrolled 19 subjects and treated 18. They received a single dose of three times ten to the sixth CD34 positive cells per kilogram of an earlier generation product. The subjects are between ages 12

and 35, and the study's primary objective was safety and efficacy.

The primary evidence of efficacy and safety came from a pair of Phase 3 studies, HGB-207 and HGB-212, with overall parallel designs. Both of these are also single-arm, open-label, multi-national studies which share the primary objective to evaluate efficacy and safety of beti-cel. Notably, HGB-207 enrolled only those with non-beta-zero-beta-zero genotype, whereas HGB-212 enrolled those who had the beta-zero-beta-zero genotype.

In addition, HGB-207 prospectively divided the subjects into two cohorts, one being for those aged 12 to 50 and the second for pediatric subjects who are less than 12 years of age. Because these Phase 3 studies are still ongoing, the data originated from an interim analysis with a data log date in March of 2021. All subjects completing 24 months of follow-up in these mentioned studies were to then enroll in a long-term safety follow-up study called LTF-303 and undergo a total of 15 years of additional safety following the

infusion of beti-cel.

The next couple of slides will provide additional details of these Phase 3 studies. So to expand on the design of the Phase 3 studies, each consisted of four stages. First, the subjects were screened with a careful documentation of transfusion needs, hospitalizations, laboratory, and chelation history. Then, the subjects underwent stem cell mobilization and apheresis. After which they received myeloablative chemotherapy and then beti-cel infusion. And, finally, they were followed for 24 months.

Both Phase 3 studies share the following inclusion criteria. All participants had to be aged 50 or below and needed to have a diagnosis of transfusion-dependent beta-thalassemia with a documented history of at least 100 milliliters per kilogram per year of red cells transfused over a two-year period that precedes enrollment. Alternatively, those subjects who are at least 12 years of age could be managed under a standard thalassemia guideline and have received at least eight transfusions per year in a two-year period.

Now I will shift to the genotype eligibility criteria. So, because HGB-207 enrolled those with non-beta-zero-beta-zero thalassemia, the beta-zero mutation on both human beta-globin gene alleles was exclusionary. And conversely, HGB-212 enrolled only subjects with beta-zero-beta-zero, thus any mutation other than beta-zero with these alleles was exclusionary. Of note, after amendment five of the protocol, subjects who had a functionally equally severe mutation called IVSI110 were included in Study HGB-212 as this mutation is considered equivalent to beta-zero with nearly negligible beta production.

Subjects from the Phase 3 studies would be excluded if they were found to have any of the criteria you see in this slide, such as chronic viral infections, active infectious diseases, cytopenias, history of cancer, or organ impairment.

Now I would like to move on to efficacy endpoints. Because Phase 3 studies had a primary efficacy endpoint that focused on the clinical benefit of transfusion independence, which was defined as

maintaining a weighted average hemoglobin concentration of at least nine grams per deciliter without any red cell transfusions over a period of at least 12 months at any time in the study following beti-cel infusion, the time period in addition had to start no sooner than 60 days from the last post-transplant red cell transfusion.

The study's secondary endpoints evaluated additional features of transfusion independence as well as transfusion reduction compared to baseline. And they also included endpoints related to iron overload and quality of life. The safety assessments of the study focused on parameters such as hemopoietic stem cell engraftment, transplant-related mortality, overall survival, clinical adverse events, laboratory parameters, as well as insertional oncogenesis.

And at this time, I'd like to move on to study results. This slide outlines disposition of the Phase 3 study subjects. Of the 51 who gave assent or consent to participate, 5 failed screening, and 3 withdrew their consent prior to starting mobilization. Then,

one subject from each Phase 3 study discontinued following mobilization. A total of 41 subjects, therefore, underwent conditioning and infusion of beti-cel with 23 from HGB-207 and 18 from HGB-212.

The Phase 3 study demographic information is presented in this slide. The efficacy analysis population again was made up of 41 subjects who were infused with beti-cel. Key points I would like to highlight include that overall the participants were very young, with median ages of 12.5 and 15. The numbers of subjects in various age categories were protocol-specified. And both studies enrolled the same number of pediatric subjects less than 12 years of age with an N of eight.

Similarly, the proportions of genotypes non-beta-zero-beta-zero versus beta-zero-beta-zero were directed by protocol. And lastly, the participants were well-balanced by sex.

Briefly, I'd like to point out some of the key baseline thalassemia-related characteristics of the efficacy analysis population. With respect to

genotype, the most common was beta-zero beta-plus in the pooled population followed by beta-zero and beta-plus-beta-plus. Subjects in either study had similar baseline transfusion requirements and were transfusion-dependent with a median annualized retro transfused volume of 198 milliliters per kilogram per year. The subjects had a similar baseline weighted average in nadir hemoglobin of 9.6 grams per deciliter.

I will now present the summary of the primary efficacy analysis. Because the Phase 3 studies are ongoing, not all 41 subjects who received beti-cel have had sufficient duration of follow-up before the time of data log. So 36 of the 41 are evaluable for transfusion independence, and the remaining 5 are not. This table presents the percentages of subjects achieving transfusion independence per each study cohort and each study, as well as a total Phase 3 population.

You'll notice 93 percent of the 12 years old and above, Cohort 1, in Study HGB-207 achieved transfusion independence, whereas 86 percent of Cohort

2 subjects at the pediatric less than 12 years old received transfusion independence, which was the same percentage as the total Study HGB-212, and the pooled Phase 3 total was 89 percent. Below the percentage of subjects with transfusion independence, you'll find listed that two cited 95 percent confidence intervals. For each study and each cohort, the prespecified success criteria were met.

Not shown here, transfusion independence outcomes did not differ substantially by genotype, nor by age less than 18 versus 18 years of age and above. But males did have a somewhat higher transfusion independence rate compared to female subjects. And, lastly, four subjects, two from each study, failed to achieve transfusion independence.

The secondary efficacy endpoints, which are listed here, provide additional information about duration and quality of transfusion independence. In summary, once they achieved transfusion independence, the subjects remained free of transfusion needs. The duration of transfusion independence was a median of 26

months ranging to a maximum of 39 months as of the time of data log. And the subjects achieving transfusion independence were able to sustain a level of hemoglobin of 11.5 grams per deciliter, which meets or exceeds their baseline hemoglobin values. The median time from beti-cel administration to the last needed transfusion after treatment with beti-cel was less than one month.

Other secondary efficacy endpoints looked at hepatic and cardiac iron burden using magnetic resonance imaging techniques. And not shown here, overall, the liver and cardiac iron burden parameters at first tended to worsen between baseline and Month 12, and then reverse and started trending to baseline by Month 24.

Here I'd like to reiterate the overall efficacy results of beti-cel in the subjects with transfusion-dependent thalassemia. Beti-cel treatment was associated with a transfusion independence in 89 percent of the Phase 3 study subjects. And they had a median duration of transfusion independence of 26 months with a range of 13 to 39 months at the time of

data log.

At this point, I would like to turn our attention to the safety of beti-cel. The FDA's safety analysis was performed on data originating from Phase 1/2 Study HGB-204, which provided supportive safety data and, again, included 18 subjects in addition to the two Phase 3 Studies HGB-207 and HGB-212, where 41 subjects were treated with beti-cel. And, thus, it gave a total safety population of 59 subjects, and these were followed for a median of 2.5 years with a range of up to 7.

As you'll find presented in this slide, the subjects had comparable exposure to busulfan myeloablation and were then infused with comparable doses of beti-cel. Although, Study HGB-204 subjects were treated with an earlier generation product, and thus, the viral vector copy number in the infused dose was lower compared to the Phase 3 studies.

Here I would like to present an overview of the adverse events. This graph depicts the number of subjects and percentage of the most frequent adverse

events, or AEs, reported in the 59 beti-cel recipients between Day 1 and Month 24. The list includes AEs reported by 40 percent or more of subjects arranged by descending order by frequency. Laboratory-based adverse events were analyzed using shift table analysis.

I'd like to point out that, because beti-cel is infused shortly after myeloablative chemotherapy, the observed adverse events included myelosuppression, and, as shown in the top of the graph, cytopenias were universal. Also very prevalent were gastrointestinal adverse events, which included emesis and mucositis. Febrile neutropenia was likewise common, experienced by 54 percent of the subjects, although severe grade infections were not. Four subjects, which is 6.8 percent, had an AE of sepsis.

Now I'd like to shift your attention to the serious adverse events, or SAEs. A total of 25 subjects experienced 55 SAEs between Days 1 and the last follow-up. This table shows the most common SAEs, listing only those that were observed in five percent

or more of the subjects. And the rightmost column suggests that the majority of the SAEs, except for fever, tended to be of high grade.

Most SAEs, such as cytopenias, infections, and liver veno occlusive disease are associated with busulfan myeloablation, and these were attributed to study interventions other than beti-cel. The FDA attributed three thrombotic events to previous dosing factors, such as indwelling catheter and concomitant medications.

There were two SAEs related to thrombocytopenia that we attributed to beti-cel. One was a serious adverse event of Grade 4 thrombocytopenia that triggered a clinical severe epistaxis requiring hospitalization at Day 69 and occurred in the context of delayed platelet engraftment thus was attributed to beti-cel. In addition, there was one SAE of Grade 3 thrombocytopenia from Day 114 through 163.

The remainder of the safety section will concentrate on the FDA safety concerns. These were a special focus of the review because of the potential

safety signal consisting of prolonged thrombocytopenia, observation of cases of abnormal bone marrow morphology in some subjects with thalassemia, along with hematologic malignancies and insertional oncogenesis that were noted in subjects treated with other products manufactured by the applicant using related or identical lentiviral vectors for other diseases.

First, I'd like to turn your attention to cytopenias and engraftment. This slide looks at neutrophil engraftment after beti-cel administration. Subjects getting myeloablative chemotherapy are expected to develop severe cytopenias, including neutropenia. And then they undergo reconstitution of hemopoiesis and recover.

Many dynamics, including the use of growth factors, can affect the time to hemopoietic recovery. For example, granulocyte colony-stimulating factor, or G-CSF, which is an exogenous pharmaceutical agent, which raises neutrophil counts, can be used to hasten neutrophil engraftment. Per protocol, neutrophil engraftment was defined as the sustained neutrophil

count of 0.5 times 10 to the 9th per liter on three consecutive days within 42 days of beti-cel administration.

And conversely, failure of neutrophil engraftment was determined if neutrophil engraftment did not occur by day 42. The applicant reported neutrophil engraftment by median day of 23 with a range of 13 to 39. Therefore, all subjects appeared to achieve neutrophil engraftment. But there is a caveat, which is that G-CSF was used by 52 percent of the subjects after beti-cel infusion, and, more importantly, 17 percent of them were requiring continuous G-CSF for at least one week beyond the point at which neutrophil engraftment was determined by the applicant. However, G-CSF use can confound determination of true time to neutrophil engraftment.

So, given this potential confounding from G-CSF, the FDA performed additional analysis evaluating time to neutrophil engraftment once subjects were no longer receiving G-CSF. And this analysis revealed a median Day 25 with a range of 13 through 77 to reach

neutrophil engraftment.

Two subjects continued to require G-CSF beyond Day 42, thus raising the question of neutrophil engraftment failure. And overall, these results suggest a degree of delay of neutrophil engraftment following beti-cel when compared with allogeneic transplant for beta-thalassemia where the median day to neutrophil engraftment is reported to range between Days 9 and Day 21.

Even more concerning was delayed reconstitution of platelets following beti-cel. Per protocol, platelet engraftment was defined as three consecutive platelet values of 20 times 10 to the 9th per liter, barring any platelet transfusions within the preceding seven days.

Beti-cel recipients achieved platelet engraftment at a median Day 46 ranging between Days 19 and 191. This is notably delayed compared with allogeneic transplant for beta-thalassemia where, as was shown before, the platelet engraftment is generally reported by approximately Day 25.

The time to platelet engraftment is depicted here in this histogram with subjects clustering around Day 40 to 50, except for outliers. The one subject on the right side of the graph achieved platelet engraftment only by Day 191, and as will be further mentioned, this subject met criteria for lentiviral vector oligoclonality and had a lentiviral integration into a proto-oncogene.

So as mentioned earlier, in order to achieve platelet engraftment, it's only necessary to reach a sustained platelet count of 20 times 10 to the 9th per liter, which is clinically still Grade 4 or severe grade thrombocytopenia. But beti-cel treated subjects did continue to experience slow platelet reconstitution beyond 20 times 10 to the 9th per liter, for example, to a platelet count of 100 times 10 to the 9th per liter. The data analysis showed that, to reach a sustained platelet count of at least 100 times 10 to the 9th per liter for three consecutive measurements without platelet transfusion, beti-cel-treated subjects required a median of 86 days with a range of up to 891

days.

And, to consider another way of looking at this slow platelet recovery, even at 80 days following beti-cel infusion, 17 percent of the subjects still continued to experience Grade 3 or Grade 4 thrombocytopenia. Another reminder, Grade 3 thrombocytopenia is 25 to less than 50, and Grade 4 is less than 25 times 10 to the 9th per liter of platelets.

Lastly, the platelet recovery after beti-cel was apparently incomplete even as late as Month 24. This graph shows the mean platelet values of beti-cel treated subjects. If you look at the leftmost bars of the graph, it demonstrates baseline platelet values, and you'll note that there are approximately 320 to 420 times to the 9th per liter in the three study populations. The timepoints to the right show recovery at Months 6, 12, 18, and 24 post-beti-cel. If we now focus on the rightmost bars, the mean platelet values at Month 24 are approximately 210 to 300 times 10 to the 9th per liter of platelets.

And even though these mean platelet values are well in the normal range, they remain notably lower than they had been at baseline. The cause of this apparent decrease in platelets post-beti-cel remains unknown. But lentiviral integration and gene transduction within hemopoietic stem cells is a possible mechanism. And it is unknown how this bodes for potential development of MDS in the future.

Serial bone marrow biopsies were collected on the Phase 3 Study subjects in order to assess evolution of dyserythropoiesis after beti-cel. And, considering the impaired and incomplete platelet reconstitution observed at beti-cel, independent review of the bone marrow samples was performed and will be discussed.

So here I will summarize some of the bone marrow morphology abnormalities that were observed in the study subjects. As an exploratory efficacy endpoint, all Phase 3 Study subjects underwent marrow biopsy at baseline Month 12 and Month 24, which was aimed to evaluate if beti-cel treatment could lead to improvement in the thalassemia-related marrow changes

or dyserythropoiesis.

And the data are limited because the studies were not clinically intended to evaluate cytopenias, and the pathologists were unable to order ancillary molecular cytogenetic or other studies on the samples. There were baseline morphological abnormalities, which were present among several subjects and which were likely due to their thalassemia. These included limited percentages of ring sideroblasts as well as some dysmegakaryopoietic changes.

Among four of the subjects, ring sideroblasts were only reported in the post-beti-cel marrow samples, but it was not possible to determine and evaluate the baseline status of this finding due to lack of appropriate sample stains at baseline. Furthermore, in one subject, the pathologist reported emergent monolobated megakaryocytes at the Month 12 marrow sample, but then the subject declined follow-up bone marrows for further evaluation.

Overall, the presence of abnormalities such as ring sideroblasts and dysmegakaryopoietic changes

present both in baseline as well as in post-beti-cel marrow samples may impair detection of emergent pathology.

I'd like to now switch and discuss potential risks of lentiviral integration. Lentiviral vector gene therapy carries a risk of insertional oncogenesis due to the potential for integration into host genome during transduction. Consequently, all subjects treated with beti-cel are being screened with integration site, or ISA, analysis in the peripheral blood, which reports the relative frequency of integration sites.

If this testing were to reveal abnormal relative frequency, or abnormal integration patterns, then the subjects would undergo additional analysis using quantitative polymerase chain reaction with specific integration site primers to evaluate if there are any clones that meet the criteria for clonal predominance or oligoclonality.

The definitions of clonal predominance and oligoclonality are listed at the bottom of this slide.

I'll just point out that the proposed definition of oligoclonality is having an integration site with a relative frequency of at least ten percent. And a vector copy number of at least 0.1 copies per deployed genome.

I would like to now briefly summarize integration site analysis findings. So, among the 59 beti-cel recipients who were analyzed, no cases of malignancy or clonal predominance were reported to date.

However, I wanted to focus on three subjects who did meet the oligoclonality definition. One of these subjects has expansion of a clone with integrations into proto-oncogene XP07 and CBFB, and this subject had notable thrombocytopenia with profoundly delayed platelet engraftment only at Day 191. The subject's platelet counts did not reach 100 times 10 to the 9th per liter as of Day 737 post-treatment.

There was another subject with integration site relative frequency patterns that was suggestive of

a clone with multiple integration sites. And one of these integration sites was into the proto-oncogene BCR. This subject likewise experienced prolonged thrombocytopenia with platelet counts not reaching 100 times 10 to the 9th per liter until after Day 501.

There was a third subject who also met the criteria for oligoclonality only at the most recent lab visit. And this one had integration into a gene called MAP4K2, which is involved in single transduction pathway. This subject had unremarkable platelet recovery.

So the oligoclonal lentiviral integration experienced by these subjects, the location of the lentiviral integrations into proto-oncogenes in two of them, as well as their association with prolonged thrombocytopenia were of concern.

The FDA found frequent lentiviral vector integrations into other genes, which were notable. For example, 56 percent of subjects treated with beti-cel were found to have lentiviral vector integrations into a gene called VAMP4. While VAMP4 integration does not

appear to correlate with the late platelet reconstitution, integrations into VAMP4 concern the FDA because VAMP4 integrations were also discovered in a predominant clone within leukemic blast cells of one subject treated with a product for sickle cell that was manufactured by the applicant using an identical lentiviral vector as used in beti-cel. And this will be further discussed in the next slide.

At this time, I would like to introduce a lentiviral vector product called lovo-cel, which is being developed by the applicant for treatment of sickle cell disease. Lovo-cel shares the same lentiviral vector structure as well as gene payload as beti-cel, although there are some manufacturing differences.

Acute myeloid leukemia has been reported after lovo-cel treatment in 2 out of 49 subjects treated with lovo-cel for sickle cell disease. One of these subjects had leukemic blast cells that contained prominent integrations into the VAMP4 gene, although the causal role of VAMP4 gene integration in the AML

has not been proven.

At this time, I'd like to also highlight additional cases that we found worrisome for MDS, which were reported after lovo-cel therapy. So two other subjects with sickle cell disease that were treated with lovo-cel developed anemia and underwent bone marrow biopsy for evaluation. MDS was diagnosed in one subject based on the marrow morphology along with cytogenic aberrancy of trisomy 8 and tetrasomy 8 detected by fluorescent in situ hybridization, or FISH. The diagnosis of MDS was later changed to transfusion-dependent anemia after another marrow test was negative for trisomy 8 and showed some improvement in myelopoiesis.

A second subject with sickle cell disease and anemia underwent bone marrow evaluation and was found to have erythroid dysplasia with persistent trisomy 8 and tetrasomy 8, which were also worrisome for MDS, but the workup is still ongoing because of concurrent vitamin B12 deficiency.

The potential role of lentiviral vector in

these cases has not been proven, but the FDA is concerned about the reported cytogenic abnormality, or trisomy 8, because this has been associated with hematologic malignancies. I'd like to now discuss another lentiviral vector product with integrational oncogenesis concerns.

The applicant is developing a third lentiviral vector product called eli-cel for a rate disease called cerebral adrenoleukodystrophy. Eli-cel is a lentiviral vector product, which is manufactured using a lentiviral vector that is related to beti-cel.

Eli-cel has been given to 67 pediatric subjects, and two eli-cel recipients then developed MDS with a predominant clone containing lentiviral vector integrations into an oncogene called MECOM with EVI1 overexpression. A third eli-cel recipient with MDS has lentiviral vector integration into a genetic variant of MECOM called PRDM16.

In addition to these three diagnosed MDS cases with predominant clonal extension containing lentiviral vectors into either MECOM or other oncogenes, there

were at least four other cases where the FDA has had concern about possibly evolving insertional oncogenesis. These subjects have integration sites with increasing relative frequency into proto-oncogenes. For example, all have had MECOM integrations. One of these subjects appeared to have delayed platelet engraftment and has required administration of an agent like eltrombopag, a thrombopoietin agonist, to elevate the platelet counts.

In summary, the overall safety profile of beti-cel is largely as expected with autologous hemopoietic stem cell transplant. There was a prevalent delay in platelet engraftment, and this was associated with an apparently incomplete return of platelets to baseline and potentially emergent bone marrow abnormalities in at least some subjects.

While no subjects were reported to have clonal predominance or insertional oncogenesis after beti-cel treatment, one subject who received a product manufactured with an identical lentiviral vector for sickle cell disease developed AML with VAMP4 lentiviral

integrations, and two others were observed to have cytogenetic abnormalities and anemia. One of them they know of will become transfusion-dependent after treatment.

Lastly, among subjects receiving lentiviral vector-based eli-cel product for CALD, there are three cases of MDS reported with integration into proto-oncogenes and clonal expansion plus some additional subjects with clonal expansion and cytopenias.

The FDA has not drawn definitive conclusions with respect to the role that lentiviral vector integrations may play in the development of platelet engraftment problems experienced by platelets treated with beti-cel. However, hematologic malignancies observed after treatment with lentiviral vector products for sickle cell disease and CALD do increase our concern that the abnormal platelet reconstitution may progress to MDS.

We're now reaching the conclusion of this presentation. Eighty-nine percent of the Phase 3 study subjects achieved transfusion independence, and,

regardless of age and genotype, this clinical outcome appears durable through approximately 39 months of follow-up. The safety profile of beti-cel is largely consistent with known effects of busulfan myeloablation that precedes beti-cel administration. But beti-cel is also associated with prevalent delay in platelet engraftment and prolonged thrombocytopenia.

Though no clonal predominance due to lentiviral integration or lentiviral vector-mediated oncogenesis has been reported in beti-cel-treated patients, AML and MDS have been reported with the applicant's products manufactured with identical or related lentiviral vectors in subjects with sickle cell disease or CALD respectively.

Therefore, the slow platelet recovery with some marrow morphological abnormalities in subjects with beta-thalassemia and the hematologic malignancies reported in studies with other lentiviral vector-based products make it challenging to assess benefit/risk of beti-cel. And thus, we are looking forward to the Committee's discussion regarding benefit/risk of beti-

cel for the treatment of patients with transfusion-dependent thalassemia.

I am now happy to address any questions that the Committee may have.

CLARIFYING QUESTIONS TO PRESENTERS

DR. LISA BUTTERFIELD: Terrific. Thank you very much. We appreciate the perspectives of the FDA and your review of all of these data.

So we now have time for clarifying questions from the Committee. So I'm going to adjust my screen and watch for those raised hands. Terrific, I see a lot of raised hands, and so we're going to start with Dr. Coffin, Dr. DiPersio, and Dr. M., and then we'll from there. So, please, Dr. Coffin.

DR. JOHN COFFIN: Yes, thank you for those interesting, informative presentations. A question regarding the apparent frequent oligoclonality in the VAMP4, is there any indication from the orientation or location of the integration sites within the gene that

these are indeed likely to be affecting gene expressions (inaudible) from one individual to another?

DR. RICHARD COLVIN: Yeah, so, with regard to VAMP4, yes, we have frequent integrations into VAMP4, but there's no oligoclonality into VAMP4. All of those insertion sites are actually at a very, very low relative frequency to other insertion sites in the patients with beti-cel treatment. I'll ask Dr. Bonner to comment further on your second question.

DR. MELISSA BONNER: Thank you, my name is Melissa Bonner. I lead the research team here at bluebird bio. To reiterate what Dr. Colvin just said with respect to VAMP4, there is no oligoclonality with the exception of the one patient who had AML in 2021. And in that particular patient, the transgene was in the same orientation as VAMP4 as we did detect fusion transcripts. But by and large, from the remaining instances of detecting a single insertion in VAMP4 across many patients, it is heterogeneous in terms of the orientation.

DR. JOHN COFFIN: VAMP4 is a fairly poor

target in vitro in the experiments that we've been looking at, so it would suggest there has been some selection for it. But that selection need not be oncogenic even if it could happen (audio skip) or some other (inaudible) feature.

One other question, in the cases where there is apparent oligoclonality, have the cell types involved been analyzed?

DR. RICHARD COLVIN: So you point out that there are two patients that we showed that have oligoclonality, and I'm going to ask Dr. Coleman Lindsley to come up and talk about the integration sites that these two patients have. What I will point out first is that, first of all, the oligoclonality has been stable over a number of years. And, secondly, these patients are clinically stable.

And part of the change you see in the two -- can you bring up Slide number 2, please -- in these two patients is that previously there was a different method for measuring insertion site analysis, which was in the gray shaded area. That was by LAN PCR. In the

not shaded area where they've remained stable as well, that is when it was done by SEPTS. Dr. Lindsley?

DR. COLEMAN LINDSLEY: Hello. I'm Dr. Coleman Lindsley. I'm the director of clinical genomics and hematologic malignancies at Dana Farber Cancer Institute. In the patient in the right, the two insertion sites in XPO7 and CBFB merit further discussion. XPO7 has not been found to be recurrently mutated or genetically altered in hematologic malignancies or in AML. There are conflicting data, laboratory-based data regarding its potential role as either an oncogene or a tumor suppressor.

CBFB is a partner in a recurrent translocation implicated in AML. Its oncogenic activity, unlike MECOM rearrangements, where the oncogenic activity is related to overexpression of EVI1, is dependent on its fusion partner, which is the smooth muscle myosin-heavy chain which mediates polymerization, aberrant cellular localization, and altered core finding factor transcriptional activity.

DR. JOHN COFFIN: My question really was, has

any cell sorting been done to see what cells these are in?

DR. RICHARD COLVIN: No, these are just in preferred blood mononuclear cells. I would like to point out something too as well. So when you look at the insertion site analysis between our different programs, the insertion sites that are seen in lovo-cel and beti-cel treated patients are very similar. Those that are in eli-cel are very different range of insertion sites, suggesting that the different vectors insert differently.

DR. JOHN COFFIN: That seems very unlikely. I would argue actually the more suggestive may be different selectors than features going on following a transplant. Our experiences are that these patterns are very consistent even among very different cell types. As the original integration has said.

DR. LISA BUTTERFIELD: Any other questions, Dr. Coffin? Or shall we move on?

DR. JOHN COFFIN: Yeah, I'm done.

DR. LISA BUTTERFIELD: Thank you very much.

Dr. DiPersio, then Dr. M., Ott, Gordeuk, Shah, and we'll carry on.

DR. JOHN DIPERSIO: Thanks, Dr. Butterfield. I have two questions really. The first relates to -- obviously, the clinical benefit seems to be quite significant. But the bar is also a little bit higher here because these patients can live with their disease for quite a period of time, even though there are great difficulties and challenges. I wonder, when they were going over the patients that were actually screened failures, they were N percent of the patients that had signed consent that were screen failures.

I'm wondering what is your estimate of how many patients were considered for the study, but never got to the consenting process that would potentially be candidates? What percent of the actual reasonable candidates are we excluding? Patients with mild liver disease, et cetera, et cetera. I'm just curious.

DR. RICHARD COLVIN: Yeah, I'm going to ask Dr. Thompson to comment on this since she screened a lot of the patients who were in the study.

DR. ALEXIS THOMPSON: Thanks, Dr. DiPersio. I think that's a little bit tough to answer. I do think that we certainly have seen a range of iron burdens in the liver, and liver cirrhosis or any evidence of fibrosis is the most common reason for that. We also certainly would exclude patients who have evidence of previous viruses, so hepatitis B, C, or HIV, which we think is prudent. We've also had at least one patient who was excluded because of a reduced iron in 2T star in the heart, suggesting high iron burden in the heart.

I certainly would point out that for those individuals who have high ferritins or high liver iron contents without fibrosis or low 2T stars, their exclusion can be temporary. There certainly is a possibility of intensive chelation and allowing those individuals to come back into the program. We certainly recognize that there may be patients who have evidence of prior hepatitis B or C, and, as long as we're not seeing any active disease and evidence that they've had successful treatment, one could make the argument that they might be appropriate for treatment.

DR. JOHN DIPERSIO: Yeah. Thanks. I think my comment had to do with really the potential for benefit for patients out there that may have been excluded. That would potentially be benefited by this treatment. I'm just trying to get an average estimate of how many patients that would be.

My second and final question has to do with the product itself and the slow count recovery. There were four patients that really had slow count recovery, and there's been an exhaustive analysis of those four patients. That all had to do with integration site analyses and et cetera. Are we looking under the lamppost too much here and not focusing on other events that may be happening? For the sickle cell patients at least, as we discussed yesterday, we thought the kinetics and the cytogenetics and the mutations were more consistent with treatment-related diseases as opposed to insertional oncogenesis.

And I'm wondering, do we have information on those four patients that had very slow count recovery and on the patients that may have a question of MDS, et

cetera, with other sequencing data? In other words, not just looking at integration site analysis, but looking at clonal evolution of specific premalignant clones that really have nothing to do with an integration site analysis that may be related to conditioning for the treatment?

DR. RICHARD COLVIN: Yeah, so I think just taking a step back to think about engraftment in general, it's very clear that there's a very strong relationship with the presence or absence of a spleen. And we've talked about that, and I think that that's the first step. I'm going to ask Dr. Bonner to come up again and speak to the specific patient you're referring to and if there's anything that we have to be able to talk about there.

DR. MELISSA BONNER: Thank you. So in the patients that have been highlighted as potentially being at risk for MDS, I want to clarify. We're talking about some of the patients are coming from the lovo-cel program as well, correct?

DR. JOHN DIPERSIO: Right.

DR. MELISSA BONNER: And the patients with the two alpha-globin gene deletions. So those patients are extremely polyclonal. By integration site analysis, they have no signal insertion site greater than even a fraction of a percent. And also, we have done next-generation sequencing using hematological malignancy panels to look at potential emergence of clones from a vector-agnostic perspective.

And, while we have detected mutations, most of them variants of unknown clinical significance that are likely germline because they are present pre-treatment in baseline screening samples. We have not seen the emergence of any novel variants post-treatment in those patients.

DR. JOHN DIPERSIO: So what you're telling me is that there's no common recurrently mutated genes that we see in AML or MDS that appear, especially in these patients that have slow recovery?

DR. MELISSA BONNER: Yes, and if we could have Slide 2 up, please? And to go even further, so, as I stated, we have no malignancy driver mutations

identified, which you just stated as well. We have high polyclonal reconstitution with integration site analysis.

We have done karyotyping on bone marrow and they are both normal. There was a transient trisomy 8; it was only detected with FISH. It was not detected on karyotype. And there is no diagnostic evidence of MDS or AML from peripheral counts. And I would like to also add that both subjects have benefitted from the treatment.

DR. JOHN DIPERSIO: All right, thank you.

DR. RICHARD COLVIN: One other thing while we're talking about those two patients, again, I'd like to ask Dr. Williams to come up for a moment and comment on the alpha-globin deletion status of these patients and information that he has as well.

DR. DAVE WILLIAMS: Yeah. Thank you. I'm Dave Williams. I'm chief of hematology/oncology at Boston Children's Hospital and Dana Farber Cancer Institute, and Leland Pike's professor of pediatrics at Harvard Medical School. I have no financial interest in the

outcome of the proceedings today. Although, I was the coordinating investigator for the trial discussed yesterday in ALD. And I've worked in this field since 1982 when I developed vectors for transfer genes into hemopoietic stem cells as a post-doc at MIT.

We have a trial in sickle cell disease that's quite different than the trial that was referred to here, the bluebird trial, in the sense that our vector, which is a lentiviral vector, instead of transferring an additional copy of a globin gene, transfers an engineered sequence called a schmear, which is an SHRNA embedded in a micro-RNA that modulates the expression of a gamma-globin repressor called BCL11A.

We have a Phase 1 trial that's just completed treating ten patients. The efficacy is quite good, just like the bluebird trial. And in that trial, we have one patient out of ten who has two alpha gene deletion alpha thalassemia trait. And in that patient, who's had efficacy from a VOE standpoint, we do see, while there's an increment in the hemoglobin that's significant, over one gram and a half of hemoglobin,

that patient's hemoglobin after therapy is likewise lower than the other patients in our trial, leading us to believe that potentially there's a modifying effect on the response to modulation of fetal hemoglobin in the presence of two alpha gene deletions, which would be, in some ways, similar to the finding that bluebird has had.

I just want to make one other comment since I have been in the field for so long. The FDA has concerns about the insertional mutagenesis potential comparing beti-cel with eli-cel. And, as a person who's worked on vectors my entire career, there's really a distinct difference between those two vectors.

As we talked about much of yesterday, the eli-cel vector has an MND LTR in the middle of the vector, and we know that MND LTRs have mutagenic potential from experience in animals as well as experience in other trials. So I think the comparison, while I understand the concern, is not one that most of us in the field would make. Thank you.

DR. LISA BUTTERFIELD: Thank you very much.

We want to maintain focus on the specific clarifying questions from the Committee, please. Dr. DiPersio, anything else from you?

DR. JOHN DIPERSIO: No. No, thanks, Dr. Butterfield.

DR. LISA BUTTERFIELD: Thank you. We'll move into Dr. M., and then we'll hear from Dr. Ott.

DR. JAROSLAW MACIEJEWSKI: Am I on?

DR. LISA BUTTERFIELD: Yes.

DR. JAROSLAW MACIEJEWSKI: I just wanted to clarify one thing. Those two patients with clonality by insertion, they did not have any clonal hematopoiesis by NGS, is this correct?

DR. RICHARD COLVIN: The two patients that we just were speaking about that Dr. Lindsey were here, that is correct. By NGS, there's no sign of clonality.

DR. JAROSLAW MACIEJEWSKI: Got you. Among your patient, given the age, I mean you, Dr. Coleman, published a paper or is a co-author of a paper showing not increased rate of, at least in sickle cell anemia, of clonal hematopoiesis. One would think that the

stress hematopoiesis in patient with beta-thalassemia or other hematopoietic anemia would generate a higher rate of evolution of clonal hematopoiesis. What you are saying is that you did next-generation sequencing in all of your patients, and there was not a single case of clonal hemopoiesis by NGS, correct?

DR. RICHARD COLVIN: Well, we didn't do NGS on patients at baseline and patients with thalassemia. And, in terms of the other question about whether or not the stress hematopoiesis is similar in patients with sickle cell disease versus patients with beta-thalassemia, I'm going to ask Dr. Thompson to comment on that.

DR. ALEXIS THOMPSON: Thank you. I think that this is an opportunity to continue to reiterate while these are both beta hemoglobinopathies that this is certainly one area where there does seem to be a distinction. There's a tremendous amount of interest in trying to understand the contribution of stress erythropoiesis and chronic inflammation in clonal hematopoiesis in sickle cell disease.

It's worth noting that the degree of inflammation that's seen on the bone marrow and that one can see markers for in the peripheral blood in sickle cell do not appear to be present in individuals who have thalassemia. So it would suggest that it is not surprising that some of the findings that continue to raise concerns and that continue to be areas of active research in sickle cell are not being seen in beta-thalassemia.

DR. JAROSLAW MACIEJEWSKI: I think my question was a little bit deflected. I mean, it's just a simple question. Using clonality measures that we use clinically, was there any clonal hematopoiesis detected in the patients who were transplanted? Or, if you didn't do it, it's okay. Just tell us.

DR. RICHARD COLVIN: If your question is about the ISA, we do know that where we saw oligoclonality -- and, by the way, it comes to we did not do NGS routinely on these patients, and we did not see any evidence in those that we of any clonality.

DR. JAROSLAW MACIEJEWSKI: Okay. This is

fair. You just did not search for clonal hematopoiesis and therefore (audio skip).

DR. RICHARD COLVIN: Oh, that's correct. Based on our baseline understanding that patients with beta-thalassemia are not at increased risk for hematologic malignancies and when we think about allogeneic transplant donors, for example, who are also not thought to be at risk for having increased clonal hematopoiesis, we did not screen at baseline to see if there was any evidence of that for patients with beta-thalassemia in these studies.

DR. JAROSLAW MACIEJEWSKI: Well, clearly patients who undergo autologous stem cell transplantation for other indication are at much higher risk for clonal hemopoiesis -- many papers -- and at higher risk for malignancies. You didn't see it; it's great. I just wanted to make this comment.

One more question. During the duration of the study, luspatercept was FDA approved for congenital hemolytic anemias. Does it affect the sort of indication, or you saying that luspatercept is not have

been -- and forgive me, I'm not an expert on these diseases -- was not enough of a game-changer to somehow change the equation in terms of the benefit given presence of this easily administrable drug?

DR. RICHARD COLVIN: Yeah, I'm going to ask Dr. Thompson to comment.

DR. ALEXIS THOMPSON: With regard to luspatercept -- and this is full disclosure. I've been an investigator on both the trials for luspatercept in transfusion-dependent as well as non-transfusion-dependent thalassemia. The mechanism of action of luspatercept is not entirely elucidated, but it's fairly clear that it works on a committed red cell precursor and induces late erythroid maturation.

The degree of improvement in patients even with transfusion-dependent thalassemia was noteworthy and clinically meaningful. However, it would not achieve transfusion independence. It may reduce the frequency and the total volumes of their transfusions. And currently, it's only been approved for adults.

DR. JAROSLAW MACIEJEWSKI: Got you. I mean,

this is a very good point, I think, and important to know. Thank you.

DR. LISA BUTTERFIELD: Thank you very much. We're moving to Dr. Ott and then Dr. Gordeuk and Dr. Shah.

DR. MELANIE OTT: Yes, thank you. I have a question regarding safety and the delay of platelet engraftment. Probably Dr. Singh or Dr. Bonner. I wonder whether you have checked whether your promotor is leaky in the megakaryocyte lineage and could explain why there is a delayed engraftment there?

DR. RICHARD COLVIN: I'm going to ask Dr. Bonner to respond to this.

DR. MELISSA BONNER: We have not checked specifically in the megakaryocyte lineage. I think the best piece of data that we have to support that we don't see any leakiness of our promotor would be due to the investigation that we had into our sickle patient who developed AML in February of 2021. Because in that case, we were able to enrich the CD34 positive blast population and conduct RNA sequencing analysis. In

that analysis, if I could have Slide 1 up, please, as you can see at the top right corner of the screen, this is detecting transcripts of HBB.

And this includes the transgene beta-A-TD7-Q. And in the CD34 positive, both bone marrow and peripheral blood populations, you can see that there is an extremely low level of transcript detected here. And, in fact, the majority of the transcript is actually coming from the endogenous beta-F. Notably, the CD34 positive population is the non-erythroid-containing population. And, of course, in the CD34 negative bone marrow population where you would expect erythroid cells, we see a substantially higher level of HBB expression.

DR. MELANIE OTT: Okay. My second question is regarding efficacy. And I was interested to hear more about the four patients. I believe it was four patients who did not achieve transfusion independence. It sounded as if this was due to transduction efficiency or VCN later but would like to hear what happened there and what conclusions you draw out of

this.

DR. RICHARD COLVIN: Yes. Can we please have Slide 2 up? These four patients had among the lowest values for the percentage of transduced cells in the drug product. Because of these and other results, we did a retrospective analysis, and the analysis identified that certain manufacturing parameters could be responsible for these low numbers. So I want to draw your attention to, on the slide, that the top and those blue dots that are the top-level across, those are all patients who became transfusion-independent.

Those in the middle did not become transfusion independent and kept receiving transfusions. And those five dots on the bottom were those patients that I talked about earlier in my presentation that have recently become transfusion-independent because the amount of time has gone by to be able to evaluate. You can see that those dots in the middle, those beige dots, are on the lower side of the chart. And as you go left to right, you can see that the probability of becoming transfusion-independent increases as you move

to the right with a higher percentage of cells that are transduced. One thing to point out of course is that not all cells have been transduced in any patient.

The analysis we did showed that there could be some manufacturing parameters that could be responsible, therefore manufacturing controls were tightened. And these are included in the proposed acceptance criteria for the percentage of transduced cells in the drug product. All patients treated since the process has been more precisely controlled have achieved transfusion independence.

DR. MELANIE OTT: What is the number? The percentage of transduction?

DR. LISA BUTTERFIELD: I'm going to ask for real concise questions and answers because we have to get to a lot of people, please.

DR. RICHARD COLVIN: Yeah, so you can see where it is on the chart. It's around 60 percent.

DR. MELANIE OTT: Okay. Thank you. That's all.

DR. LISA BUTTERFIELD: Thank you very much.

Dr. Gordeuk and Dr. Shah and Dr. Wilkins. Please.

DR. VICTOR GORDEUK: This is actually Victor Gordeuk on the screen right now, so should I ask my question?

DR. LISA BUTTERFIELD: Yes, please.

DR. VICTOR GORDEUK: Yeah. I'm just interested in the fact that the platelet counts at Month 24 were substantially lower than the platelet counts at baseline. But could it be that those platelet counts at Month 24 are more reflective of the normal population than at baseline?

Because certainly, the bone marrow is with the (inaudible) is undergoing quite a bit of stress, and there could be a stimulate to platelet production that has been relieved by the more normalized platelet count that Month 24. So could one look at the background population, some statistics, and match it to the patients at Month 24 and see if actually they have more normal platelet counts versus the number here?

DR. RICHARD COLVIN: Yeah, thanks. I'm going to ask Dr. Thompson to answer.

DR. ALEXIS THOMPSON: Dr. Gordeuk, that is precisely how most of us would have interpreted that data. They are lower than they were at baseline, yet they're within the normal range, and I do think that a very plausible mechanism would be that they have more normal hemopoiesis after beti-cel therapy. And that it would, as a result, result in a platelet count that is still within the normal range but lower than baseline.

DR. VICTOR GORDEUK: Okay, yeah, thank you. That seems logical to me as well. And I have one other question. In terms of iron overload resolving after the transplant, does it only resolve with a phlebotomy or iron chelation? Or is there some resolution of iron overload without phlebotomy or iron chelation after transplant?

DR. RICHARD COLVIN: Again, I'm going to turn to Dr. Thompson, who's treated a number of these patients.

DR. ALEXIS THOMPSON: There was actually a subset of patients who did not get any post-beti-cel therapy. Not surprisingly, they were patients who came

in with remarkably well-controlled iron coming into transplant. And their MRIs and serum ferritins following it were within a range that their treating clinicians have opted not to treat them. Having said that, I think the one area that we are particularly excited about is that once individuals are able to -- if I can have Slide 1 up -- when you get to the point where patients have achieved iron reduction with chelation in this place following beti-cel therapy and then you continue to follow patients after they stop chelation. What's quite gratifying is that their iron homeostasis has modified at that point, so that they do not reaccumulate iron.

Is it possible that some of them would have reduced some without chelation? I suppose, but I think many of us are fairly satisfied with the safety parameters for either chelation or phlebotomy to recommend that routinely after transplant. And what's satisfying is that once achieving that reduction, it seems to be sustained.

DR. VICTOR GORDEUK: All right, that's

excellent. Thank you.

DR. LISA BUTTERFIELD: Thank you. So we're going to go to Dr. Shah next, and then I wanted to allow for a quick comment from Dr. Kasamon after that.

DR. NIRALI SHAH: Perfect. So I have just two questions. One of mine was already answered. The two questions I have, if you found an association between having a spleen or having a splenectomy and the association with prolonged thrombocytopenia. I wanted to ask what your thoughts about there was and if you had looked at spleen size or sequestration and the potential etiology for that.

My second question is I wanted to know if any of your patients had received any type of TPO agonist or something to kind of improve the platelet count? I just didn't hear much about that.

DR. RICHARD COLVIN: Okay. I want to ask Dr. Singh to respond to your question.

DR. AJAY SINGH: Yes. So, Dr. Shah, we were able to look at spleen size in our Phase 3 studies. If I could have Slide 2 up, please? So just to orient you

here, this is a six-month platelet count. In the right left are patients that don't have a spleen. The second bar, these are (inaudible) are patient that have a spleen but no splenomegaly. And, most importantly, the third one are ones that we had splenomegaly identified by volume.

But then there is evidence that not only does the spleen make an effect, but it's also the size of the spleen and probably hypersplenism. And tell me the second question? It was the growth factors. We did not routinely give growth factors. Dr. Thompson, do you have any comment on that?

DR. ALEXIS THOMPSON: I think the only additional comment I would make is that platelet counts in thalassemia, in my opinion, are confounded by the physiology of thalassemia. We are not surprised that there are going to be some patients who have some degree of hypersplenism, which will make it very difficult to differentiate those aspects of platelet recovery that are associated with platelet engraftment and those that are peripheral destruction.

Ideally, those are in balance. After a hemopoietic stem cell transplant, we would hope that there is normalization of many things, especially given that these individuals stop transfusions. And so, the sensitization and the stimulation of their spleen improves, but it certainly is the platelet engraftment. I can appreciate that from the FDA's perspective that that is one area of great concern to the extent that it's related to the procedure. I would point out though in the thalassemia world it is not surprising though to have great difficulty in interpreting it given that these patients typically have hypersplenism.

DR. LISA BUTTERFIELD: That answer your questions, Dr. Shah?

DR. NARALI SHAH: I think I wanted to confirm that for the patients who have not received TPO agonists? I think that's the second part of the question.

DR. RICHARD COLVIN: No, they do not.

DR. LISA BUTTERFIELD: Great. Thank you, Dr. Shah. All right then. Let's move to Dr. Kasamon, and

then our two patient representatives, Dr. Singh and Trieu.

DR. KARL KASAMON: Thank you. I wanted to comment about the, I think, reasonable but somewhat charitable hypothesis that it's potentially the functional curative impact of beti-cel that may affect the underlying thalassemia and therefore remove the antecedent sort of secondary thrombopoiesis thus lowering the platelets thereafter. But I think that would be a, obviously, considerable diagnosis of exclusion, and also, in my perusal of allogeneic transplant literature, I haven't seen as much of this impact.

I would assume that replacing a faulty marrow with thalassemia with a donor marrow would potentially have the same impact if it were simply a correction of the thalassemia.

Second question I had, or two perhaps small ones, were aimed just what Dr. Bonner. We wanted to maybe seek some clarity regarding the two sickle cell subjects who had the debatable MDS cases. So we wanted

to clarify the statement that they both gained benefit from the treatment and, depending on which endpoint is looked at, one of them developed de novo transfusion-dependence. In other words, before she was treated, she did not require transfusions, and now she appears transfusion-dependent. So we wanted to ask about that.

And then the second issue was the transiency of the trisomy 8 in the second subject, the male subject. We understood that it was not transient, and we wanted to see if that's the case. Thank you.

DR. RICHARD COLVIN: Yes. I will start with the second question, again about these two patients. Pull up Slide number 2 please, again. This is similar. This is what Dr. Bonner had shown earlier today. But I think one of the key pieces here is that these patients are fully polyclonal. In any way you look, whether it's through insertion site analysis, they have more than 30,000 unique integration sites. The highest one is less than one percent in both of these patients.

When it comes to evidence of alpha-globin/beta-globin mismatch, we've seen some evidence

of that, but we've also seen that this occurs in another program where there's a patient with alpha-globin deletion. For these reasons, we've made an exclusion -- the protocol's ongoing -- that these were going to be the case.

In terms of the clinical benefits that these two patients have had, I'll start with the younger, the young man first, who's about 14 years old now. He was having frequent VOEs. He is maybe mildly anemic at this point, but he's not had any VOEs since. And he's doing extremely well. He and his family evidentially are very happy with how things are going.

In terms of the trisomy 8, I'm going to ask Dr. Lindsey to comment on the trisomy 8 and what we're seeing there. And because we have seen -- when we looked at the karyotype of these patients -- and I do believe it's still the gold standard -- we counted more than 200 metaphases, which were similar numbers than there are in terms of what was looked at with FISH. I'm going to ask Dr. Hasserjian to come up and talk about the FISH results. And also the bone marrow's

from these patients since he reviewed them.

DR. ROBERT HASSERJIAN: Thanks. I'm Robert Hasserjian. I'm a hematopathologist at Massachusetts General Hospital and a professor of pathology at Harvard Medical School, and I have interest and expertise in both clinical and research in the diagnosis and classification of MDS. And I did review these patient samples.

And, as Dr. Colvin said, the karyotypes of both these patients was entirely normal. And, in fact, FISH is not recommended to be performed if a karyotype is done with 20 normal metaphases. It's not uncommon to see borderline levels of abnormalities, especially in numerical, like trisomy 8. As we've seen, these numbers were five percent, seven percent. They were very low, near the cutoff that one would expect and could be false positive and shouldn't have been done anyway, because normal karyotype of 20 metaphases is considered to sort of exonerate cytogenic abnormality, and FISH shouldn't be performed.

Morphologically, the changes I saw were

entirely consistent with stress erythropoiesis. And, importantly, as you heard, there's no evidence of clonality by integration site analysis and clonality is the sine qua non of MDS. So I think that's very strong evidence that there's not a clonal process going on.

DR. RICHARD COLVIN: And there was a second question? I wanted to make sure we get to as well. And can you rephrase that, please? The first question.

DR. LISA BUTTERFIELD: Dr. Kasamon, anything remaining?

DR. KARL KASAMON: Well, I guess, the second part was the part about the benefit. There may be sickle cell disease endpoint benefit, but this could be explained by becoming transfusion-dependent and thus being given adult hemoglobin. And so, she became de novo. The second subject became de novo transfusion-dependent, which we believe is not a benefit.

DR. RICHARD COLVIN: Understood. And I just want to point out too that the first patient, the one you're referring to with the persistent FISH, most recently, we had a peripheral blood FISH that was

negative. No sign of trisomy 8.

DR. KARL KASAMON: All right. One more little point. I believe that patient with the transfusion dependence also had a potentially germline ATM mutation. I just wondered if you could comment on that, on the implications.

DR. RICHARD COLVIN: Yeah, thanks. Dr. Lindsley will comment on that.

DR. COLEMAN LINDSLEY: Yes, there was a likely germline splice site alteration in ATM that was identified prior to treatment. And after treatment, this was because of the persistence before and after as well as the variant allele fraction, which was approximately 50 percent, was presumed to be germline. Heterozygous splice site or, in this instance, variants in ATM are rather common and do not, on their own, correlate with a markedly increased risk of malignancies.

DR. KARL KASAMON: Thank you.

DR. LISA BUTTERFIELD: Okay. Dr. Kasamon. Let's close out the question period by hearing from our

two patient representatives. First, Dr. Singh.

DR. NAVDEEP SINGH: Hello. Yeah. I just had a general question. There was one slide earlier on where you had the red slide, and you were showing these were the patients that had to continue transfusions. I was wondering, was there any common trend or common -- what was the reason basically that these patients, was there any commonality, any common denominator that these patients, that they all had that why these patients had to continue transfusions?

DR. RICHARD COLVIN: Yeah, so there were no clinical features in common with these patients. The only commonality was that they had relatively low percentages of transduced cells. And so, for that reason, they weren't able to make enough of the transgenic T87Q hemoglobin in order to become transfusion independent.

DR. LISA BUTTERFIELD: Okay.

DR. NAVDEEP SINGH: Okay. Thank you.

DR. LISA BUTTERFIELD: And then, Dr. Trieu. We can't hear you.

DR. JANELLE TRIEU: As a follow-up to that question or in regards to the four patients unable to achieve transfusion independence, what is known about their eligibility to undergo therapy a second time?

DR. RICHARD COLVIN: Yes, so as of this time, because a second transplant may be more risky for the reasons that we know about either allogeneic or autologous transplants, at this time, people are not eligible to undergo a second transplant. But I'm going to let Dr. Olson comment a little bit further on second transplants for such indications.

DR. TIM OLSON: Hello. I'm Dr. Tim Olson. I'm the medical director of blood and marrow transplant at the Children's Hospital of Philadelphia. And I think I can answer this question. When a patient has undergone a busulfan-based regimen once, we would not repeat a busulfan-based transplant a second time. However, if there are donor options that are available there are alternative conditioning regimens that could potentially be available for allogeneic transplant.

DR. LISA BUTTERFIELD: That answer your

question?

DR. JANIELLE TRIEU: Thank you.

DR. LISA BUTTERFIELD: Thank you very much. So with that, we need to close out this very robust question and answer period. I'd like to thank everyone for the important discussion. We will now reconvene in 30 minutes at the top of the hour for the open public hearing. Thank you very much.

MR. MICHAEL KAWCZYNSKI: Everyone, stay online just for a minute. Wait till we're clear.

[LUNCH BREAK]

OPEN PUBLIC HEARING

MR. MICHAEL KAWCZYNSKI: Welcome back to the 72nd Cellular Tissue and Gene Therapy Advisory Committee meeting. Let's get started after that lunch, and I'm handing it back to our Chair, Dr. Butterfield, and our DFO, Dr. Christina Vert. Take it away.

DR. LISA BUTTERFIELD: Thank you very much.

Welcome to the open public hearing. I'll start by reading the announcement for particular matters involving specific parties.

Welcome to the open public hearing session. Please note that both the Food and Drug Administration, FDA, 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 expenses in connection with your participation at this 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. That being said, I now turn it over to Christina Vert for the open public hearing session.

MS. CHRISTINA VERT: Thank you, Dr. Butterfield. Before I begin calling the registered speakers, I would like to add the following guidance. FDA encourages participation from all public stakeholders in its decision-making processes. Every Advisory Committee meeting includes an open public hearing, OPH, session, during which interested persons may present relevant information or views.

Participants during the open session are not FDA employees or members of this Advisory Committee. FDA recognizes that the speakers may present a range of viewpoints. The statements made during this open public hearing session will reflect the viewpoints of the individual speakers or their organizations and are not meant to indicate Agency agreement with the statements made. With that, we will move on to the

first speaker. Janet Kwiatkowski.

DR. JANET KWIATKOWSKI: Great. We're on Slide 1. Good afternoon and thank you for the opportunity to speak today. I'm Janet Kwiatkowski. I direct the thalassemia program at the Children's Hospital of Philadelphia where I've helped care for individuals with thalassemia for over 20 years. I also currently serve as the Chair of the Medical Advisory Board of The Cooley's Anemia Foundation.

Next slide, please. I have participated in the beti-cel and lovo-cel clinical trials as shown on this slide, and I've also consulted for bluebird bio in the past. But I have no financial interest in the outcome of the BLA.

Slide 3, please. Individuals with thalassemia may experience a number of different clinical complications. These can broadly be divided into complications due to the life-sustaining transfusions and complications from the anemia and ineffective red cell production. Repeated blood transfusions cause iron accumulation, and, if not well controlled with

medications, this leads to a number of complications including heart disease, diabetes, and other endocrine problems and liver fibrosis, which increases the risk of hepatocellular carcinoma.

Other complications with transfusions include a risk of developing antibodies to red cells that can make transfusion difficult and acquiring a bloodborne infection. Complications also can occur due to ineffective red cell production and anemia, including growth delay, facial bone changes, extramedullary hematopoiesis, and other problems as listed here.

Slide 4, please. Over the past few decades, significant advances in conventional therapy have been made, including the availability of oral iron chelation and the ability to monitor iron burden with MRI, but conventional therapy is still arduous. This slide provides an overview of treatment.

Regular blood transfusions typically are administered every two to five weeks. These visits take several hours, meaning a missed day from work or school. Iron chelation therapy is given to control the

iron burden. This involves taking either an oral medication once to three times a day or deferoxamine as a subcutaneous infusion given over 8 to 12 hours.

Side effects to the medication, such gastrointestinal upset or liver or kidney problems, can occur. And finally, regular monitoring is required to assess the effectiveness of treatment and to monitor for possible side effects.

Slide 5, please. As you can see on this slide, the comprehensive care needed is burdensome with a number of tests and specialists visits required at least yearly, and, in the setting of a complication, even more frequent testing is needed. The burden of treatment often negatively impacts quality of life and things that we take for granted, like taking a vacation, all need to be carefully planned to fit in with the transfusion and treatment schedule.

Slide 6, please. Thus, curative therapies are desperately needed for individuals with thalassemia. We've known that allogeneic hematopoietic stem cell transplant is an excellent treatment option,

particularly if a matched sibling donor or a well-matched unrelated donor is available. However, outcomes are best for young children.

There's a risk of graft versus host disease, and this treatment option is not available for over half of the patients because of the lack of an appropriate available donor. Gene therapy with beti-cel offers another potentially curative treatment option to fill this gap. There is no need to find a donor and no risk of graft versus host disease as the donor is the patient.

As you have seen earlier today, rates of transfusion independence are excellent. Importantly, the outcomes did not vary by age, which opens up treatment options for adolescent and adult patients where allogeneic transplant outcomes are worse. I've had the benefit of caring for a number of patients who participated in the beti-cel clinical trials, and I can tell you that patients and their families all report that this treatment option has changed their lives.

I strongly support the approval of beti-cel,

which provides a much-needed treatment alternative for patients. Thank you.

MS. CHRISTINA VERT: Thank you. Next speaker will be David Wiseman.

DR. DAVID WISEMAN: Hello. Thank you. Can you hear me?

MS. CHRISTINA VERT: Yes, we can hear you.

DR. DAVID WISEMAN: Thank you. I have no conflicts. The first title of this slide is a title slide number 1. Please see our written remarks. In these excellent deliberations bluebird, FDA, NAH, and the panel have wrestled with complex risk benefit and their issues in trial analysis and molecular biology. We thought -- with decades of medical development experience, I can say this is what FDA review is supposed to look like.

So where is the same excellence in FDA's handling of COVID vaccines? We heard in Tuesday's VRBPAC meeting that 73 percent of Americans had reservations about COVID gene therapy vaccines, hardly meeting OTAT's goal to increase public confidence in

novel technologies.

Next slide 2. Moderna and BioNTech expected to see their COVID vaccines regulated as gene therapies. Meeting FDA's biological definition, infectious disease vaccines are excluded from FDA's guidance.

Next slide, 3. Despite this, OTAT has six labs working on gene therapy, flu vaccines, and COVID. Next slide, 4. Last September, FDA asked this Committee about other viral vectors and adverse events resembling those seen with COVID vaccines, cancer, liver, blood, nerve issues, and -- next slide 5 -- other concerns requiring 5 to 15 years of follow-up but ignored by VRBPAC.

Next slide, 6. These concerns show up as VERS safety signals. Next slide, 7. CDC now recognizes MIS-V to include blood, liver, and neuro elements. Next slide, 8. COVID vaccine neuro effects are now also recognized by NIH.

Next slide, 9. What about pseudouridine toxicity? Next slide, 10. What are the effects of human gene sequences in untranslated regions? Next

slide, 11. BioNTech flags genome integration in DNA vaccines and mRNA transient issues.

Next slide, 12. For Pfizer's FOIA files, we know little about the kinetics of the mRNA or its spike protein product. Next slide, 13. Their persistence in this study for at least eight weeks causes concern. Next slide, 14. This contradicts CDC's information.

Next slide, 15. Evidence here, a reverse transcription of vaccine mRNA to DNA invokes Dr. Sahin's fear of insertional mutagenesis. Next slide, 16. Where are the carcinogenicity or genotox studies? What are the insertional risks from residual DNA impurities described in this EMA report?

Next slide, 17. From CDC data, does negative vaccine efficacy reflect gene therapy guidance concerns about infection? Next slide, 18. Other studies concern waning and negative efficacy plummeting below FDA's 50 percent guidance. Next slide, 19. Boosted vaccine efficacy wanes rapidly.

Next slide, 20. The wisdom of frequent boosting is questioned in EMA and in CDC's ACIP as the

last whack-a-mole. Next slide, 21. EU data showed limited periods of beneficial association between boosting and all-cause death emits detrimental periods, especially in the under 60s. Next slide, 22. CDC data reveals similar detrimental associations.

Next slide, 23. Is FDA hiding its gene therapy COVID vaccine concerns? Has FDA consulted its own experts in OTAT? And if not, why not? Next slide, 24. FDA toxicologist and FDA's AMBAC committee critically reviewed mutagenesis in the COVID drug molnupiravir.

Last slide, 25. The critical review here of bluebird's platform shows that OTAT can increase public confidence in novel technologies. So why has FDA not increased public confidence in COVID vaccines, not acknowledged COVID vaccines as gene therapies, and not afforded the public fully informed consent? Getting to why the COVID vaccination for children, this Committee must dissect their risks. What say you, Drs. Bryan and Butterfield? Thank you.

MS. CHRISTINA VERT: Thank you. Next speaker

will be Wanda Sihanath.

MS. WANDA SIHANATH: Hi, everyone. My name is Wanda Sihanath, and I was one of the first patients in the bluebird biogene therapy clinical trial for beta thalassemia. Specifically, I was diagnosed with E-beta thalassemia. This transplant took place at Lurie Children's Hospital in Chicago, Illinois in 2014.

When I signed the consent form the day after my 18th birthday, eight years ago, I had no clue my life would end up the way that it did. Until that day, I was set with the fact that I would never leave the Chicago area because that's where my parents and I were comfortable receiving my care. I had a monthly routine where I would miss a day of school and spend it at the transfusion center. Because of these regular transfusions, I also had to make sure my iron levels were maintained and taking the necessary chelation medication and doing proper bloodwork and scans necessary.

I thought this was the routine I would have for the rest of my life. When I presented the

opportunity that a clinical trial was going to begin for gene therapy for thalassemia patients, I was both excited and scared. Being one of the first, there was some miscommunication about expectations between my care team and myself. This included discussions about my length of stay in the hospital, how long I would be in isolation without visitors, and if I would lose any of my hair due to the chemotherapy.

One of the concerns I have to this date is whether or not my fertility was affected. I was not offered egg freezing as a covered option in the study whereas everyone following me in the study was. This is something I'm still pessimistic about. Being 18 at the time of consent, I do believe I was a bit naïve, and looking back, I wish I did receive some sort of counseling so I was able to understand everything that will and could've happened more thoroughly before proceeding.

The process of collecting my T cells through apheresis took four 10-hour days. After the cells were shipped to a lab and was done, I spent about a month in

the hospital where things moved very fast. I was given four days of chemotherapy to prepare my body for transplant of the new cells. I was told the drug was pretty aggressive, but I was exercising every day and even requested an exercise bike for my room.

Soon after the chemotherapy was done, a 15-minute IV transfusion was all it took for the new (Audio skip) to be transplanted. Everything went smoothly, and the most inconvenient bumps in the road were mouth sores that I got from the chemo and an infection from my pick line, which probably added about a week to my stay. I was discharged from the hospital after a month, which was quicker than expected, and I had to do daily, then every other day, then weekly checkups for about a month. And now, eight years out, I only go back for a follow-up annually.

I'm currently taking chelators to bring my ferritin down as my body has become stagnant on relieving it naturally. My hemoglobin has also been slowly dropping over the last eight years, and it was at a 9 when measured last month. We haven't determined

if this was because the drug is wearing off over time or if my body needs an extra boost to continue producing hemoglobin by its own.

I personally would like to avoid going back to regular transfusions, and I was also asked recently if I would do this all again if I wanted to become transfusion free moving forward, which I believe I would do so.

Taking the steps to be a part of this clinical trial was one of the best decisions that I've made. I hope to allow others to follow suit and feel the freedom that I have not being limited by my own disease. With my transplant in March 2014 and my last blood transfusion that following month in April, I've not taken these last eight years for granted. The freedom I have not being tethered to my transfusion center and not feeling the burden of the long-term effects of iron overload and accompanying chelation.

I had moved to Arizona for college, then England to do my master's degree, and now I'm currently residing in California. My career in biomedical

engineering and research also may or may not have been inspired by my experience with gene therapy. Had this experience never had happened, who knows what my life would be like today or where I would have decided to take my career.

I could not be more grateful of the opportunity gene therapy has given me to direct my life, and I know all of my thalassemia friends -- or what we like to call thal pals -- live vicariously through me and I look forward to celebrating their potential journey of cured in the near future. Thank you for your time.

MS. CHRISTINA VERT: Thank you. The next speaker is Jenine Abruzzo.

MS. JENINE ABRUZZO: Hello. My name is Jenine Abruzzo, and I have beta thalassemia major. Thank you for allowing me to explain my experiences with thalassemia and why it is important to thalassemia patients to have the opportunity to undergo a gene therapy procedure as a possible curative option.

Today, I am 48 years old and considered to be

one of the older patients living with thalassemia major. Stephanie, my older sister, did not receive the same medical interventions as me, and she passed away. My sister was born in 1960 when doctors were unknowledgeable about this disease. They transfused her regularly. However, science was not prepared for the complications of iron overload from the ongoing transfusions.

Medications can remove excess iron called an iron chelator was not available to patients until 1978. With no way to remove excess iron, she suffered a splenectomy and heart, liver, and kidney failures throughout her life. Thalassemia major is a hematological genetic blood disorder that affects people of Mediterranean, Asian, and Middle Eastern dissent. Our bone marrow produces red blood cells that lack a sufficient amount of hemoglobin needed to survive, causing a person to become severely anemic and totally dependent on chronic blood transfusions.

Although the blood transfusions are necessary, they can hurt us without the use of an iron chelator

just like my sister experienced. Iron chelators can be injected or taken orally. I use the injection because I cannot metabolize the oral chelators. I infuse the medication each night subcutaneously using a battery-operated pump that fully releases the medication over seven hours. I've been doing this since I was five years old, and I am thankful for this medication because without it I would not be alive today.

Being diagnosed at six months old, I have received blood transfusions my entire life. That means that for me, once every two weeks, I cannot go to work and instead go to my treatment center to get transfused with two units of red blood cells over six hours. While there, I am medicated which makes me extremely tired and achy. I take the entire next day for my body to acclimate to the new blood cells I received. After a transfusion, I can understand what it may feel like to be cured of thalassemia major.

I have a normal hemoglobin, energy, rosy checks, less pain, and I feel happy, energized, and very much alive and a part of life. This feeling lasts

for approximately one week. Thereafter, my hemoglobin starts to weaken, and I can feel my body slowing down. I become easily fatigued, achy, foggy, pale, and I increasingly feel secreted of energy and oxygen.

This condition worsens until I return for my next blood transfusion and I want to feel better again. My life does not stop because I need blood. There are no holidays from a being wife, mother, caretaker to my parents, or a full-time special education teacher. I work very hard to overcome the fears and challenges of having thalassemia. Since losing my beloved sister 19 years ago, my biggest fear is dying and leaving my children motherless and my husband widowed.

I worry about developing complications as I age and how they may affect my future health. I think about being an older person still getting blood transfusions every two weeks and wonder if my veins will continue to hold up if I am stuck with needles so often. I think about the possibility of a natural disaster and how that could limit me from getting a transfusion. I pray that the blood supply continues to

remain safe and that it does not pose a risk to my health.

Today, people with thalassemia are being cured through trial gene therapy procedures, and they are living their lives without needing biweekly blood transfusions, medication, and medical care. They are fortunate to have science be able to correct the genetic mutation to give them a new future filled with promise, health, safety, and the potential to live a long, fulfilling, energetic life. I wish for the day when all thalassemia major patients are able to undergo this miraculous gene therapy procedure. Thank you.

MS. CHRISTINA VERT: Thank you. The next speaker is Susan Carson.

MS. SUSAN CARSON: Good afternoon. I am the nurse practitioner for the Thalassemia Center of Excellence at Children's Hospital Los Angeles. I have no financial relationship. We are one of a few centers around the country who are expert in treating thalassemia. I have 26 years' experience. Thank you for the opportunity to speak to the Committee about the

real-life impact of living with a true forever disease.

I cannot say that I have walked in my patients shoes, but I will walk with them on this journey. The CDC states that chronic diseases are defined broadly as conditions that last one year or more and require ongoing medical attention or limit activities of daily living or both. I am sure my patients would be ecstatic if their thalassemia diagnosis lasted only one year. Even a few years would be incredible, but it doesn't go away, ever. Thalassemia is a true chronic life-long disease.

26 years ago, the outlook for patients was grim. Early death reduced quality of life and very burdensome treatments. Over the years, care improved increasing their lifespan and reducing mortality and morbidity, but still, the burden of living with thalassemia is massive and affects every aspect of their lives as they grow and develop.

Many families are referred to me through newborn screening when their precious baby is diagnosed with a rare illness that can only be cured with bone

marrow transplant from a sibling match donor. Most do not have a match. Some patients are adopted from other countries where they were orphans, abandoned because they had a chronic illness.

Here now, in the U.S., they have access to care but no cure. Most do not live near Center of Excellence and make large annual trips for their comprehensive evaluation. I see patients from all over the U.S. who come to us. At home, they may be the only one in their clinic. It is hard for providers to have any expertise unless you care for a larger population of patients.

Throughout life, events are interrupted by blood transfusions every two to four weeks, which take all or most of the day. Work and school is missed due to frequent hospital visits. Parents and patients have been fired from missing work. Time and money is spent coming to the hospital. Many travel long distance for their transfusions.

The pandemic showed how fragile our blood supply is. Many were denied blood or given less than

they needed. Medications to treat iron overload are expensive and, if approved, may still incur large copays. Clinic staff spend hours convincing insurance companies to cover these meds and are not always successful. Patients spend their childhood wondering why they have to come into the hospital all the time while their friends do not.

As teenagers, they just desperately want not to be different. Adolescence is a dangerous time for all of us. Add in a chronic illness and the stakes are even higher. Nonadherence with medication is common and life-threatening and become a constant lifelong struggle. Some of my patients go through waves of pills to take leading to dangerous levels of iron overload.

I care for a beautiful young lady who transferred to my center as a teenager. I asked about her plans after high school and offered my help in planning if she was thinking of go away for university. It's doable but lots of work. She started crying. She assumed she could never go away for college due to her

thalassemia.

In adulthood, finding employment can be difficult. Will they be able to get insurance? Will it cover their care and medications? Can they find an adult provider with any knowledge of thalassemia? Most do not, and access to care is a huge issue and affects quality of life and outcomes.

Patients try and fit families, life travel, all the stuff we take for granted, but everything is limited by and bookmarked by blood transfusion. And that need never stops. Despite all this and because of it, I think, thalassemia patients and their caregivers are amazing. They inspire me with their resilience and perseverance and zest for life.

I'm humbled by their strength and consider myself lucky they allow me to care for them and be part of their lives. But I don't want them to have this forever chronic illness. I want them to have a chance at a cure, which gene therapy will offer. Thank you.

MS. CHRISTINA VERT: Thank you. The next speaker will be Ralph Colasanti.

MR. RALPH COLASANTI: Good afternoon. My name is Ralph Colasanti, and I would like to thank the Committee for this opportunity to speak on behalf of the gene therapy application from bluebird bio. I'm speaking today as the national president of the Cooley's Anemia Foundation and also as a thalassemia patient for over the last 60 years. My story is quite similar to many others my age.

When I was diagnosed, the doctors -- and the outlook was grim. My life expectancy was supposed to be mid-to-late teens, maybe early 20s. Doctors didn't give us much hope for a better life than that. So as thalassemia patients, we just went by, worried about quantity of life, not quality of life. We just wanted to get another day.

Fortunately, there's been significant changes and advances in treatment for thalassemia in my lifetime, which gave us a better outlook and better than anticipated -- chelation therapy options, noninvasive iron measurement, better understanding of iron regulation in our bodies and other developments

has really excelled us and made us beat the forecast that we were originally given.

Even with these advances, living with thalassemia is not easy. The constant need for blood transfusions, the difficulty of maintaining appropriate iron balance in your body, the complications when patients developed persistent challenges over time -- for example, I have severe vision loss, and that's been happening since my late 30s, early 40s. And this is due to the chelation toxicity.

My bones are fragile, and I have osteoporosis, and as an almost 60-year-old male, that's something that you don't really think about. And as far as that, the doctors monitor my liver and heart function very carefully. As the national president of the Cooley's Anemia Foundation and an active member of the thalassemia community, I know my patients have it far worse than I do. Yet, patients born today are more likely to face complications as early as I did.

With hope, they will have better outcomes, but they are not risk free. And we don't know what is

coming down the pike for them. More importantly, the ability of a thalassemia patient depends on receiving expert care from experts in thalassemia. These doctors are few and far between, and the foundation estimates that only about half our patients actually receive regular care at a thalassemia treatment center. And even those patients who are treated regularly by the experts still face significant issues.

One of the challenges doctors have is that what works for one thalassemia patient may not work for another. And what treatment is working today may cease to work further down the line. It's constant monitoring and evaluation is necessary. Even then, some patients simply do not respond to any of the treatments available. This is why a curative option is so crucial for the thalassemia community.

Few people have access to bone marrow transplantation just simply because of lack of a match, and even if they do have a match, some of the risks involved sway our patients to do other things and just to live with thalassemia. This is why the fundamental

hopes of this Committee will find that data presented from bluebird bio on gene therapy today will meet your approval and is worthy of your approval.

Another curative option would be amazing for us. I thank you for your time and hope that we could learn to live without thalassemia.

MS. CHRISTINA VERT: Thank you. The next speaker will be Nathan Connell.

DR. NATHAN CONNELL: Thank you for this opportunity to speak about beta thalassemia and betibeglogene autotemcel. My name is Dr. Nathan Connell, and I'm a hematologist at the Brigham and Women's Hospital and Dana-Farber Cancer Institute in Boston, as well as an associate professor of medicine at Harvard Medical School.

My work in systems-based hematology is focused on optimizing care delivery systems for patients with blood disorders, including the cost effectiveness of therapies, and I've been caring for patients with thalassemia of various types for over 10 years including many with transfusion dependent beta

thalassemia major or intermedia.

Importantly, I have no financial conflicts of interest related to this product, but I do care for a number of patients who may benefit from this therapy or related future therapies in gene therapy and gene editing. While we've made huge advances in therapy, including the use of chelation to manage iron overload, the treatment of thalassemia has relied heavily on hyper transfusion protocols that have not changed in several decades.

Patients are tied to their clinical sites and cannot be away for more than a few weeks at a time before returning for transfusion therapy. And while other therapies has been studied to minimize the need for transfusions including splenectomy, TGF beta therapies that do decrease MAB 2, 3 signaling, none of these other than allogeneic transplants have been truly curative. For instance, luspatercept, which we thought was going to be a major step forward, trades one chronic therapy for another.

As you've heard from others today, many

patients living with thalassemia already report good quality of life. However, the unpredictable nature of the blood supply, particularly given challenges during the COVID pandemic, has created anxiety in those dependent on transfusions to live. While many will choose to continue transfusion therapy even when this is approved, the possibility of transfusion independence with minimal or manageable side effects will be a significant step forward for this population.

Even though transfusion independence is the overall goal, just even a reduction in transfusions will result an improved quality of life, reductions in health resource utilization and decreased chelation risks. I have patients, as you've heard, who have to negotiate time off with their employers in order to continue their life-sustaining therapies.

Earlier today, Dr. Alexis Thompson presented about the impact of this therapy and what it would mean to those living with thalassemia, and I would like to echo Dr. Thompson's statements. And I agree with her completely. What I would like to convey more than

anything else is that increasing the number of treatment options for people living with beta thalassemia and other hemoglobinopathies will increase the quality of the care and quality of life for affected individuals and their families.

While this therapy will likely be initially limited to large centers with expansive resources, it will be important to ensure access in a diverse and equitable way, especially given the hemoglobinopathies are prevalent in communities of color and those historically marginalized by the healthcare system.

I am in support of the approval of this therapy, which will move to therapeutic field forward, not just for patients living with hemoglobinopathies, but other hematologic disorders such as hemophilia. Thank you for your time today.

MS. CHRISTINA VERT: Thank you. Our next speaker will be Sarah Baqueri-Connolly.

MS. SARAH BAQUERI-CONNOLLY: Hi. My name is Sarah Connolly, and I would like to start off by saying thank you to the Food and Administration for allowing

me to share a little bit about my daughter Dana.

Dana had beta thalassemia major, and she passed away on January 8th, 2015, just a few short weeks before her third birthday. When our daughter was born, we knew that we had a long road ahead of us, but because we were lucky enough to live in a country with such strict rules regarding blood safety and such great access to premium healthcare, we were ready to face this rare genetic blood disorder as informed and mentally prepared as possible.

When we first found out about Dana's blood disorder, we were terrified. We were first-time parents and weren't sure if we were ready to take on a special needs child with a fatal blood disease. However, we were lucky enough to be connected with the Cooley's Anemia Foundation, and with their guidance and encouragement, we finally felt ready to take on this blood disorder.

We met with so many patients and families. We saw thalassemia patients who were thriving, children who were going to school and participating in sports,

graduating college, getting married, starting families of their own. We saw patients in their 50s and 60s, and we were told that if there was ever a time to have thalassemia, it was now. Look at all of the advances. There were oral chelators, clean blood supplies, Centers of Excellence, and honestly, what more could we ask for?

We found out the answer to that question less than three years later. On New Year's Day in 2015, my daughter was ringing the new year with her two best friends. The next day, on Friday, she came home from daycare with sniffles. Saturday and Sunday, she laid on the couch watching Frozen on repeat in and out of naps. We knew she was under the weather, but we thought she had a cold and needed to rest. So we let her. She wasn't eating very much. So we made sure that she was taking her oral chelator. We never, ever skipped a dose.

By Monday morning, she wasn't getting any better, so we took her to the pediatrician. Before we left, she finally said that she was hungry, and she had

asked for apple sauce. And that was the last thing she ever ate. Apple sauce with her chelator. That was also the last time she ever spoke. By the time we got to the pediatrician's, she was starting to lose her ability to focus. We were instructed to rush her to the emergency room because she seemed dehydrated.

They said her liver enzymes were high and that she had tested positive for RSV. We said that her liver enzymes had just been checked three weeks prior at her last blood transfusion, but they said they couldn't explain it. We were transferred to Mount Sinai Hospital where a team of 10 to 15 doctors couldn't figure out how her condition deteriorated so quickly, and after two days, she had no brain activity. And we were asked to make the decision to take her off of life support.

The reason why I share this story is because Dana didn't have many options for treatment. She had blood transfusions and oral chelators, which we are very grateful for. At the same time, I believe they also played a huge part in her loss. The only curative

option that we were offered was a bone marrow transplant, which came with so many risks that we weren't ready to face.

Another young patient had passed away at age 3 or 4 that October before Dana, and he had had a bone marrow transplant. But his body rejected the procedure. At the time, I couldn't imagine going through the pain those parents went through. Yet, there I was, three months later saying goodbye to my only child at the time.

Had we been given the chance to let Dana participate in a gene therapy trial, at the time, I can't say that we would've been opened to experimenting on a two-year-old, but since 2015, we've personally watched friends, who have become family, participate in gene therapy trials and be cured of this painful disease. They no longer need blood transfusions. The iron in their liver and heart are slowly but surely disappearing.

The painful side effects that they felt their whole lives may not be completely gone, but it seems

that they're on their way. They're finally able to live a life that doesn't revolve around hospital stays, blood draws, and medications. Parents are able to take a breath, a full breath that isn't cautiously held back waiting for the next shoe to drop.

I believe gene therapy gives patients and their families hope, a hope that we didn't have, and I pray that our friends and families that we've met over the last 10 years will one day find hope for a cure for thalassemia. Thank you for taking the time to hear my story.

MS. CHRISTINA VERT: Thank you for sharing. Next speaker will be Androulla Eleftheriou.

DR. ANDROULLA ELEFTHERIOU: Yes. I'm Androulla Eleftheriou, Executive Director of Thalassemia International Federation, and I have no financial conflict. Honorable chair and dear members, we would like to thank you for providing the Thalassemia International Federation for the opportunity to convey the perspective of hundreds of thousands of patients globally, including other 1,000

patients in the U.S.A. on beti-cel drug therapy.

Of the global voice of thalassemia patients and their families in 68 countries across the six WHO regions in the world, through 270 national patients associations, TIF feels overwhelming appreciative to the health and scientific communities, the academia and industry who have listened and acknowledged the voice of the heart of thalassemia patients, and their families and having vested time and resources and succeeded despite the many and markable challenges collateralizing a genetic and rare, in most countries, disease in making these long-awaited gene therapy a reality.

TIF was established in 1986 initially by a very small group of patient-parent support associations, medical professionals under the guidance of the World Health Organization. We've been wishing for a world in which treatment that would allow a long survival could be available to our patients wherever they may be. The dream for a total holistic cure has been the ultimate goal of all those involved in this

fight right from the beginning, especially as allogeneic hematopoietic stem cell transplantation practice in the case of this disorder since the early years with varying success depending on the expertise centers, has limitations both in the context of (inaudible) therapy criteria for success but importantly in the context of numbers as well, who can benefit and which did not surpass 25 percent of the patients.

In addition, despite improvements and related match and related haploidentical hemopoietic cell transplantation approaches, there remains a 5 to 20 percent transplant related morbidity and mortality risks.

Certainly, a final cure still remains a dream for every one of us following a great disappointment last year when we witnessed the devastating developments that led to the withdrawal of the first authorized gene therapy for the treatment of thalassemia from Europe. It is truly unacceptable for kids that such an advanced curative therapy that took

decades to develop through rigorous clinical trials, proving safety and effectiveness, and which cumulated in EMMA and European commission authorization was so abruptly discontinued.

We as a global organization protecting the rights of patients are fully determined to continue to fight with undivided attention so that this is never repeated and is not met with the same fate in the United States for our patients.

Ladies and gentlemen, despite the huge advances that have been achieved in the management of this disorder for in the last three decades, what we refer to as routine care is well beyond a transfusion and drug related approach. It is, in fact, the complex series of everyday lifelong interventions administered for effectiveness and success by a well-coordinated multidisciplinary team of experienced specialists across many medical scientific and technical disciplines.

It includes, among others, the development and close networking of specialized expert centers and

benefits from the exchange of best practices involving state of art transfusion services and research activities and ongoing continuous education of healthcare professionals as well as the active and meaningful involvement of patients and families.

The aim being to meet the lifelong needs of the match organ disorder, we have a huge genetic diversity and consequently, with diverse clinical outcomes. Aiming to achieve a quality of life and full or nearly social integration is today referred to as optimal care, which is sadly applied almost exclusively in very few countries of the western world, with very high rates of morbidity and premature death with the average age not exceeding 20 years in the majority of the low and middle-low-income countries where the other 75 percent of patients with this disorder are born and live. Poor quality management is not a characteristic of only this country, since the rarity of this condition in some of the industrialized countries of the world as well may result in many patients receiving an inappropriate level of care.

In fact, only a minority of patients under the optimal care of expert reference centers are now the leading examples of what comprehensive care can achieve. A curative approach by a gene therapy has been an enduring dream for more than five decades.

Now with every patient envisioning the opportunity to eliminate the huge and lifelong burden of this chronic and debilitating disease, even for those who receive optimal or near optimal care, who dreams for a normal life and hope to have lifelong monthly blood transfusions, frequent hospital visits, daily adherence to chelation treatment -- a challenging and often painful treatment -- and many other essential components of care and monitoring all together invading on an everyday basis, their personal, family, professional life, often not avoiding the development of many and complex medical complications when at the same time the stigma for a chronic genetic disease still exists to a small or large extent.

And for a small percentage of patients who cannot, for medical reasons, obtain standard care, gene

therapy was and still is the only solution. For those patients living in countries of the developing world, gene therapy, ladies and gentlemen, was and remains a dream for a chance in life.

Gene therapy today as it stands and with a reference to beti-cel could make the wishes, dreams, needs, and expectations of our patients in the U.S.A. and beyond come true. This is making -- this is about lifting the huge violation of their life as humans and patients.

MR. MICHAEL KAWCZYNSKI: Time.

MS. ANDROULLA ELEFTHERIOU: Even as the --

MR. MICHAEL KAWCZYNSKI: Please.

MS. ANDROULLA ELEFTHERIOU: Time.

MR. MICHAEL KAWCZYNSKI: Please wrap it --

MS. ANDROULLA ELEFTHERIOU: Yeah.

MR. MICHAEL KAWCZYNSKI: Yeah. Please wrap it up.

MS. ANDROULLA ELEFTHERIOU: -- transfusions -- yes -- empowerment to every patient to follow the U.S.A.'s footsteps. So making it the right for all and

not a privilege for some is where TIF aims. Therefore, we do hope as TIF that FDA will indeed grant this opportunity to our patients. Thanking you, indeed, for giving us the opportunity to express the global patients' perspective.

MS. CHRISTINA VERT: Thank you. Next speaker is Kate Jones.

MS. KATE JONES: Hi. My name is Kate Jones, and I'm a parent of a child who participated in Phase 3 of the bluebird clinical trial. I'd like to add here that bluebird did pay for our treatment, our housing expenses, and a daily stipend during the treatment time to cover daily expenses.

My hope is to give you a glimpse into our world, the world of thalassemia, a disease we thought was incurable, so that you could know how this treatment has impacted our lives. I'm a mom to five children, two who are adopted from China and three who are biological. We keep very busy around here.

We were first introduced to the world of thalassemia when we saw a picture of a sickly, pale,

16-month-old little girl who was waiting for a family to adopt her. We researched and met others who had children with thalassemia, and we knew we had to be her family. In China, our daughter received blood every two to four months, just barely enough to sustain her life and keep her alive, but not enough to grow or truly live.

We knew that there had to be a better life for her with proper medical care and a family. We were prepared for a lifetime of hospitals, doctors, clinics, needles, medications, and blood transfusions. We knew we had lots to learn, but we were committed to giving her the best life that we could. When we brought her home, we did transfusions every two to three weeks and followed the thalassemia standards of care, and she began to grow and thrive.

Once we were settled and didn't feel like we were drowning in a sea of medical appointments learning the world of thalassemia, I started following a Facebook page of a female adult who was starting the bluebird clinical trial. I read every single update

with nervous excitement and a hope for a better future for those with thalassemia, a world where there is a cure with no graft versus host disease, an option not needing a close relative match.

I studied the trial results as much as I could. We then found that our thalassemia center was participating in this clinical trial, and with fear and trepidation, we reached out for more information. We met with the study doctor, our pediatrician, our hematologist, other thal families, and finally came to the conclusion that we were in, and we were ready to do this. We were hopeful that treatment for our daughter would lead to a life free of being tethered to a chair and an IV pull every two to three weeks; a life free of a central line that caused many extra hospital trips with each and every fever; a life with less iron stored in her major organs; a life without transfusion reactions; a life where she doesn't miss school, sports, and things that she looks forward to because of thalassemia.

Once we had signed to be part of the study, we

flew to California for testing and then again for apheresis. When her cells were ready, we moved our family of seven to California for transplant. Our daughter was one of the youngest patients participating at just five years old when her transplant happened. There were long and hard days watching my child become sick, lose her hair, and not eat for weeks on end, but we still had hope for a bright future that would be transfusion free, a life free of blood that gave her life for so many years, but also the same exact thing that wreaked havoc on her body causing iron overload in her heart, liver, and other organs, also, having to take a medication that ridded her body of that iron but it had nasty side effects.

Today, I am now happy to say that she has been transfusion free for two years, two months, two days -- excuse me, two years, two months, two weeks, and one day. We celebrate each and every day as she continues to thrive and grow. She is now a happy, healthy second grader who is on a competitive gymnastics team and living a life that we never imagined possible for her.

We hope this treatment will become widely available to others with thalassemia, and that it would stretch worldwide to help cure those with thalassemia globally. We are so grateful for this treatment and that we had the opportunity to participate in this trial for her cure. Thank you so much for your time.

MS. CHRISTINA VERT: Thank you. Next speaker is Radhika Sawh.

MS. RADHIKA SAWH: Hi. This is Radhika. Thank you for this opportunity. I have no conflicts to report. As someone diagnosed with thalassemia major only days after birth, I know firsthand what it means to live life tethered to an IV pole, forced to make every decision based on my relentless need for blood transfusions in order to simply survive. The promise of gene therapy is that of a life untethered and without limitations for those born with transfusion dependent thalassemia.

I began what would become a lifetime of blood transfusions when I was only 18 months old. At first, I received only one unit of blood every few months

because of my size. As I got older and continued to grow, my blood requirements increased. By elementary school, I required two units of blood every month. By high school, I needed blood every three weeks. By my mid-20s, I required blood every other week. I am now 47 years old, and it is estimated that I received over 1,600 units of blood in my lifetime.

Being dependent on regular blood transfusions has shaped every aspect of my life from the decision of where we should live to where I could go to college to my choice of career, even my decision to enter into a long-term relationship and start a family. It is incredibly overwhelming to consider how reliant I am on blood transfusions, something which cannot be manufactured but must be given freely by another human being.

I am grateful that I live in a country where it is possible to get transfused regularly. However, I'm constantly reminded that the blood supply I so desperately depend on fluctuates, at times reaching critically low levels. During the pandemic, I worried

about how I would be able to get blood. I knew that I could only last a few weeks without blood and that the blood banks would need to ration the blood supply to those who urgently required it.

Thankfully, I was able to get my blood transfusions without interruption. Yet, many patients in other parts of the country were either given one unit instead of their usual two or had their transfusions delayed by days, sometimes weeks, putting their quality of life and survival in jeopardy.

Managing thalassemia involves more than just blood transfusions. Secondary hemochromatosis developed due to the regular blood transfusions necessitating chelation therapy, which comes with its own challenges. Hemochromatosis causes associated comorbidities, thereby requiring specialized surveillance and, if present, treatment. All of this comes with a hefty price tag, placing a heavy financial burden on thalassemia patients.

When I was five, my parents were given the opportunity to enroll me in a trial investigating the

impact of a subcutaneous chelator on individuals with thalassemia major. They took the calculated risk, and because of that choice, the course of my life changed tremendously. That chelator prevented toxic iron overload from building up in my body due to my frequent blood transfusions and kept me from developing the ensuing comorbidities, which caused the premature death of thalassemia patients before me, including my elder brother and only sibling.

Now we stand today at a new precipice with the advent of gene therapy. It is time to allow patients with thalassemia to consider a new opportunity to change the trajectory of their lives. Studies have provided ample data demonstrating the efficacy and safety of gene therapy, and it is time to allow those born with thalassemia to live life unburdened by the constant need for blood transfusions and chelation therapy.

Gene therapy has been the dream of those with thalassemia for as long as I can remember. You have it within your power to make this dream a reality. Thank

you very much for your time and consideration.

MS. CHRISTINA VERT: Thank you. Next speaker will be Jennifer Schneiderman.

DR. JENNIFER SCHNEIDERMAN: Hi. Hello. My name is Jennifer Schneiderman. Thank you so much for this opportunity to speak today. I'm a pediatric hematologist/oncologist, and I specialize in hematopoietic stem cell transplants. I work at Lurie Children's Hospital in Chicago. I'm an associate professor of pediatrics at the Northwestern University Feinberg School of Medicine. I'm also the medical director of our therapeutic apheresis program.

In the last year, I have been compensated for participating in an advisory board for bluebird. I have been a transplant physician since 2007, and in this role of taking care of many patients with beta thalassemia major who sought cure for their disease through allogeneic transplants -- and when I think back, there have been patients who have done well and remained transfusion free without too many bumps in the road.

I have also had the honor of taking care of many of the brave patients who have participated on the bluebird clinical trial since 2014. While neither of these approaches are without risk, patients who undergo gene therapy, as you have heard, do not have the burden of searching for a donor, and they don't have the risks of graft versus host disease after transplant.

Having seen patients unable to receive an allogeneic transplant who go on to continue to receive regular transfusions and experience iron overload and patients undergoing regular allogeneic transplants, I can give real-life examples of 20-year-olds who die suddenly from cardiac failure due to iron overload and children suffering from severe graft versus host disease after their allotransplants who have been in the hospital sometimes for well over 200 days, many of whom -- with their acute graft versus host disease, many of whom suffer long-term sequela.

The availability of gene therapy gives patients, their hematologists, and the patients' families discretion to weight the risks and potential

benefits and broadens their options and opportunities for cure should they choose to pursue it using that pathway. Thank you very much for your time.

MS. CHRISTINA VERT: Thank you very much. That was the last speaker. So this concludes the open public hearing, and I will now pass the meeting back over to Dr. Butterfield.

DR. LISA BUTTERFIELD: Terrific. I really want to thank all of the participants of the open public hearing, particularly the patients, patients' families, the clinicians treating these patients. These are all very powerful stories that are very helpful.

Before we go on to session 5, the discussion and voting, we've had a request from bluebird bio for a quick one or two minute opportunity to respond and provide some clarification to one of the questions from the patient representative. Please, Bluebird.

DR. RICH COLVIN: Yes. Thank you, Dr. Butterfield. This is a question that Dr. Singh and Dr. Trieu had asked before. Can we pull up the slide on

the screen, please? It was about, again, thinking about those four patients who did not become transfusion independent. I just want to start out by saying we've learned a lot starting with Phase 1 and 2 through Phase 3.

Over the course of that time, we believe that we've made it more likely that patients will become transfusion independent as we learn more. In Phase 3 studies, we learned about the level of transduced cells that would be required in order for a patient to likely become transfusion independent. You can see by the dotted line -- all those dots on the right of that dotted line, that's 31 patients, all of whom became transfusion independent.

So a hundred percent of those patients who had above that level of transduced cells, they become transfusion independent. So, right now, we're working with the FDA to come up with release specifications so that it becomes highly likely that patients who get treated with beti-cel will become transfusion independent and improve upon that 90 percent rate that

we already have. Thank you. Thank you for that time.

SESSION 5: BETA-THALASSEMIA DISCUSSION AND VOTING

DR. LISA BUTTERFIELD: Thank you for that clarification and showing us those data again. So, we are now close to the top of the hour. And what's next is the Session 5: beta-thalassemia Discussion and Voting. So, what's going to happen now is I will read a series of four questions in turn. And for each of these questions we have a discussant who will begin our discussion with some initial thoughts. So we really encourage all of our members -- all of our Committee members and temporary Committee members to participate so that we can have a full discussion of everything we've read and everything we've heard today.

So, here's Question One: "Hematologic malignancies have not occurred in transfusion-dependent beta-thalassemia (TDT) subjects treated with beti-cel. However, the beti-cel lentiviral vector is similar to the vector used in sickle cell disease and is related

to the vector used for the CALD that we were speaking about yesterday, and there have been cases of hematologic malignancies in both the sickle cell and the CALD patients in other studies.

"In this setting, what is the likelihood that the constellation of delayed platelet reconstitution, abnormal bone marrow morphology findings, and insertion site analyses will predict future development of heme malignancies in the beta-thalassemia patients treated with beti-cel?"

And so, that's the first question that we're going to discuss. And to start us off, please, Dr. DiPersio.

DR. JOHN DIPERSIO: Okay. Thanks, Dr. Butterfield. So, the major issue here is the -- number one, the association between what we saw with CALD patients versus thalassemia or sickle cell patients. And I think we discussed this at length yesterday, and I'll just reiterate my thoughts, which haven't changed at all. And that is that the pathways for developing these malignancies seem quite different in some

regards.

Obviously, there's much more of a smoking gun with insertional mutagenesis with the TLD patients, and for the sickle cell patients and obviously for the thal patients where there hasn't been any, there's no evidence of that. That's number one.

Number two, the kinetics, morphology, cytogenetics mutational analyses are consistent with treatment related or busulfan related disease in sickle cell patients and probably occurring with a higher frequency because of the stress marrow issue and the chronic inflammation that occurs in sickle cell patients. And that is not as an obvious situation in the thalassemia patients.

So, I don't think that there is any link between those two -- between the CLVV patients and the sickle cell patients. Now, the constitution of symptoms in -- the constitution of delayed platelet reconstitution, some very subtle morphology findings, very subtle.

Questionable cytogenetic abnormalities in the

thalassemia patients is something that has not resulted in any clinical impact. So, for instance, I don't see -- even though the platelet counts are still low and I still -- and for most patients -- some of the patients are delayed -- and there's a few patients that have not completely recovered -- I still don't think that this is for the most part clinically significant. And so, even though platelet recoveries are slow, neutrophil recoveries are slow, I don't think that they're clinically significant.

And I'm not sure if this is related to the spleen issue or not. I would suggest that one other -- there's another very important possibility. And that is that we know exactly what the impact of stem cell numbers are on engraftment. And stem cell numbers are very important, especially for platelet engraftment.

And in a normal marrow situation or an autologous transplant setting we use these numbers that we've gotten from historical data that 5 times 10 to the sixth CD34 cells provide rapid and consistent platelet engraftment in most patients, which is the

case. But in these patients, it's a little bit different because, number one, they have a spleen, which was touted as the main problem. But I'm not sure I agree with that.

The other issue is that you're actually ex-vivo manipulating stem cells. You're expanding them. By definition, the stem cell -- multi-potential properties of these cells has changed once you do that. And we know that if we do it for too long a period of time, they have no function -- in mouse models, at least. So I'm thinking that we need to do -- or they need to do a little bit better job categorizing or describing some of the flow characteristics of these products before they go in.

So, one of the issues that was just brought up just a minute ago was the incident -- the issue of transduction efficiency. So, I would argue that that may be the reason why some people haven't become transfusion independent. But another possibility is that the frequency of the primitive stem cell populations in these manipulated products is

exceedingly low. And in fact, instead of needing 5 times 10 to the sixth CD34 per kilogram to get rapid platelet recovery, in these patients that get manipulated products it might be more like 10 or 15 because of the losses in the normal differentiation of these stem cells.

So, I would say that there's nothing clear about what's happening here except that I think we ought to not take our eye off the ball, that the product itself and the process itself may be diminishing stem cell numbers. It may not be related so much to transduction efficiency but to the total number of immunophenotypically defined primitive stem cell populations that the patients are getting infused with.

And as far as the issue of leukemia recurrence, I think that there needs to be a better, proactive approach to looking at mutations in these patients, before and during and in the follow-up period. And we asked a number of questions; I still am not sure I understand the answers yet. But I guess

that they have not looked in most of these patients.

And my recommendation would be, especially in the thal patients which have some low blood counts and certainly in the sickle cell patients, that this be done proactively and prospectively in the next -- for the next few years at various time points so we can track not only insertion site analyses and integration site stuff but also the presence or absence of clonal hematopoiesis and the presence or absence of subclones that we can identify by routine sequencing panels or by more sensitive error corrected sequencing panels so that we really know what's happening here, especially in this group of patients where the malignancies are more treatment related as opposed to insertional mutagenesis -- insertional oncogenesis related. I'll stop there.

DR. LISA BUTTERFIELD: Super. Thank you very much. That was really helpful. And you also touched on some things I think that help with Question Four in terms of following the patients going forward. So, for continuing to discuss Question One I'm watching for

raised hands. So, let's go to Dr. M, please. And then we'll carry on from there. Thank you.

DR. JAROSLAW MACIEJEWSKI: Can you guys hear me?

DR. LISA BUTTERFIELD: Yes.

DR. JAROSLAW MACIEJEWSKI: Sorry for lack of trust. But there was a lot of technical things, and I am still afraid of --

DR. LISA BUTTERFIELD: Yes.

DR. JAROSLAW MACIEJEWSKI: -- IT manager, who is very tough. In any event, we are the centers that sees most of the aplastic anemia and other bone modal failures due to other causes in United State as a single center. And consults for single lineage cytopenia not complete recovery after autologous transplant or after chemotherapy are quite common.

And there are two things: is the cytopenia indicating ongoing process -- the single lineage persistent thrombocytopenia, or is it just a scar? And we have to accept and -- you know, that despite looking for everything -- I mean, you know, in certain cases

the confusion has to be is this a scar? And it's just not going to be -- going to be (inaudible) ever, you know. And it's going to linger and maybe in moments of increased usage.

It's sort of like slalom skier who breaks his leg, he might be skiing but he is not going to be a gold medalist anymore in this particular realm. So, this is one -- an important issue that I wanted to mention to everybody.

And the second point is the sequencing. And here's a -- the pathologist who spoke on behalf of the company mentioned that it was not needed to order the FISH. The truth is, cytogenetics is approximately two metaphases, which is approximately 10 percent sensitivity, 20 percent sensitivity. FISH has much greater sensitivity. Patient has cytopenia that is a concern. To order FISH is totally reasonable. One has just to know that anything below six percent is normal or whatever it is -- the cutoff value -- particularly for the deletions.

So, I agree with John that the

pharmacovigilance or the follow-up should include NGS panel for driver mutations if there is a concern. And everybody is talking about the concern of clonal level issue in these patients. This would be the way to go potentially, even doing this type of assay on the harvested cells. It doesn't take much DNA, and it would, of course, be of a tremendous scientific importance to establish this. Thank you.

DR. LISA BUTTERFIELD: Terrific. Thank you, very much. Okay. Next, we'll hear from Dr. Gordeuk and then Dr. Ott.

DR. VICTOR GORDEUK: Yeah. I'd just like to emphasize this matter -- this kind of general observation of delayed platelet reconstitution. Again, it's really hard to say if it really is delayed on the average. And in the case of sickle cell disease, if somebody has a low platelet count, I immediately see if they have SC disease and splenomegaly. And then their platelet counts are easily baselined below 100,000. So, I don't think that just saying that this patient didn't achieve the pre-transplant platelet count really

defines some problem with bone marrow. I'm done.

DR. LISA BUTTERFIELD: Thank you. Dr. Ott.

DR. MELANIE OTT: Yes. Hello. I just wanted to support what Dr. DiPersio just said about the potential toxicity of the -- of the manipulation of the drug product and the transduction -- the weighing between toxicity and the transduction efficiency. There's no doubt that if you use a high MOI of a lentiviral vector to achieve higher transduction efficiency that this is toxic to especially vulnerable cells in the population.

So, I'm really glad to hear that bluebird and the FDA are working together to actually balance these two effects, one which could cause or could be supporting the late platelet reconstitution and the other on that is, of course, enhancing efficacy and success of the product.

But I think this is a critical issue that I think needs to be carefully looked upon and regulated in the future. Thank you.

DR. LISA BUTTERFIELD: Thanks very much. So,

do we have any other thoughts on Discussion Question One? I can summarize some things I've heard so far. So, I'm looking at my computer. So, the question, again, what is the likelihood that the -- some of the constellation of delayed reconstitution, abnormal bone marrow morphology insertion site will predict future heme malignancies?

So, we've heard that it's really -- and this reiterates things that we talked about yesterday. Different disease states, different vectors, and the lack of evidence of insertional mutagenesis to date makes this less of a concern, that the adverse events are more consistent with expected AE's in this disease state. The clinical significance of delayed reconstitution isn't totally clear. The spleen role isn't clear.

The transduction efficiency may be really critical. The primitive stem cells in the product may be critical. Some cytopenias may be long-term side effects. So, those are some things that I heard.

And then really, perhaps more relating to

Question Four, recommendations for specific testing which we'll go on to in more detail in a few other questions. But tracking the importance of percent transduction efficiency, tracking the insertion integration sites, clonal hematopoiesis in subclones and primitive stem cells should be tracked, NGS for driver mutations, and consideration of FISH for its greater sensitivity.

So, those are some things to help continue to track the safety of this product in the future and address the potential development of heme malignancies. Anything to add or shall we move to Question Two? All right. We'll move to Question Two, please.

So, Question Two: "Please discuss whether patients with TDT should be screened for potential germline and somatic mutations predisposing to heme malignancy prior to administration of beti-cel. What screening tests, if any, for such mutations would you recommend?" And so, again, we'll turn to Dr. DiPersio for the initial discussion.

DR. JOHN DIPERSIO: So, I don't recommend -- I

wouldn't recommend screening for germline mutations. The issue there, of course, is if you find a germline variant of DDX41 or something like this and someone has a horrible case of thalassemia, are you going to not perform gene therapy on that patient without any evidence that this may result in any kind of clinical scenario which is worse than expected for someone that age in the general population? I just think you can't do that.

However, I do think that a much more rigorous prospective proactive approach to not only looking at integration site analyses, which they are really fixated on, but on the evolution and expansion of subclones that can be measured by regular next generation sequencing. And it would probably have to be a sensitive enough panel to pick up mutations the level of 0.2 to 0.5 percent. So, I still think most of the general sequencing panels are not going to be sensitive enough to track these clones.

So, that would be one thing that I would recommend. But I would not recommend germline

screening because we certainly have no evidence now that, even though there's a slightly increased rate of hematologic malignancies in sickle cell anemia, for instance, there's no evidence that those patients have increased incidence of variants involving the 150 or so genes that we think may be involved in inherited predisposition to either MDS inherited thrombocytopenias or AML.

And so, I think that's -- I think that's all I would say at this point. And I think they need to be just a little bit more broad-based and less looking under the lamp post and considering sort of the common things that result in treatment related MDS and AML which may be accelerated by this process.

DR. LISA BUTTERFIELD: Great. Thank you very much -- and for some of those specifics. And so, let's go to Dr. Coffin, please.

DR. JOHN COFFIN: Yeah, sorry. I agree with that perspective completely. With the addition that I -- a post-hoc analysis in the case of where there is something that's worth looking at, a search for

germline mutations could be made at that point to see if there are things that are likely to be associated with a bad outcome seen.

But in terms -- in -- since the issue of looking at integration sites was raised here, I -- yes, they emphasized it a lot, but they don't analyze it very well. And that really is annoying to me. The frequency of things that you see as frequent gene hits, for example -- they mentioned VAMP14 in this particular context -- is pretty much meaningless unless you know what you started with. Is this a -- different genes vary tremendously in their ability to serve as integration targets in in-vitro integrations as is done here.

And it would not cost them very much to get baseline information in the sense of taking a very small sample, probably a few hundred thousand cells worth, which is a very tiny fraction of the cells that they're doing, and do integration site analysis on that before they do the transplant and then see what -- whether the frequencies of specific gene hits have been

increased relative to what they start with. Otherwise, it's basically uninterpretable.

So, all of those integrations -- I found that quite impressive, the integration of the VAMP14. But it's based on the analysis of our data which may -- which are likely to be very comparable to what they would see if they did the experiment. But they're not exactly the same. They might be different. And in our case, VAMP14 is a very poor target. It's about number 3,000. If you list all the genes by their quality of the number -- the number of hits we saw in the in-vitro integration experiment, VAMP14 is about 3,500. There are 3,400 and something genes that are better targets, that yield more integration sites than that one.

And therefore, seeing that in the numbers of integration sites that they looked at -- which we don't know because they couldn't answer that question yesterday and I would assume they couldn't answer that question today -- but that's not -- that would suggest that there has been some selection for that. That doesn't -- being selected for it, however, does not

necessarily mean that this is an oncogenic process.

There are other bases -- there have been reported other bases on which gene specific integrations might be selected in a context like this that have to do with ability to cells to engraftment and things like that improving and some other factors that aren't well understood but almost certainly are not oncogenic related in terms of selecting for integrations in certain cells at the point of transplant.

And so, these experiments really need to be done by them in a way that are more interpretable to -- in terms of what's really going on here than we've been able to get so far.

DR. LISA BUTTERFIELD: All right. Thank you. Thank you, Dr. Coffin. And then, Dr. Shah.

DR. NIRALI SHAH: Yes. I agree with what the others have said. I think the one thing that I wanted to add, aside from the germline and somatic mutations, I do like the idea of getting the baseline bone marrows. I think the data that was presented is that

we really do not know a lot about the bone marrow architecture at baseline in the thalassemia population. And by doing the baseline that they did it allowed a little bit of information. So I do think that that ends up being important, particularly as these patients are hopefully going to be cured of their underlying disease.

And I think that if there are patient who have prolonged thrombocytopenia that there are certain time points where a subsequent bone marrow evaluation would be done. And I would recommend standard cytogenetics as part of that evaluation both at baseline and at follow-up.

D**R. LISA BUTTERFIELD:** Thank you. Thank you for that addition. So, let's see. So, I've got something in the chat. So -- yeah, so if we want, bluebird bio has looked at correlation between drug product attributes and delayed platelet engraftment if we want to learn more from the sponsor.

For Question Two, are there any other comments about screening tests, or shall I sum up what we've

presented so far? Okay. So what I've heard so far for Question Two is that there isn't a recommendation for potential germline somatic mutations predisposing to heme malignancy prior to administration, that that would have unclear importance relative to the disease itself and that that would be -- that sort of analysis would be more of a follow-up for adverse events suggestive of a role for germline predisposition.

That in addition to integration site, NGS for subclone analysis at a sensitivity of 0.2 to 0.5 percent is suggested and better analysis of the baseline cells for integration site analysis before transplant. And also, baseline bone marrow and cytogenetics before and after treatment would also potentially add very useful data going forward.

So, that's what I heard about screening assays. Looking for hands if there's anything to add before we go on to Question Three. So, not seeing additional hands for additional comments. Let's move on to Question Three.

"Please discuss the adequacy of the proposed

post-market pharmacovigilance program, including the long-term follow-up study and registry study and discuss additional recommendations for safety monitoring for hematologic malignancies." And here, we'll ask Dr. M to begin the discussion.

MR. MICHAEL KAWCZYNSKI: Could you tip your camera down, Dr. M? Thank you.

DR. JAROSLAW MACIEJEWSKI: Okay. Yes, yes, yes. Well, I mean, this is the same question that we discussed essentially in Question one and two (audio skip) to it. You know, there are two purposes for monitoring and pharmacovigilance. If we are worried about evolution of tonal disease following counts, looking whether patient is microcytic, develop new cytopenias or worsen existing cytopenias with and maybe at less frequent intervals, next generation sequencing would be important.

However, it's not that early detection of evolution would change anything, it might inform administration of this product to new patients if there would be sadly, at certain point, increased frequency

of this type of event. So, you know, in hematologic disease, like (inaudible) early intervention plays very little role in terms of the outcome of the treatment. So, it's important, but, you know, I mean it will not -- it would not (audio skip) with the patient.

However, I think that defining the bone marrow at the beginning is also very questionable. Because what is a baseline? Is a baseline before the transplant, or is the baseline after transplant? If the baseline is after transplant, when is it, right? Is it one month, two weeks? Some bone marrow failures the counts can recover and the bone marrow biopsy, of course, is done in one small place. And hyperosmolarity, for instance, is not really reflective of the bone marrow function.

In fact, one would think that the blood output production is better reflective of the bone marrow assay as an organ rather than a single site biopsy. One could do two weighted images and see how much is bone marrow upon recovery. But this would be more recent question rather than pharmacovigilance. In

terms of the other things such as integration and so on, I think we discussed it in -- on the other occasions. These are reasonable things to do.

It just, you know, in many ways, the pharmacovigilance is not going to alleviate any risk. We have to be aware of it. It might alleviate and inform subsequent steps in terms of redesigning the transplant strategy, et cetera. But I think that in addition to the proposed counts, which are a sort of no brainer, the only thing I would add the NGS and maybe viral integration site assay.

DR. LISA BUTTERFIELD: Okay. Thank you very much. So, other Committee members who want to weigh in here on Question Three? We have had fair amount of discussion around this, as Dr. M points out. Okay. So, I think I'm going to call on -- okay. So I'll circle back to bluebird. Dr. Shah, perhaps this is in the same theme of what we're talking about. And then Dr. M again. And then we'll hear from the sponsor on a particular point. Dr. Shah. We can't hear you.

DR. NIRALI SHAH: Can you hear me now?

DR. LISA BUTTERFIELD: Yes.

DR. NIRALI SHAH: Perfect. So this might actually be a discussion as it relates -- so just in follow-up to Dr. M's comments. I do think that they can use some of their primary endpoints as it relates to neutrophilic engraftment and platelet engraftment. And if they don't achieve that, that that would be a timepoint to do a follow-up bone marrow to at least look at the cellularity.

So, the one question I did have -- and I don't know if they can come back or not -- but it seems like they probably got a pretty good collection up front. Has there been the thought that if patients do have hypocellular marrow that they would get a stem cell boost? Or has that been a consideration, or has that ever been needed? It was not reported, so I don't think that's happened. But are there remaining cells that are non-transduced that are left over?

DR. LISA BUTTERFIELD: Okay. I'll refer that then to bluebird. So why don't we bring them back to address that specific question and then another

question that came up.

DR. RICH COLVIN: Great. Thank you. First, I'm going to turn it over to Dr. Seth Pollard (phonetic) to talk about some of the questions.

DR. SETH POLLARD: Hello. During the question period quite a few issues have come up around the drug product and the cell dose. And I just want to point out that as head of analytics, in my analytics group we've done a lot of work to try to understand what product attributes are responsible for outcomes, including engraftment.

So, can I have slide one? So, as was pointed out, five million per kg is the standard minimum dose. Oh, wait, it's coming. And we've actually infused many patients, you know, up to 15, some 20, one even 40 million cells per kg. We'll wait until the slides come up. Oh, yeah. They're coming.

DR. LISA BUTTERFIELD: There for a moment.

DR. SETH POLLARD: Sneak peek.

DR. LISA BUTTERFIELD: Yeah.

DR. SETH POLLARD: All right. There we go.

And so, looking at neutrophil and platelet engraftment we don't really -- really just don't see a correlation between dose and platelet engraftment.

So, if the hypothesis was that our manufacturing process -- which is designed to be very rapid and basically has no cell expansion as a part of it, is designed to preserve stem notes -- if that was the case, if we were damaging the cells, then you would see at the low end of the cell dose there would be an association with long, prolonged time. And we just don't see it. I mean, some of our fastest engrafting drug products had very low dose.

We took it a step further because this is something I'm really interested in. How does product impact dose? And we multiplied it by our colony forming assay to either look at percent colony forming cells or colony forming dose. And again, we don't have that slide here. We can provide it. But again, no association.

So we went further. Slide two, please. Phenotyping was brought up. Flow-based phenotyping is

really limited for hemopoietic stem cell products because there's just so many markers and we have cytokinetic culture which changes marker expression. So we actually put all the markers together into one massive CyTOF panel. Basically, you name your favorite hemopoietic marker, it's probably in there.

And we profiled every single beti-cel and eli-cel product that has been infused. And what we see is that there is a lot of patient to patient variability. You know, you can look at the HSC compartments. We tried modeling things like HSC dose and not just simple models but more extensive models. We just don't see an association between phenotype and time to engraftment.

And then finally, the issue on doing drug product ISA. So, ISA is a destructive technique. So if you're going to sample cells for ISA, you're going to sample, let's say, one million cells out of the 500 million that would be infused. And by definition, you have removed those clones that you find by ISA out of the drug product.

Also, as I mentioned, because our

manufacturing process is very rapid and preserves stemness, there's really no clonality to our drug product cell. So, if you do ISA on drug product, which we've done in pre-clinical work, you see a ton of integration sites. But those would not translate to the integration sites that are in the rarest subset of cells within our product that actually engraft.

So, given that, doing the ISA on drug products is really a futile effort because it doesn't tell you about the ISA that will come up in the patients. Thank you.

DR. LISA BUTTERFIELD: All right. Thank you.

DR. RICH COLVIN: And in response to Dr. Shah --

DR. LISA BUTTERFIELD: Yes.

DR. RICH COLVIN: Excuse me, Dr. Butterfield. Yes.

DR. LISA BUTTERFIELD: Please. No, please go ahead.

DR. RICH COLVIN: Okay. Thank you. And with respect to Dr. Shah's question. We haven't used any

stem cell boosts. Main reason is that all the patients have engrafted. And secondly, that if we did a stem cell boost then those cells would not have been corrected or having an introduced transgene into them.

DR. LISA BUTTERFIELD: But the cells are -- but there are some of those cells in existence, just to complete the question?

DR. RICH COLVIN: We have rescue cells in case patients do not engraft. But those cells have not been transduced. Those are the baseline cells that were collected at the time of apheresis.

DR. LISA BUTTERFIELD: Thank you. Okay. Let's go back to the Committee. Dr. M, Dr. Coffin, and Dr. Ahsan.

DR. JAROSLAW MACIEJEWSKI: I think, you know, I mean very beautiful data in terms of the composition of the infused cells. I think it might be very important in terms of, let's say, a (inaudible) precursors that underrepresented in people who have subsequent thrombocytopenia.

I think if we are worrying about clonal

evolution and you want to establish the causative relationship between your manipulation or excluded, if you do mention sequencing for driver mutations on the harvested product -- before transaction or after transaction doesn't matter. This would, of course, will allow you then, should you have a positive event later on to assume that this clone has been already in a patient before, excepting, you know, sensitivity of course. But anything is -- has their limitations. And conversely, you could say that the clonality and the driver mutation detected later was a result of, let's say, conditioning regimen.

I think this would be a good thing to recommend. Whether FISH would be another thing to do, I don't know. I agree with the pathologist from Harvard that this is not an useful test. But particularly there is high risk of -- high level of suspicion and one would save the patient from doing the bone marrow and the cytogenetics, the FISH is totally reasonable for the most common chromosomal abnormalities.

DR. LISA BUTTERFIELD: All right. Thank you. Dr. Coffin and then Dr. Ahsan.

DR. JOHN COFFIN: Yeah. Hi. Just wanted to respond to the response to my comment about the pre-implantation analysis of integration site distribution.

While it's true that the cells that you take for such analysis would be gone from the site, it's not true that that's -- that doesn't mean they're not representative of what you implanted. In 100 million cells, which is sort of a minimal number of the number of cells they implanted, there will be 100 million proviruses. The numbers they showed shows that their cutoff is going to be approximately one provirus per cell on average. And given that, any decent (audio skip) will be represented many, many, many times in the population. I strongly recommend the bluebird people read our papers on this topic, actually.

And so, when they're talking about seeing a lot of integrations in VAMP14 again, I don't know if that means that there were that many integrations to begin with in that particular gene. Even though the

specific ones might have been lost, there will still be lots of others -- there will still be lots of others in that gene. Even if the gene is not a terribly good target, there will still be quite a few. In 200,000 sites we saw 12, for example. And they'll --- they can look at -- they can look at that many easily in a -- in quite -- really what's quite a small fraction of the total cell population.

So, the ability to interpret just the number of integrations that they see is very, very limited if they look at what is the product of likely to be various kinds of selection afterwards. And it doesn't mean anything unless you can interpret it in terms of what the frequency of integrations in the starting -- in that particular gene in the starting pool is.

And they will not have removed all of the integrations in any given gene by a long shot by taking a small sample for analysis. So, my recommendation strongly stands in this.

DR. LISA BUTTERFIELD: Thank you for that -- for the further detail there. Dr. Ahsan and then Dr.

DiPersio.

DR. TABASSUM AHSAN: Thanks. Yeah, I wanted to speak a little bit more about the sponsor's data on the phenotyping. So, I think what's come about and has been consistent throughout the comments is that small sub-populations are being over-represented in terms of the impact of the drug product once it goes in-vivo. And so, taking those large categories and assessing phenotype that way is not sufficient. We really need to look at the smallest populations.

And then to build on what Dr. Ott said about lentivirus, especially when you do things at high MOI, have effects on these cells. As you admit, you have a very rapid manufacturing process. So, I think it's really important as you move forward that you also evaluate the cell's health of these small sub-populations immediately post-(inaudible) formulation, let's say.

Because we do need to understand what is -- what's the state of the cell when they're going into the patient. And I don't think that the phenotypic

analysis that you provided is sufficient because it's very broad, and what we know is that there's over representation at later time points.

So, I think that that's going to be a key thing to evaluate over time as you start increasing the number of patients that are being treated with this to really have a deeper understanding of the drug product so that we can understand the risk. Again, right, we're -- I don't think what was echoed in question number two and the rest of it, which is we don't have enough information to screen, but we do start having to build it -- that data, have a deeper understanding of the mechanism so that then we could screen, if necessary.

DR. LISA BUTTERFIELD: Thank you. And then I think to close out our discussion Question Three, Dr. DiPersio.

DR. JOHN DIPERSIO: I was reassured by the immunophenotyping data you showed. Thank you very much for that. That's great.

With all due respect though, I still think

that there are some clear examples using really, let's say, mouse models where stem cells are taken out, and then they're expanded. And they're competed directly against unexpanded stem cells. And there is a difference. Depends upon how long you expand them and how you expand them.

So, there's no doubt that your product is different than a fresh product. And so, I would be interested also to know what is the immunophenotyping look like before and after expansion and genetic manipulation. Are there any smoking guns there that you're seeing that might explain some of these few patients that have slow platelet engraftment? That's my only point. I'm done.

DR. LISA BUTTERFIELD: Thank you. Okay. So, thinking about Question Three, I think we had a diversity of opinion of things that -- of assays that might be done in the post-marketing pharmacovigilance program.

We heard pluses and minuses about bone marrow analysis, detailed phenotyping, the need to include

more rare subclones in that detailed phenotyping, looking at differences between original and expanded products and the baseline -- the baseline fills before transduction and after.

So, a lot of potential things to look at. I'm not sure I heard a lot of firm agreement over particular tests, although some of the phenotyping that was shown by the sponsor was certainly appreciated.

So, let's move to final Question Four. "Please discuss recommendations for specific testing for heme malignancies following administration of beti-cel, to include frequency of testing in the patients with transfusion dependent beta-thalassemia." And so, here was start with Dr. M, please.

DR. JAROSLAW MACIEJEWSKI: Yeah. Thank you. I think -- I mean, we -- these questions are very related to each other. So, we spent a lot of time discussing it.

And I think we have almost consensus in terms of a CBC. I mean, obviously as, you know, there can be some mandated frequency of testing and -- in which

might be increased in patients who develop or who have persistent cytopenia or whose counts are going down.

I would strongly remind everybody that we went to bone marrow aspiration for diagnosis of something that is not there -- should not be a routine part and should be left up to the discretion of the physician. Again, in patients who don't have much hemocytopenia it would be inconsequential.

Earlier detection would be -- of a malignant process would not be medically that important. It would not offer bigger, better chances of intervention. And it's quite invasive and intrusive given the mildness of the symptoms.

So, in addition to some baseline counts that could be implemented on a sort of -- you know, depending, again, whether the patient is doing very well. And these people get the transplants. They have been medical victims for long, long time now. They are getting better. And it has to be also accounted for.

I think next generation sequencing in the product and then once a year in all patients would not

be intrusive. We don't need a bone marrow for it. It could be done on peripheral blot. It would be reasonable. Unless there is a sudden drop in count which one could insert the sort of interventional per discretion of the physician.

I am not going to comment, as I am not the specialist, on the viral stuff. But it seems to me that unlike in the previous protocol this has not been such an issue here. So I am less worried about it. But there is a certain standard of care for this. And I would defer to somebody like Dr. Coffin or others.

DR. LISA BUTTERFIELD: All right. Thank you very much. So, let's go to Dr. Gordeuk.

DR. VICTOR GORDEUK: This is a very simple test. But I think the LDH would be worth getting along with the CBC. I found that that can be a marker of an early developing hematologic malignancy.

DR. LISA BUTTERFIELD: Thank you. Any frequency for that over time that you would suggest? Oh, you're gone already.

DR. VICTOR GORDEUK: I'm back. Yeah. I think

it should be done every time the CBC is done.

DR. LISA BUTTERFIELD: Okay.

DR. VICTOR GORDEUK: And maybe at six monthly intervals would be good.

DR. LISA BUTTERFIELD: Great. Thank you, for that. All right. Dr. M?

DR. JAROSLAW MACIEJEWSKI: Yeah. You know, LDH, you know, it would not be a marker of anything in patient with homologous except for homologous. So, it's a cheap test and it's reasonable. So, I just wanted to know. I mean, in somebody with hemolytic anemia you are not detecting leukemia because patient has LDH elevated.

DR. LISA BUTTERFIELD: I see. So your recommendation would be that that would more likely be signaled by --

DR. JAROSLAW MACIEJEWSKI: I think that it's reasonable, but this would --

DR. LISA BUTTERFIELD: -- homologous --

DR. JAROSLAW MACIEJEWSKI: -- this would be more response evaluation rather than pharmacovigilance

for evolution of leukemia.

DR. LISA BUTTERFIELD: Thank you. All right. Other discussion on the recommendations for specific testing for heme malignancies following infusion of the cell products? Yes. Dr. Ott.

DR. MELANIE OTT: Yeah. I just want to support what we had said earlier in response to another question already where it was mentioned that really the clonal expansion should be monitored frequently. And I would say I would still do the ISA nor sort of perhaps but really mandatorily in the follow-up registry study.

And I would probably do it more frequently at the beginning and then more on a -- more in a yearly or more, you know, longer time between the individual tests later after and during the follow-up. But I would definitely keep both parameters closely monitored.

DR. LISA BUTTERFIELD: Thank you. And that's clonal hematopoiesis and ISA?

DR. MELANIE OTT: Correct.

DR. LISA BUTTERFIELD: Thank you. Okay.

Other thoughts to add on Question Four? And then, I guess at this point I will ask FDA if they have other questions for discussion by the Committee. Dr. Bryan.

DR. WILSON BRYAN: No, thank you. I think that's all our questions. I would -- if we could get a little bit more on the frequency of the testing of the CBC and the clonal hematopoiesis and ISA. Initially what should that frequency be?

DR. LISA BUTTERFIELD: Okay. And let me refer this to Dr. M about the CBC which was at --

DR. JAROSLAW MACIEJEWSKI: CBC begins --

DR. LISA BUTTERFIELD: -- you know, at --

DR. JAROSLAW MACIEJEWSKI: If the patient established semi-normal counts, I mean, you know, I think every three months -- monthly to every three months or every six weeks would be reasonable, I mean, because of the price and less volatility. I think every six months for the first year and then maybe annually the clonality unless for cost. This what we are referring as to monitoring in all patients rather than interventional in patients who have cytopenia

whereby it would at the discretion of the physician in my opinion.

DR. LISA BUTTERFIELD: Thank you. Anything else, Dr. Bryan?

DR. WILSON BRYAN: No. Thank you. That's very helpful.

DR. LISA BUTTERFIELD: Okay. And we have one more hand up by Dr. DiPersio before we go to the vote.

DR. JOHN DIPERSIO: I just say that for the sequencing stuff if you look at the incidence and kinetics of MDS in leukemia in these patients, it's happening in the context of the usual timeframe, like three to four years. So I would say yearly maybe for five years, I would think. Something like that. It can happen after that, but I think the highest risk period is between three and five years after accolade or exposure. Now, it's different for the other products where there's more risk of insertional oncogenesis.

DR. LISA BUTTERFIELD: Great. Thank you. All right. With those specifics and the conclusion of the

discussion, let's move to voting. And so, let me bring back Christina Vert, please, to talk about the process.

MS. CHRISTINA VERT: Thank you, Dr. Butterfield. Only our six regular members and seven temporary voting members, a total of 13, will be voting in today's meeting.

And with regards to the voting process, Dr. Butterfield will read the final voting question for the record. And afterwards, all regular voting members and temporary voting members will cast their vote by selecting one of the voting options, which just like yesterday will be yes, no, or abstain. And you'll have one minute to cast your vote after the question is read.

And please note again that once you cast your vote you may change your vote within the one-minute timeframe. However, once the poll has closed all votes will be considered final. Once all the votes have been placed, we'll broadcast the results and read the individual votes out loud for the public record. And does anyone have any questions about the voting process

before we begin?

DR. LISA BUTTERFIELD: No. Nothing --

MS. CHRISTINA VERT: Okay.

DR. LISA BUTTERFIELD: -- nothing comes up. Thank you.

MS. CHRISTINA VERT: Okay. Great. Okay. Dr. Butterfield, please read the voting question.

DR. LISA BUTTERFIELD: We have a single question. Do the benefits of beti-cel outweigh the risks for the treatment of subjects with transfusion-dependent beta-thalassemia?

MS. CHRISTINA VERT: Thank you. You may -- once the voting pod's up -- yep, the voting pod's up. Go ahead and start voting.

Okay. Time is up. That's one minute. Looks like all the votes are in. We can broadcast. Okay. Okay. Let's see. All right. Again, there are a total of 13 voting members for today's meeting. And the vote is unanimous. We have 13 out of 13 yes votes, zero no votes, and zero abstained votes.

And I will read the responses. Okay. Let me

see. Okay. Janelle Trieu, yes; Jaroslaw Maciejewski, yes; Lisa Butterfield, yes; Bernard Fox, yes; John Coffin, yes; John DiPersio, yes; Randy Hawkins, yes; Melanie Ott, yes; Victor Gorduek, yes; Navdeep Singh, yes; Nirali Shah, yes; Jeannette Lee, yes; Taby Ahsan, yes.

And that is the list. And this concludes the vote for today. Thank you very much. And I'll pass the meeting over Dr. Butterfield.

DR. LISA BUTTERFIELD: All right. Thanks everyone. We are once again unanimous. And so now I have to go through and we're going to ask each one of you. And because we all voted yes, we are to explain our votes. And I'll call everyone out by name one by one. And please include discussion of your -- any recommendations for any risk monitoring and mitigation for patients who receive beti-cel in addition to rationale for the yes vote.

So, I have here a list in front of me of the six voting members and then the seven temporary voting members. And so, one by one I'll go through this list

asking for the explanation for the vote.

So, my name is first. And so, my reason for voting yes was the impressive efficacy data and minimal risk data as shown by the sponsor in all the briefing documents and with the discussion of all the experts across the panel. And I do not have any specific recommendations for risk monitoring other than what the Committee has already discussed over the last hour. Let me move now to Professor Fox.

DR. BERNARD FOX: Okay. So, I agree. I think the 88.9 percent transfusion independence is remarkable. I think that the risks with neutrophil engraftment and platelet engraftment are clear. But the benefits clearly at this point outweigh the risks to the patients. And so, this provides the benefit. I think that's enormous versus -- the graft versus host disease risk that we heard from both physicians that take care of these patients as well as from the patient representatives.

I also agree with Dr. Butterfield. I would support the monitoring proposals that have been put

forward by our colleagues with more experience in this area. Thank you.

DR. LISA BUTTERFIELD: Thank you very much. Dr. Lee, the reason for your vote.

DR. JEANNETTE LEE: I have the same feeling. The efficacy, I think, was outstanding. And the opportunity to be transplant independent I think is really life changing of the patients. And I felt the safety risks were definitely outweighed by the benefit. And I will defer to my colleagues on the risk monitoring and mitigation. Thank you.

DR. LISA BUTTERFIELD: Thank you. Dr. Ott.

DR. MELANIA OTT: Yes. I totally agree with everybody. The efficacy is great. I also want to point out that I was impressed by the stable expression over seven years that was provided which is, I think, very reassuring that this is going to be a long-term benefit. I would say the safety data were very good in the absence of any real clonality and malignancy here.

And I refer to what we discussed at length in the last hour to the recommendations, especially when

it comes to clonal hematopoiesis and ISA.

DR. LISA BUTTERFIELD: Thank you. Dr. Shah.

DR. NIRALI SHAH: Hi. So, I also agree with the risk benefit assessment. I feel that the benefit clearly outweighs the risks that have been stated. One comment that I specifically want to make is that just given sort of the underrepresented minority and the ethnic and racial predisposition of this disease that we are sure to include also reporting for patient reported outcomes and sort of what the distribution is over the course of this therapy and its utilization.

In terms of the risk mitigation, I agree with what's been stated. I would again continue to endorse the use of a baseline marrow. I think it will be informative at least while we learn a little bit more about these patients and how they're treated -- and would consider an enhanced monitoring program. And I think that would have to be determined later for patients who have delayed platelet engraftment for evidence of oligoclonality.

DR. LISA BUTTERFIELD: Thank you for that.

Dr. Ahsan.

DR. TABASSUM AHSAN: Yes. I'll echo what everyone else said, which is the durable clinical outcome outweighs the concerns about engraftment at this point. I think I'll leave the risk and monitoring issue to what's already been discussed. But I will reiterate that I do think that a deeper understanding of the drug product in terms of the smaller populations and characterizing the cell health is critical for a deeper understanding of mechanism of action.

DR. LISA BUTTERFIELD: Terrific. Thank you. And now we'll go through and hear from the temporary voting members. Dr. Trieu.

DR. JANELLE TRIEU: I also have to agree with everyone. We've seen compelling data to support the benefits great -- that benefits greatly outweigh the risk of the treatment. But also, there is a significant improvement in the quality of life after treatment that I don't think should be taken lightly. I think given the minimal risks and favorable results we've seen specifically from this treatment I don't

have anything to add to the post-treatment monitoring that hasn't been mentioned already.

DR. LISA BUTTERFIELD: Thank you very much. Dr. M.

DR. JAROSLAW MACIEJEWSKI: Thank you. It seems that there is a clear benefit to the patient and therapeutic option and that might be really paradigm shifting. The currently use drugs and the ones that were recently introduced are not as much of a paradigm shift that would preclude or necessitate prospective comparison because it seems to be a game changer. So, I think it was not -- given the low toxicity, except for the original procedure which it's inherent to. But the retroviral product by itself -- the lentiviral, I think this is a clear yes.

DR. LISA BUTTERFIELD: Thank you. Dr. DiPersio.

DR. JOHN DIPERSIO: Okay. I feel that same way. Tremendous benefit, minimal risk. And also, minimal risk compared to standard of care as far as quality of life and transplant. That's a very

important -- also important comparison.

Second is that the monitoring, I do agree with Nirali that a baseline bone marrow would be important. I think going forward these are -- you know, there's three places where a somatic mutation can occur, right. It's already there. It's generated by the procedure, or it's amplified afterwards. And whether the integration amplifies it further or not is another question. So, I do think that having those initial marrows would be very important.

In retrospect, one could go back and even do the kinds of things that you'd really want to do if one of these malignant clones progressed. And that's do digital droplet PCR to see if it was there before or after the manipulation. But I think this is an important part of the overall forward progressive plan to monitor these patients, I think.

DR. LISA BUTTERFIELD: Thank you for those details. Dr. Coffin.

DR. JOHN COFFIN: Yes. I certainly have little to add to the risk/benefit balance. I think

it's very, very clear here, including quality of life issues, as we already heard.

As far as recommendations going forward, certainly, they need to keep monitoring clonality. But I'll say again that the integration site analyses are not very meaningful. They're meaningful if you see something that's 10 percent or more of the population. But as far as frequencies, unbalanced frequencies in specific genes mean nothing unless you know what you started with.

The frequency of integration sites in in-vitro infection as they're doing here can vary by a thousand-fold from one gene to the next. It's enormously variable. And then once you know what those numbers are, you can't learn really very much about what you see after periods of time that involve some kind of selection. Or maybe not. Maybe it's just chance. But you can't tell what you know without what you started with.

I will be happy to offer myself to the sponsor if they want any more discussion on this point because

I think it's very important for understanding these experiments. And the general point here is that I think a lot of the experimentation that should be done and the monitoring that should be done should be in the vein of using that to understand what's going on as much as being predictive for clinical care.

There's trailblazing studies -- sort of trailblazing therapies. And it's really incumbent on these sponsors to really try to learn as much as possible about the science that's going on for the sake of further improvements in the process.

DR. LISA BUTTERFIELD: Thank you. Dr. Singh.

DR. NAVDEEP SINGH: Yeah. I support the study and going forward with the plan. As I said earlier, this treatment option affords someone like me who doesn't have a sibling -- so bone marrow transplant wasn't really offered for me. And so, to be able to be offered the chance of being transfusion independent and even with luspatercept, I mean, we're still getting transfusions. So this gives a lot of hope to my community. And yes, I'm looking forward and having

nothing -- no other recommendations in terms of monitoring. I think -- I'm very happy about this.

DR. LISA BUTTERFIELD: Thank you. Dr. Hawkins.

DR. RANDY HAWKINS: Yes. So, I'm in agreement. As proceeds, quality of life really, really important. Low risk is apparent. I would defer monitoring to experts on the -- on this Committee.

I would again emphasize the importance of taking this opportunity with whatever medical branch informs the populous of the need for potential donors to increase the number of individuals who avail themselves of the ability to be a donor for allotransplants. Thank you.

DR. LISA BUTTERFIELD: Thank you for that note. And our final -- let's hear from Dr. Gordeuk.

DR. VICTOR GORDEUK: Yeah. It looks like the benefits are really wonderful, outweigh the risks. There's a clear way forward for regular monitoring at least on a simple basis for the development of any hematologic complications. So, I'm just highly in

favor.

DR. LISA BUTTERFIELD: Terrific. Thank you. So that concludes the Committee vote explanation. So, with that, I think we move now to some closing remarks by Dr. Peter Marks.

CLOSING REMARKS

DR. PETER MARKS: Thanks, Dr. Butterfield. First of all, I just -- I have a couple of thanks mainly here. I want to say that it has been quite an impressive two-day meeting. Really appreciate everyone's participation.

I want to thank our Advisory Committee staff for doing an incredibly skillful job putting everything together. And the technical execution of this meeting was excellent. Really appreciate that. Want to also thank the staff at FDA who did an incredible job here under Dr. Bryan's leadership. Really appreciate that.

Also, I want to thank all of the Committee members and particularly thank you, Dr. Butterfield,

for doing an incredibly great job chairing this meeting. It went off really, really very, very nicely. The level of dialogue at this particular series of meetings was at a level that is quite impressive. And I think you may have set a standard for both the conduct and the content of our Advisory Committee meeting. So thank you very much for that.

I think this will be a very meaningful for patients also, and it's very thoughtful the advice that you've provided us. So, thank you very much. And I don't want to keep anyone any longer on a Friday afternoon. So thank you. I will turn it back over.

DR. LISA BUTTERFIELD: Thank you so much, Dr. Marks. And so, with that, let me hand this off to Christina Vert to close the meeting.

MS. CHRISTINA VERT: Thank you, Dr. Butterfield. I want to also thank you for chairing the meeting. It really was -- you did an outstanding job, and everything went very smoothly with your leadership. And I also want to thank the members, temporary voting members, speakers, patient reps, for making this

meeting go so well and for your contributions and the public that contributed also to the docket and to the open public hearing. Thank you all. And I adjourn the meeting.

DR. LISA BUTTERFIELD: Thanks, everyone.

MS. CHRISTINA VERT: Bye, everyone.

MR. MICHAEL KAWCZYNSKI: All right. With that, this meeting has concluded.

[MEETING ADJOURNED]