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Advisory Committee on
Cellular, Tissue and Gene Therapies

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P R O C E E D I N G S (8:00 a.m.)**Agenda Item: Call to Order and Introduction of
Committee**

DR. SNYDER: Welcome back to those of you at yesterday's meeting, and welcome for the first time for those of you attending this meeting for the first time. So we'll call to order the meeting of the cellular, tissue and gene therapies advisory committee. And we'll start off by Gail Dapolito reading the conflict of interest statement.

Agenda item: Conflict of Interest Statement

DR. DAPOLITO: Good morning. Thank you, Dr. Schneider. This brief announcement is in addition to the conflict of interest statement read at the beginning of the meeting on September 22, and will be part of the public record on September 23, 2011. The committee will discuss HDE BH110018, CliniMACS CD34 Selection System, Miltenyi Biotec Incorporated for processing allogeneic human leukocyte antigen-matched hematopoietic progenitor cells-apheresis from a related donor to obtain a CD4 (sic) positive cell population intended for hematopoietic reconstitution following a myeloablative preparative regimen without the need for additional graft-vs-host disease prophylaxis in patients with acute myelogenous leukemia in first or second morphologic complete remission.

This is a particular matter involving specific

parties, and I hope I don't have to read that again. Based on the agenda and all financial interests reported by members and consultants, no conflict of interest waivers were issued in accordance with 18USC, section 208B3 and 712 of the Food, Drug and Cosmetic Act. Dr. Gregory Curt is serving as the industry representative, acting on behalf of all related industry. He is employed by AstraZeneca. Industry representatives are not special government employees and do not vote.

This conflict of interest statement will be available for review at the registration table. We would like to remind members, consultants and participants if the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that you may have with the sponsor, its product, and if known, its direct competitors. And finally, we ask that you silence all electronic devices. Thank you.

DR. SNYDER: Thank you very much. So as we did yesterday, we'll start off going around the room and doing just a brief introduction of your name, where you come from

and your area of expertise. This is particularly necessary because there are new people on the panel.

(Intro around table)

DR. SNYDER: Thank you. Dr. Witten, who is the director of the Office of Cellular, Tissue and Gene Therapies will give an introductory statement.

Agenda Item: FDA Introduction

DR. WITTEN: Good morning. I would like to provide a very brief background for today's meeting. The purpose of today's meeting is to discuss the Humanitarian Device Exemption, or HDE, submitted by the sponsor, Miltenyl Biotec. This HDE is for the CliniMACS device in the treatment of patients with acute myeloid leukemia or AML. We appreciate the importance of this application, not only for this sponsor, but also for patients with AML and their families.

Because the HDE pathway has not been previously considered by this committee by this application, we'll start today's meeting with an FDA presentation on the regulatory pathway for humanitarian device exemption products before proceeding to the sponsored FDA presentations on the specific matter at hand. We're asking the advisory committee members to discuss issues related to risk benefit for the indication for which approval is being sought, as well as to provide input into certain issues

regarding benefit, safety, labeling and device performance.

I'd like to thank the advisory committee members and the FDA staff for their work in preparing for this meeting. I appreciate the advisory committee's consideration of the questions for this meeting, and look forward to today's discussion. Thank you.

DR. SNYDER: Just before we introduce Dr. Stevens, I wanted to acknowledge a new member to the committee, Dr. Patrick Hwu from MD Anderson. And our next speaker is going to be Dr. Theodore Stevens, who is associate director for information management of The Office of CTGT at CBER. And he'll be giving the committee a summary of the regulation for humanitarian device exemption products, which is quite pertinent to the product we'll be talking about which we'll be talking today.

Agenda Item: FDA Introduction - Regulation of Humanitarian Device Exemption (HDE) Products

DR. STEVENS: Good morning. My name is Ted Stevens and I'm with CBER's Office of CTGT. And because the committee is going to be asked to provide advice on humanitarian device exemption application, I will provide a presentation on the regulation.

In 1990, Congress passed the Safe Medical Devices Act, which included provisions for humanitarian use devices, similar to other orphan products. The

humanitarian device provisions are meant to encourage development of devices that are targeted to patient populations too small to be otherwise economically feasible.

AS you can see here, there have been some changes in the regulations after the initial 1990 legislation that created the HD pathway for medical devices, to treat rare diseases or conditions. To highlight some of these, in 1997, the FDA Modernization Act identified a 75 day review clock for FDA action, eliminated a previous requirement for renewal of HDE approval every 18 months, and allowed emergency use without prior IRB approval. And as a result of changes in 2007, HDEs approved for pediatric populations or subpopulations after September 2007 may be eligible to be sold for a profit.

The standard marketing application for a new type of medical device is a pre-market approval application or PMA. For a humanitarian use device, the application is the humanitarian device exemption, or HDE application. Even though it has exemption in its name, an HDE, like a PMA, is a marketing application, and HDE approvals are subject to the same adverse event reporting requirements as PMAs. The main difference is the main difference is the information required to gain approval. An HDE can be approved even without the reasonable assurance of effectiveness that the

law requires for PMAs.

Instead, in addition to safety, the requirement is probable benefit. When an HDE application is approved, that authorizes the marketing of the humanitarian use device. Local institutional review board approval is also required for use of an HUD. It's up to the IRB whether they want to require separate approval for each case, or grant a blanket approval for use at their institution. Because it is a marketed device, there is not FDA requirement for informed consent, as would be needed for an investigational device. However, some IRBs do ask for informed consent to insure that patients are aware of the device's status.

Also, because effectiveness has not been established for an HDE, labeling for a humanitarian use device must state that clearly. To be eligible for humanitarian use status, a particular device cannot already be approved or cleared for marketing, and there cannot even be a comparable device available. And as I said earlier, the device must show safety, as well as probable benefit.

So how do we decide that the device meets the safety and probable benefit bar? We review the evidence provided, and for approval, we have to establish that the device does not expose patients to unreasonable risk of illness or injury, and that the probable benefit outweighs

the risks. And this is done in the context of other available therapies, which don't have to be devices.

So now that I've given you that overview, I'll go over our review process. The first step is to determine if a device's target population falls under the required 4000 cap. This is determined by the Office of Orphan Products, and HUD status has already been established by the use for the use being sought for the device under consideration later today.

When evaluating the number of potential patients in the population, the Office of Orphan Products can consider subpopulations to arrive at the 4000 number. But they require that any subset be medically plausible and not an artificial delineation. After HUD designation, the sponsor can submit their HDE. The administrative review includes whether the device is already marketed, and if comparable devices exist.

And then, scientific preclinical and clinical information is reviewed, including a device description, results of non-clinical testing, as well as any clinical experience with the device. This could be from sources such as formal studies, marketing experience outside the US, or with the same device in the US, but for different indications. HDE submissions usually do not contain randomized controlled clinical trials, because of the small

sample size involved and because comparable devices do not exist.

We also review manufacturing information. Good manufacturing practice for devices is to find in the quality system regulations. And these are applied, just as they would be for a PMA device. For combination devices, with a drug or biologic component, GMPs may apply. Labeling is reviewed, and as stated earlier, it must contain a statement that effectiveness has not been demonstrated. We also verify the cost accounting to ensure that no profit will be made, with the exception of for pediatric indications.

So to recap, HDE is the marketing approval for humanitarian use device. For an HDE approval, the sponsor need not establish effectiveness, but must show probable benefit. Even after HDE approval, local IRB is required to use the device. Also, even though sponsors have the option of submitting a traditional PMA or 510(k) later on, there is no requirement for that. However, if a PMA or a 510(k) is approved for the same indication, similar devices cannot be considered under HDE. However, having an approved HDE does not prevent others for the same indication.

FDA has found that there are some common points of confusion around HDEs. One stems from the word exemption in humanitarian device exemptions. It sounds

similar to the investigational device exemptions, so some assume that HDEs are investigational, which is not the case. IRB approval is required, but FDA does not require informed consent. However, informed consent is often required by state, local or institutional authorities.

As with other approved devices, a clinical trial for a new indication does require an IDA for significant risk devices. And so far, all HDEs have been for significant risk indications. For more complete discussion, there's an HDE guidance document in question and answer format which was provided to the committee in their briefing packets. The easiest way to find it is by entering HDE guidance in the search bar on the FDA webpage, or if you're feeling brave, you can try to write down the link.

The Center for Devices and Radiological Health has a page listing approved HDEs with a link to their summaries of safety and probable benefit. You can find it by entering HDE approvals in the search bar. The Center for Biologics has not yet approved any HDEs. And that concludes the overview of the HDE regulations. Here's my contact information at the top line, and for our office, the regulatory staff contact is Patrick Riggins. The last three names you see are CDRH's HDE staff and those are the people that administer the HDE program for the Center for

Devices. And I'd be glad to take any questions if there are any.

Agenda item: Q & A

DR. SNYDER: We will take the Q&A for all comments and Q&A for the day. The best way to do that is one, please identify yourself, please speak into the microphone because sometimes you can't be heard, and we're also being web cast. And finally, we'll take the questions in the order in which people identify themselves. And all you need to do is just make a gesture or raise your hand, and either Gail or myself, will note it. We'll put you in a queue and we'll go down the queue and acknowledge you so you can ask your question as they come in. So with that, you were first.

MR. FLATAU: So an HDE, can it be approved for a second indication for a different disease?

DR. STEVENS: Yes, if there's a second orphan indication, a device can be improved with another HDE for a second orphan indication. The same device could also be approved for a different indication under a PMA, if it doesn't fall under the orphan devices.

MR. FLATAU: I guess I'm wondering about the 4000 patients. If there were two indications, would that be up to 8000 patients, 4000 in each, or would that just be 4000 in total?

DR. STEVENS: So each indication would be independent, as long as they're both separate indications. They each would be under the 4000. So if you've got multiple indications for an HDE, each of which could have up to 4000.

DR. COUTURE: So you indicated that no other product can be available or device could be available. So if you get an HDE and subsequently a product becomes available through PMA or 510 or something, does that then invalidate the HDE or is the device still available?

DR. STEVENS: It doesn't go away automatically. If a PMA or a 510(k) is cleared for the same indication, we could withdraw the HD, but it doesn't happen automatically. We'd have to go through a process for that. Often, if a PMA is approved, it will be the same sponsor that had the HDE. I'm not aware of any cases in CDRH where an HD has been withdrawn because of an approval of another device.

DR. COUTURE: So does an existing HDE preclude another HDE being issued in the same indication?

DR. STEVENS: Not for an HDE. You can have multiple HDEs for different devices from different sponsors for the same orphan indication.

DR. SNYDER: I had one question. So the demonstration of probable benefit, that's not a statistical benchmark, that's an opinion?

DR. STEVENS: It's a weighing of the risk versus the benefit. There's no definition in the regulations or the statute that helps us out there. It's really you have to weigh it in terms of the risks and the benefits you see with the device in the context of what else is available.

DR. SNYDER: But there's no statistical metric, it basically is a judgment call.

DR. STEVENS: Yes, though you would of course use statistics to inform that.

DR. D'AGOSTINO: In terms of the probable benefit, you must present some kind of clinical trials, of which they may not be powered enough and there may be historical controls. But there has to be something formally presented, that talks about benefit.

DR. STEVENS: It has to be something that's formally presented. It doesn't have to be a randomized controlled clinical trial. There's a definition in the regulations of what valid scientific evidence is for a device, and that includes things --

DR. D'AGOSTINO: Other than controls and so forth.

DR. SNYDER: No other questions or comments? Okay, great. Then we can move on to Miltenyl Biotec presentation on the particular product that we're going to be discussing today.

**Humanitarian Use Device Designation, ClinimACS
CD34 Selection System, Miltenyi Biotec, for the Selection
of CD34+ Cells from HLA-Matched Donors for Allogeneic stem
Cell Transplantation after Myeloablative Therapy in
Patients with Acute Myelogenous Leukemia in First or Second
Complete Remission**

Agenda Item: Miltenyi Biotec Presentation

DR. JOHANSEN: Good morning. My name is Nancy Johansen. I'm the director of regulatory affairs at Miltenyi Biotech. I wanted to thank the committee, as well as FDA, for giving us the opportunity to discuss the humanitarian device exemption for the ClinimACS CD34 Reagent System.

Today I'll give a brief overview of the company, and an introduction to the ClinimACS CD34 Reagent System. Dr. Steve Devine will present an overview of the clinical indication, and summarize the results of the probable benefit trial, BTM CTN 0303. Dr. Carolyn Keever-Taylor will summarize the cell processing data from the trial, and discuss the performance of the ClinimACS CD34 Reagent System in a multi-center setting. Dr. Marcelo Pasquini will present a summary of the data analysis study, comparing the results of the 0303 trial to a contemporary cohort of patients receiving unselected transplants. And finally, Dr. Kai Pinkernell will summarize the probable

benefit of the CliniMACS CD34 Reagent System.

Miltenyi Biotec was founded by Stefan Miltenyi in 1989 in Bergisch Gladbach, Germany. Today, there are over 1100 employees worldwide, with subsidiaries in 10 countries. In the US there are two offices, the corporate office and US distribution center which is located in Auburn, California, and on the other coast, the regulatory and clinical operations office in Cambridge, Mass.

The overall function of the CliniMACS CD34 Reagent System is to select CD34 positive cells from heterogeneous hematologic cell populations, and thereby passively depleting T-cells. The CliniMACS CD34 Reagent System is comprised of four components. The CD34 Reagent, which gives the CliniMACS CD34 Reagent System its specificity. It is a monoclonal antibody covalently linked to a iron dexstrand super paramagnetic bead. The CliniMACS PBS/EDTA Buffer is a sterile isotonic phosphate buffered saline solution, which is used as an external wash and as transport for the cells on board the instrument.

The CliniMACS tubing set is a sterile single-use tubing set, fitted with two CliniMACS columns. There are two sizes, the standard and the large scale, to accommodate different starting cell concentrations, and both were used in this trial. The CliniMACS instrument is a functionally closed software-driven system that controls the processing

of the cells. The CliniMACS CD34 Reagent is based on the principle of magnetic activated cell selection. The CD34 Reagent is added to the cell product. The cells with the CD34 surface antigen are labeled with the monoclonal antibody reagent. The labeled cells are retained in the column when it is in the activated magnetic field of the instrument, the little black box.

The negative unlabeled cells flow through into the negative fraction bag. And when the magnet is disengaged, the CD34 cells are eluted into the cell collection bag. There are 162 instruments at 97 institutions within the US. There are approximately 84 IDE protocols that utilize the CliniMACS CD34 Reagent System. Within Miltenyi Biotec, there are strict procedures to ensure that the investigational products are provided only for protocols with FDA and IRB approval.

The CliniMACS instruments are installed by qualified personnel. IQ and OQ is performed at time of installation. Any subsequent servicing or preventive maintenance are performed by Miltenyi service personnel. A comprehensive training is also provided to the customers by specially trained Miltenyi personnel, and the training is validated with a written test. Additionally, there is emergency hotline support available for anyone that uses the CliniMACS.

The CliniMACS CD34 Reagent System was CE marked in 1997. Shortly thereafter, the US Master File was submitted to support clinical trials in the US. In 2003, Miltenyi Biotec began discussion with the BMT CTN on supporting a multi-center study in AML patients, using the CliniMACS CD34 Reagent System. In May 2004, a pre-IDE meeting was held with FDA to stop the process. The IDE was submitted in September 2004. The study ran from 2004 to 2008, with the first patient enrolled in October of 2005, and the last patient enrolled in December of 2008.

During that time in 2005, the Humanitarian Use designation was granted to the CliniMACS CD34 Reagent System for use in AML patients undergoing match transplant. In December 2009, FDA and Miltenyi had a pre-HDE meeting to discuss the data from the BMT CTN trial, and to make plans for the HDE submission. At that time, FDA recommended that we compare the results of the 0303 study to a contemporary cohort of patients receiving unmatched or unmanipulated transplants. The DAP, or Data Analysis Protocol was negotiated over the next six months with FDA and finalized. It was executed in December of 2010 and the HDE was submitted in April of 2011.

As Ted went over this information pretty thoroughly, I'll skip this slide on humanitarian use devices. The multi-center phase two studies, sponsored by

the BMT CTN and supported by Miltenyi, was designed to evaluate the use of the CliniMACS CD34 Reagent System for selecting CD34 positive cells from HLA-matched related donors for allogeneic stem cell transplantation after myeloablative therapy in patients with AML in complete remission without additional GVHD prophylaxis. Thereby supporting the proposed indication, humanitarian use device authorized for use by US federal law for processing allogeneic HLA-matched hematopoietic progenitor cell apheresis from a related donor to obtain a CD34 positive cell enriched population intended for hematopoietic reconstitution following a myeloablative preparative regimen without the need for additional graft-vs-host disease prophylaxis in patients with acute myeloid leukemia in first or second morphologic complete remission.

I'll now pass the presentation to Dr. Steve Devine, who is one of the co-study chairs for the study, and will discuss the indication on medical needs and present the results from the trial.

DR. DEVINE: Thank you Nancy, and thank you for the opportunity to present these data. I'm Dr. Steve Devine from Ohio State University. I'm the director of the Blood Marrow Transplant Program there, and also had the privilege to serve, along with Dr. Richard O'Reilly from Memorial Sloan-Kettering as the co-study chair for BMT

CTN0303.

My role will be to give a little bit of background first, and then to present the study and the data and results. So as background, acute myeloid leukemia, or AML, is the most common acute leukemia diagnosis in adults. Roughly 12,000 or more cases are diagnosed in the United States annually. And unfortunately, most patients are destined to die from the disease or complications related to its treatment.

For a variety of reasons, less than 2500, or a minority of the patients actually progress to a potentially curative stem cell transplant. That's potentially a problem because based on numerous data in a recent large meta analysis, allogeneic stem cell transplantation is the single most effective therapy currently available for the prevention of relapse, and shows a significant survival benefit in patients with intermediate and poor risk cytogenetics in first complete remission.

So as I said, there are a number of reasons why patients don't make it to transplant, but fear of a devastating complication called graft-vs-host disease is one of the reasons younger patients aren't referred for transplantation. Graft-vs-host disease, or GVHD, complicates allogeneic transplant from matched related donors, as well as other transplant situations, as you

heard yesterday. The reduced instance of leukemic relapse in approved overall survival that can be realized with allogeneic transplantation often doesn't occur due to complications caused by graft-vs-host disease.

In the match related setting, roughly 35 to 45 percent of the patients may be expected to encounter acute graft-vs-host disease. Another later form, and often devastating form, of graft-vs-host disease is chronic graft-vs-host disease. And depending on the data set, between one third to 81 percent of patients will develop chronic graft-vs-host disease, resulting in post-transplant morbidity, mortality and significantly reduced quality of life.

Now, typically, immunosuppressive agents are used to prevent and to treat acute GVHD, but these drugs do not affect the incidence of chronic GVHD under most circumstances. However, previous studies demonstrate that T-cell depletion reduces both the risk of severe acute and chronic graft-vs-host disease and may be a potentially better way to prevent GVHD.

So these are just some slides showing the potential devastating impact of chronic graft-vs-host disease. This is showing relatively severe involvement of the skin, the most commonly involved organ, demonstrating erythema ulcerations, isocratic changes. This patient

actually cannot extend his elbow. You see also the areas of hypo and hyper pigmentation. A commonly involved area is also the oral mucosa, which can lead to erythema ulcerations and erosions, making it very difficult to eat and to be associated with weight loss and decreased quality of life. Other organs, including the eyes, lung, liver, joints and virtually any organ system in the body can be involved by chronic graft-vs-host disease and the results can be devastating.

Now, as I said before, chronic graft-vs-host disease can affect adversely quality of life of the patients who encounter this disorder. And there are numerous studies looking at quality of life. We cite here just a couple of them. In one study by Lee and colleagues, quality of life at six or 12 months after transplant was significantly worse in patients with acute chronic graft-vs-host disease. Now, in most patients, quality of life will improve at 12 months following transplant, unless chronic graft-vs-host disease develops.

In another study, looking at return to work, significantly less patients returned to work if they developed chronic graft-vs-host disease after allogeneic transplantation. And only about 41 percent of patients in this study with chronic GVHD returned to work at three years, compared to 95 percent of patients without chronic

graft-vs-host disease. In terms of treatment, the typical for chronic graft-vs-host disease includes the long-term administration of corticosteroids, which as you know, can have a lot of long-term consequences, including the risk of cataract formation, avascular necrosis, osteoporosis, just to name a few. And for the most severe forms of chronic GVHD, 10-year survival is less than five percent. There are really currently no very good options for the prevention of chronic GVHD and treatment options are certainly suboptimal.

So, in terms of an unmet medical need served by the CliniMACS CD34 Reagent System. As I said before, the incidence in severity of GVHD appears to be most effectively reduced by ex vivo T-cell depletion of the allograft. However, there is currently no improved method for ex vivo T-cell depletion for allogeneic transplantation in the United States. So if approved, the CliniMACS CD34 Reagent System would be the only FDA approved method of CD34 enrichment, and therefore passive T-cell depletion available for our patients.

So when we were considering developing a trial in this setting, we noted that the use of ex vivo T-cell depletion, while effective, has been limited by a number of things, including logistical difficulties and variability in various T-cell depletion methods used from center to

center, the lack of an FDA approved method. And the dogma in the field is that patients who undergo ex vivo T-cell depletion have a higher risk of leukemic relapse or graft rejection. Based on this, we felt that a multi-center trial of T-cell depletion in AML patients in first or second complete remission, using standard eligibility criteria, and the uniform method of T-cell depletion was warranted.

So for the purposes of time, I'm not going to reiterate the title of this study, plus it's almost like taking a test to read the whole title. But the BMT CTN protocol 0303 was a collaborative effort between the CTN, the NHLBI and the NCI. The results of the study have been published this year in the *Biology of Blood and Marrow Transplantation*, and I list here the co investigators on the trial.

Now, before we get started, just to give you a little bit of background on the Blood and Marrow Transplant Clinical Trials Network, the network was established in September of 2001. It was actually recently renewed in July of 2011. It's cooperatively funded by the NHLBI and the NCI. It involves 20 core center cooperative agreements, and one data coordinating set of cooperative agreement, with over 80 affiliate centers who access the trials through the data coordinating center.

So the goal of the program over all is to provide the infrastructure needed to allow for promising hematopoietic cell transplantation therapies to be developed and evaluated in high quality, multi-center studies. This is just showing you the geographic distribution of both the core and the affiliate centers involved in the BMT CTN. This is really a nationwide effort.

So when we were developing the design of the 0303 trial, we were interested in multiple single center studies from Parousia Italy, Sloan-Kettering, Dana-Farber, as well as other groups that showed reduced graft-vs-host disease with T-cell depletion, without increase in relapse rates in AML patients transplanted in remission. We also made note of one randomized prospective multi-center trial that was initiated in 1995 of T-cell depletion versus standard GVHD prophylaxis, which showed no increase of relapse rates in AML patients receiving T-cell depleted allografts.

This is just a figure from that trial that was reported in Lancet in 2005, showing the cumulative instance of relapse in the two lower curves were not significantly different between the MC group, that's methotrexate and cyclosporine standard GVHD pharmacological prophylaxis versus the T-cell depleted group. So the idea is, if done properly and with the right methodology, there may not, in

fact, be an increased risk of relapse with T-cell depletion in AML patients in remission.

So, in terms of statistical sampling and time points of the trial, the sample size estimate was 45 patients, wherein 47 patients were actually enrolled and 44 completed treatment. There were no blinding or randomization aspects to the trial. The immediate follow-up to the patients was 34 months, with a range from 11.5 to 51.5 months. Study eligibility is as follows. All patients had to be in a bona fide first or second complete remission, between the ages of 18 to 65 inclusive. They could take no more than two induction cycles of chemotherapy to induce remission. Again, the trial involved only recipients of HLA-identical sibling stem cells, no unrelated donors or other donor sources.

No more than six months could elapse from the achievement of CR to transplant, although this number was three months for the second remission patients. Other standard organ function criteria were used. Patients could not have any active or uncontrolled infection, and they had to have a reasonable Karnofsky performance status.

The primary endpoint of the study was disease-free survival at six months with a target greater than 75 percent. A number of secondary endpoints, which are standard following transplant, are listed here. This

included also an evaluation of the proportion of grafts containing more than five times ten to the sixth CD34 positive cells per kilogram, and less than one times ten to the fifth CD3 cells per kilogram. This was truly a multi-center trial and up to eight centers enrolled, at least one patient on this clinical trial. As I said before, 44 patients were available on the study.

Patient characteristics were as follows. The mean age was 46.3, median was 48.5. The donors were of similar age. There were more females compared to males entered on the trial. The majority of patients were in first remission. There were only seven patients in second complete remission. The first remission patients could not have favorable cytogenetics. They had to have either intermediate or unfavorable cytogenetics, whereas cytogenetic group was included in the second remission patients.

All patients received the same conditioning regimen. This condition regimen included hyperfractionated total body radiation given over four days from days minus nine to minus six, two doses of Thiotepa. And at the time in 2003 that we were designing the trial, we had felt that the incorporation of ATG would be important to promote hematopoietic graft in this setting. So a single dose of ATG was given on day minus four. Two doses

of cyclophosphamide were given, and then on day zero, the CD34-enriched allografts were transplanted.

In terms of how the donors were treated, all donors received daily G-CSF for mobilization following screening and enrollment. Leukapheresis was performed according to institutional standards. And daily leukapheresis with subsequent CD34 cell selection using the CliniMACS CD34 Reagent System continued until the post-selection target dose of more than five times ten to the sixth CD34 positive cells per kilogram with less than one times ten to the fifth CD3 cells per kilogram was met. And at this point, I will actually turn the podium over to Dr. Carolyn Keever-Taylor to discuss the results of the graft process.

DR. KEEVER-TAYLOR: Thank you, Steve. I am Dr. Carolyn Keever-Taylor. I'm director of the BMT Laboratories at the Medical College of Wisconsin. And I served as the laboratory representative to the BMT CTN 0303 study steering committee. So I'm going to describe the characteristics of the grafts, the products that were produced from the Miltenyi device. These data have been recently accepted for publication in the Journal of Biology of Blood and Marrow Transplantation, and are currently available online at the journal site.

So as Steve said, a secondary endpoint of the

study was to evaluate the performance of the CliniMACS CD34 Reagent System. There were leukapheresis collections for the mobilized peripheral blood products used as the graft source obtained from matched related donors. The collections were performed in order to obtain minimally those of two times ten to the sixth CD34 positive cells per kg. However, we targeted a higher dose, five times ten to the sixth or higher, to ensure rapid platelet and neutrophil. However, in no case could the graft product contain more than ten to the fifth CD3 positive T-cell per kg.

Up to three apheresis collections were allowed to achieve the minimum CD34 dose. And both the standard and the large scale tubing sets could be used for processing, depending on the number of cells that were obtained. The testing requirements for the products were defined. Cell viability was assessed using 7-AAD by photo symmetry method. Total nucleus cells and CD34 positive cell content, all of which were tested on the product at the time it was received, after the initial steps of processing, which included two washes, one to remove platelets and a second after the antibody agent had been added in order to remove the excess antibody, and then, on the CD34 enriched products.

CD3 positive T-cell content was measured at the

start, the product at receipt, as well as on the enriched products. And the enriched products were further assessed for the content of CD14 positive monocytes, B cells using either CD19 or CD20, and CD56 positive natural killer cells. There was a manual of operations for the cell processing associated with this trial, in which we did give more description of how these analyses were to be performed, including gating strategies and the fact that only viable cells should be assessed and reported.

So there were 47 patients enrolled, 44 of these did proceed to transplant. So, 86 products in total were collected for these 44 patients. In two cases, two products of low cellularity were pooled for processing on a single tubing set. So therefore, there were a total of 84 lots off the CliniMACS device that could be assessed. Four sites processed from 9 to 34 lots, while the four sites processed fewer than four lots.

So this slide summarizes the overall outcome of the 84 products that were assessed. The CD34 recovery averaged 66 percent, with a range from 30 to 125 percent. The products were purity of the CD34 content was 93 percent on average, ranging from 61 to 99.8 percent. Log depletion was vigorous with an average of 4.78, log depletion ranging from three to six logs. Viability was quite high. The cells coming off the column, on average 96.6 percent,

ranging from 74 to 100 percent.

So we also assess the variation between the centers, in their processing outcomes. For this analysis, we consider the four sites that produce greater than nine lots individually. For statistical power, we pulled the results from the four sites producing fewer than four lots. The EMMES corporation statisticians performed multi-variant analysis of the outcome data using a linear mixed effect model to account for the repeated measures since most donors were collected at least twice. Pair wise center comparisons were performed using a Tukey-Kramer adjustment for multiple comparisons.

So this slide shows the products at the beginning, before they were processed, and just to determine whether or not the starting product was uniform between centers. The bars that you see indicate where there were significant differences between individual centers. Of note, there was fairly highly reproducibility and consistency in the starting products, with some exceptions. Center two, for example, had higher cellular content for both total nucleic cells, as well as CD34 positive cells and CD3 positive cells. This may have been due to a variation in how the donors are mobilized. These initial donors who were actually mobilized with a higher dose of GCSF than we subsequently used. And as you note

with the half shaded symbols, two of those higher products had to be split to be selected, processed on two different tubing sets, because of the high numbers of cells.

For the starting liability, there was also a difference, mostly related to center four, which had slightly lower viabilities. However, again, here there was a difference likely ascribed to the flow techniques that they use, which did not include washes. Washes are known to eliminate some of the dead cells. So this was just a technical difference.

So post processing, again, I think we saw pretty consistent results among the centers. There was some difference in CD34 cell recovery, particularly involving center one, which had higher recovery. But there were at least four products in this center that actually exceeded 100 percent. So again, this implies that there may have been some technical issues regarding the CD34 assessment, likely involving the starting product.

The purity again had a fairly high consistency. Center one had a uniformly high purity in their product, which made them differ from the combined centers, five through eight. Log T-cell depletion was different only between center three and four, and again, the viability showed some differences with one center in particular, center three, having a uniformly high viability.

So I think the point that really needs to be made, despite the fact that you don't get absolutely the same product. These are biological products. However, every graft which consisted of more than one collection in most cases, contained the targeted dose of CD34 positive cells. So at the lower limit, every patient achieves minimally two times ten to the sixth. And 84 percent of the patients achieve their optimal goal of greater than five times ten to the sixth CD34 per kg.

And these products which were quite enriched with CD34 were uniformly depleted of CD3 cells. The upper limit of ten to the fifth was not exceeded, it was only barely approached by one product. And as you can see, the median doses among the centers were at least a log lower than our maximum allowed. So this shows the actual numbers of cells that comprise the grafts that were given to the patients. The median CD34 dose was nearly eight times ten to the sixth per kg, ranging from two to 30. The median CD3 dose was only .7 times ten to the fourth per kg, with an excellent log T-cell depletion.

The products were all assessed for sterility, using gram stains as an immediate measure and 14 day sterility cultures. All products were negative. And the toxin was assessed and endotoxin was uniformly below the level of detection and below 5 EU per kg. And there were

no significant infusion related toxicities that were observed.

So in conclusion, all products processed with the CliniMACS CD34 Reagent System met and most succeeded the study goals for CD34 cell content. And 84 percent exceeded the ideal infusion dose, and no product exceeded the CD3 dose. The performance of the CliniMACS CD34 Reagent System was stable and reproducible throughout the course of the study. It resulted in a consistently high degree of CD34 positive cell enrichment, a rigorous depletion of T-cell and produced products that were uniformly sterile in this multi-center setting. And so, now I'll turn the podium back over to Dr. Devine.

DR. DEVINE: So now I would like to present the results from the study, other results. The primary endpoint of the study was six month disease-free survival with a target greater than 75 percent, and this was met being 81.8 percent at six months. As we said before, there were a number of other important secondary endpoints. Obviously, we're very interested in neutrophil and platelet engraftment. Engraftment was prompt. Neutrophil recovery as defined as more than 500 neutrophils per micro liter. The median time was 12 days. Recovery of platelets to greater than 20,000 per micro liter was 16 days.

Importantly, in a trial of T-cell depletion, you

should note that there were no primary graft failures. There was one secondary graft failure at day plus 54, after this patient initially engrafted on day plus 12. The cumulative incidence of transplant-related mortality at one year was 13.6 percent for the whole group, and did not differ by remission status. The stopping guideline of less than 30 percent treatment-related mortality at one year was not exceeded. Treatment-related mortality at two years was 19.9 percent.

The cumulative incidence of Epstein-Barr virus reactivation for all patients on the trial was 18.2 percent, again did not differ by remission status. Eight patients were treated for EBV DNA levels with Rituximab at greater than 1000 copies per ml. There was one patient unfortunately who did develop post-transplant lymphoproliferative disorder and subsequently died from this. Now, the high incidence of EBV reactivation may have in part been due to the rigorous monitoring for EBV that was incorporated. We used stringent weekly monitoring of EBV DNA by PCR on this trial.

The cumulative rate of relapse for the entire group of patients was 20.6 percent at one year and 23.7 at two years. The risk of relapse for the first remission patients was only 17.4 percent at two years in first remission and 57.1 percent at two years. Again, make note

of the low numbers of patients in CR2. The cumulative incidence of acute GVHD grades two to four for the entire cohort was 22.7 percent at 100 days, and was again not different by remission group. There was no grade four GVHD observed on the trial. Published acute GVHD risks in this patient population are typically between 35 to 45 percent. The cumulative incidence of acute GVHD in grades three to four was low, at 4.5 percent at 100 days. And again, no grade four acute GVHD was observed. These were all grade three acute GVHD cases.

Another important secondary endpoint was the incidence of chronic graft-vs-host disease. The cumulative incidence of both limited and extensive chronic graft-vs-host disease at two years was low, being 19 percent, and did not differ again by remission types. Published risks of chronic graft-vs-host disease with the use of peripheral blood typically ranged from 33 to up to as high as 81 percent. The cumulative incidence of the most severe form of GVHD, that is extensive chronic GVHD at two years, was 6.8 percent.

Disease-free survival at two years was another secondary endpoint, and was 56.4 percent for the entire group. Sixty-one point nine percent for the first remission group, and 28.6 percent for the second remission group. Historical data estimates for two year disease-free

survival were typically under 60 percent in first remission.

Overall survival for the entire group at two years was 59.4 percent. Adverse events were tabulated. Toxicities were reported as adverse events. There were no unexpected grade three to five adverse events reported in the trial. AEs were due typically to regimen-related events and toxicities common to allogeneic hematopoietic cell transplantation, and importantly could not be contributed to the CliniMACS CD34 Reagent System. There were no significant fusion-related toxicities.

The most toxicities occurring within one year post-transplant were regimen-related grade three and four GI toxicity, manifested mainly as mucositis stomatitis, so abnormal liver function abnormalities in a little over a third of the patients. Grading was according to NCI's CTCAE version 3.0.

This table lists the causes of death at two years following transplantation. Not surprising for an acute leukemia trial, recurrent disease was the most common cause of death. Four patients did succumb to infection, two to idiopathic pneumonia, two from organ failure, one from other cause, we believe possible cardiac-related, and as I mentioned before, one patient from post-transplant lymphoproliferative disorder.

So in conclusion, hematopoietic cell transplantation, following a myeloablative preparative regimen, for patients with AML in first or second complete remission can be performed in a multi-center setting using the CliniMACS CD34 Reagent System without additional post-transplant pharmacologic prophylaxis. All primary and most the secondary endpoints were met, demonstrating an 81.8 percent disease-free survival at six months following transplantation. No primary graft failure and consistent neutrophil and platelet engraftment.

Rates of acute GVHD grades two to three were less than 23 percent, and no grade four acute GVHD was observed, despite the absence of any pharmacologic GVHD prophylaxis. Chronic GVHD incidence overall was lower at 19 percent, extensive being less than seven percent. Treatment-related mortality was under 20 percent at two years, and for the entire cohort, the overall risk of relapse was low at 23.7 percent at two years.

The CliniMACS CD34 Reagent System consistently produced a graft containing more than two times ten to the sixth CD34 positive cells per kilogram, with less than one times ten to the fifth CD3 positive cells per kilogram, with no reported device-related toxicities. At this point, I'll turn the podium over to Dr. Pasquini, to talk about the 0101 versus 0303 analysis.

DR. PASQUINI: Thank you, Steve. My name is Marcelo Pasquini. I'm assistant professor at the medical college of Wisconsin and assistant scientific director for the Center for International Blood and Marrow Transplant Research, CIBMTR. I was privileged to work along with Dr. Robert Swiffer as co-investigator for the comparison analysis between BMT CTN 0303 and the comparison of control group of patients enrolled in BMT CTN 0101.

Here are the titles of both studies we used for this retrospective analysis to BMT CTN 0303. It was presented by Dr. Devine, which was used to select the cohort of CD34 selected patients. And the control group, which were patients enrolled in a contemporary study to phase three, to test two forms of antifungal prophylaxis, fluconazole and voriconazole. Both studies were sponsored and conducted by BMT CTN and the data collection was similar for both studies.

The analysis presented here was requested and approved by the FDA, and it was submitted for publication and is currently under review. Here, the enrollment period of both trials are shown. First, in yellow, is the BMT CTN 0101, enrolled patients from 2003 to 2006. And BMT CTN 0303 was enrolled from 2005 to 2008. Eighteen centers participated in 0101 and eight in 0303, and three centers co-enrolled to both clinical trials.

The objective of this analysis was to test a hypothesis that sibling donor hematopoietic cell transplantation using CD34 selected as the sole form of immunosuppression demonstrated comparable in a safety profile compared to transplants with conventional GVHD prophylaxis for patients with acute myeloid leukemia in first and second complete remission. The endpoint analyzed in this analysis, include disease-free and overall survival, engraftment, graft failure, transplant-related mortality, relapse, and acute and chronic GVHD or graft-vs-host disease. The patients enrolled in the BMT CTN 0101 were followed up for one year total. We extended an independent from this analysis for the publication to follow up, using the CR2 database.

The eligibility criteria from the 0303 was applied to patients enrolled in the BMT CTN 0101, and this includes the age of 18 to 65. All patients in the BMT CTN 0101 selected for this as a control received unmodified peripheral blood stem cell allografts. They received grafts from HLA identical sibling donors. They were also in AML in first and second complete remission, and there was no restriction in the cryptogenic risk categories.

Here demonstrates the selection of the patients, among 600 patients enrolled in the BMT CTN 0101. After application of eligibility criteria, which also include a

patient's window width myeloablative conditioning. All patients in the 0101 received myeloablative conditioning. A total of 84 patients, 65 in first complete remission, 19 in second complete remission, were selected for this comparison analysis. And the BMT CTN 0303, only patients who received the CD34 selected grafts were included for this analysis, which include 44 patients, 37 in first complete remission and seven in second complete remission.

The baseline characteristics are as follows. As Dr. Devine presented earlier, there are more females, 63.6 percent in the cohort of CD34 selected patients. And the median age was 45 and 48 was no difference. And according to the FDA specified age cut off of 50 years old, there was no difference in patients older than 50 years, with 32 percent in the control and 43.2 percent in patients in the CD34 selected cohort. Regarding the Karnofsky performance status, most patients in both cohorts had scores greater than 90.

Regarding the AML cytogenetic risk profile, it was similar in both groups. The increased number in patients were patients of unfavorable cytogenetics in the CD34 selected group did not meet statistical significance. Regarding the conditioning regiment, again, all patients received myeloablative conditioning intensity regimens, as presented by Dr. Devine. All patients received a total

body radiation base conditioning regimen in the CD34 selected cohort, comparing the control group of 51 percent of patients received. The remainder received busulfan-based condition regimen, which was done according to institutional guidance.

ATG was also used in some of the centers, according to institutional preference, in total of eight percent of patients enrolled in the control group. All patients in the control group receive a calcinuric(?) inhibitor based GVHD prophylaxis that continues post-transplant. And none of the patients in the CD34 selected group received any ongoing immune suppression.

Here are the outcomes. The first outcome is the cumulative instance of neutrophil engraftment at day 30, which was defined of achievement of total of 500 cells per micro liter. The neutrophil engraftment demonstrated 100 percent at day 30 for the CD34 selected group, compared to 96.4 percent in the control group. Of note, there were three primary graft failures identifying the control group and none in the CD34 selected group. And each cohort had one patient who developed secondary graft failure.

Platelet engraftment defined as greater than 20,000 cells per micro liter. It was similar in both groups. Transplant-related mortality of both cohorts demonstrated a 16.7 percent in the control group, compared

to 13.6 percent in the CD34 selected group. Corresponding instances by disease status, CR1 and CR2. There were no differences in the four distinct groups.

Leukemia relapse at 12 months demonstrated no difference with 20 percent risk of 12 month leukemia relapse in both cohorts. As corresponding instances of leukemia relapse separated by disease status demonstrated overall patients in first complete remission had lower rates of leukemia relapse than patients in second complete remission. Among patients with first complete remission, CD34 selected cohort experience a 13.7 percent risk of leukemia relapse at 12 months, compared to 17 percent in the patients in the control. Among patients in the CR2, four out of seven in the CD34 selected group, and six out of 19 in the control group experienced leukemia relapse at 12 months.

Disease-free survival was also similar in both groups at 12 months with a 63 percent in the controls and 65.7 percent in the CD34 selected cohort. Corresponding probabilities separated by disease status, CR1 and CR2 demonstrated that there was no difference according to disease status as a time of transplant of probability of disease-free survival at 12 months. Now, the stratification requestion in the FDA data analysis plan of patients younger and older than 50 demonstrated that there

was no difference in cohorts, even though there was in patients in the control group and older than 50 years, disease-free survival 51.9 percent. However, this difference did not reach statistical significance.

Regarding overall survival now, overall survival did not differ from patients in the C34. So the group was 77.3 percent at 12 months, compared to 73.8 percent in the controls. And in separating this by disease status, a time of transplants, CR1 versus CR2, patients with second complete remission had no decrease in overall survival at 12 months.

Now, acute GVHD, grades two to four, the instance at 100 days demonstrated in the CD34 selected group was 22.7 percent compared to 39.3 percent in the control. The probabilities in the control are similar to other historical instances of grade two to four graft-vs-host disease. Again, stratification by age demonstrated by age that there was a difference which show that patients younger than 50 years old in the control group had a higher incidence of grade two to four, compared to the other cohorts.

Now, grades three to four graft-vs-host disease in the CD34 selected group was 4.5 percent, compared to 9.5 percent in the control group. And now, chronic GVHD showed a significant difference between the two cohorts. Patients

enrolled in a CD34 selected cohort experienced a 15.9 percent risk of 12 month chronic GVHD, compared to 49.9 percent in the control groups. Again, the historical published instance of chronic GVHD is within this range of 50 percent that was seen in other studies in the past. The FDA requested for a calculation of post hoc power, to try to confirm this difference based on the sample size available, and this power was calculated as 98 percent.

Regarding infections, there were a similar overall infection complication in both cohorts. In the majority of patients experienced between one to three infection complications. Regarding the microorganism, it is important to note that the monitoring for infectious complications was different in both trials. There was an active monitor of Epstein-Barr infections, explained by Dr. Devine in the CD34 selected cohort of patients. And there was no protocol specified EBV monitoring in the BMT CTN 0101.

Conversely, since the BMT CTN 0101 had a primary focus on fungal infections, there was active monitoring of fungal infections and BMT CTN 0101 as it as the primary endpoints of that the phase three trial, which demonstrated there were only confirmed cases of fungal infection. There were an additional 13 possible presumed infections in the outpatients in the 0101.

Regarding viral among these 24 cases here, eight are related to either EBV reactivation or infection, and one patient developed post transplant lymphoproliferative disorder as consequence to this. Regarding the severity of the disease, there was no difference between moderate and severe category of infections between the two cohorts.

However, there was in the category of life-threatening slash fatal disease. There was an increase in patients that received CD34 selected. However, there was no difference in infectious deaths between the two cohorts. Here are the overall lists of causes of death, and the main cause of death in both cohorts was acute leukemia, followed by organ failure and infections.

In conclusion, in the instance of chronic GVHD at one year post-transplant was significantly lower in recipients of CD34 selected grafts. And without any difference in platelet, neutrophil engraftment, acute graft-vs-host disease, disease-free survival, overall survival, TRM and leukemia relapse. Stratification based on disease status was a limit because the numbers of patients in CR2 was small, which really makes our conclusions inconclusive or needs to be taken into consideration the small sample size.

The data analysis plan conclusion is that the results support a comparable safety profile for CD34

enriched transplants, as compared to patients receiving unmanipulated grafts and conventional GVHD prophylaxis, with significant reduction of chronic GVHD. I'd like to pass the podium to Dr. Pinkernell for conclusion remarks. Thank you.

DR. PINKERNELL: Thank you. My name is Kai Pinkernell. I'm the head of clinical development at Miltenyi Biotec GmbH in Germany. And I would like to conclude our presentation by summarizing safety and probable benefit for the CliniMACS CD34 Reagent System.

So we hope that we could show you that for the performance and safety of the CliniMACS CD34 Reagent System is given, and to point this out again. The CliniMACS CD34 Reagent System consistently produced a graft with equal or more than two million CD34 positive cells per kilogram, and no graft contains more than the allowed dose of 100,000 CD3 positive cells per kilo. Eighty-four percent of the grafts actually contain the target dose of equal or more than five million cells of CD34 positive per kilo.

Importantly, there was no significantly difference between CD34 enriched and unmanipulated allografts if we look at platelet and neutrophil engraftment, acute GVHD, DFS and overall survival for the overall populations, transplant-related mortality, and relapse for the overall population. While in the 0303 CD34

enriched patient population, there were more infectious episodes seen if you look at the absolute numbers of 112 episodes of 44 patients versus 162 in 84 patients in 101. These did not importantly translate into higher infectious death rates compared between the studies. The overall death rates were 18.2 percent versus 20 percent in the CD34 enriched study.

And one thing to point out why there might be a difference in these episodes is that the 0303 protocol prospectively defined the weekly surveillance as pointed out early of EBV in the patient population, so that's eventually there could be an over estimate of some of these infection episodes based on this. So really pointing out that there might be more stringent protocol specified monitoring of EBV compared between the two studies, whereas the 0101 study where fungal infections was the primary endpoint.

The probable benefit conclusions for the CD34 reagent systems are that the system yields a consistent CD34 enriched passively T-cell depleted graft that is sterile, and which can be carried out in a multi-center setting. There were low rates of both acute and chronic GVHD without the associated risk normally seen with traditionally pharmacological GVHD prophylaxis, while maintaining consistent engraftment and an excellent DFS,

that means disease-free survival and overall survival with low transplant-related mortality and a low incidence of relapse in the overall population. There was a significantly reduced incidence of chronic GVHD without compromising survival.

So overall, we would like to conclude with the safety and probable benefit objectives, and we think that they have been met in that the CliniMACS CD34 Reagent System is safe and has a probable benefit in significantly reducing the incidence of chronic GVHD, while eliminating the need for pharmacologic GVHD prophylaxis in acute myelogenous leukemia patients in complete remission undergoing a peripheral blood stem cell graft from a matched related donor. And last but not least, we would like to acknowledge all the parties that have been involved in conducting the trial in carrying out the analysis. First of all, the BMT CTN network, the NHLBI and NCI, CIBMTR and EMMES and NMDP and all the investigators and contributors which are listed here. And of course, the patients and their families who make these studies possible. Thank you very much.

Agenda item: Q & A

DR. SNYDER: Thank you. So now we are open for questions. Again, please state your name, speak into the microphone and just indicate to Gail or myself and we'll

take the questions in the order in which we see them.

DR. D'AGOSTINO: I am interested in just a couple of comments, and I thought the presentations were quite spectacular in general. A couple of comments in terms of the selection where you were matching. You had a very large study with the 0101 and it boiled down to such a small number of subjects for the matching or for the comparison of analysis. Was there some discounting of individuals, did you take all of the ones in slide 71, where you had the criteria for cutting down? It seemed like it was such a small number that you retained in the 101. Am I missing something on that?

DR. PASQUINI: So the BMT CTN 0101 was a fungal prophylaxis that basically included all comers in a transplant center. So that was intentionally done for a capture, related, unrelated different all diseases that come into the transplant center. So when we selected the population, we wanted to have the most comparable population as possible for this. So the restrictions of the disease being on remission, just the first and second CR, it was one of the requirements as well. And some patients received bone marrow, and in the 0101 we mainly restricted to peripheral blood. So basically we tried to, on the major detriments of the trial, determine the population that would best match with that.

DR. D'AGOSTINO: From that 599, though, only 84 made it?

DR. PASQUINI: Right.

DR. D'AGOSTINO: There was none that you pushed aside, saying they could have made it, but we didn't?

DR. PASQUINI: No.

DR. D'AGOSTINO: And the other question, which I would have thought was routine in terms of analysis, I think the analysis you did was quite good, would have been to look at some subsets, especially the male and the female. And I'm not familiar why there should be a female effect. I remember once being involved with births as opposed to cancers, and the females were so much stronger than the males and what have you. And the imbalance in gender here, did you do some subset analysis comparing just the females and comparing just the males?

DR. PASQUINI: No, we didn't look that specifically. The prespecified subset analysis was basically on disease status and on the age of older and younger than 50.

DR. D'AGOSTINO: Would there be any reason to think that there's a gender effect, in terms of responding?

DR. PASQUINI: Well, the gender effect studies, there is basically a relationship between the donor and recipient gender match, and that was not looked. Meaning

that female donor to a male recipient will have increased risk of graft-vs-host disease or graft failure, vice versa.

DR. D'AGOSTINO: I'm talking about the imbalance to groups, the 101 and the 303, there are more females in the 303 than in the 101. Did you not worry about that?

DR. PASQUINI: No, I'm not worried specifically about this.

DR. D'AGOSTINO: It's usually routine to do an analysis on the males alone and the females alone.

DR. O'REILLY: I am Rich O'Reilly. There was not a specific analysis done vis-a-vis the gender analysis. The one thing to note, however, would be that the transplants in the 0303 with the predominance of females would actually address one of the major concerns that has been raised with regard to T-cell depletion, and that was the risk of graft failure, because it is quite well known that among adults receiving transplants, if you gave it a transplant into a female, these individuals are usually sensitized to alloantigen. And as a consequence of that, their risk for graft failure in unmodified or TDP grafts is increased. So from the standpoint of one of the primary objectives here, namely do we see consistent engraftment, the 0303 would be, in fact, biased towards the group, which would be more at risk for it.

DR. D'AGOSTINO: If there was a bias, it would've

been against you against as opposed to for you.

DR. O'REILLY: And with females, we would also expect less in the way of GVH because they also do not express why.

DR. BISHOP: I have three questions. The first two, I'd like to address to Dr. Taylor. One is that in that minority of individuals who did not reach the target dose of four times ten to the sixth, was this primarily due to low CD34 starting dose or poor efficiency in recovery or a combination of the two?

DR. KEEFER-TAYLOR: I have a nice graph, I think, that will show you exactly what the doses were, and for the different collections, and I think it will hopefully answer your question. So this graph shows the centers one through three, I have a second for the rest of them. And the color coding here is the aphaeresis, for each individual aphaeresis collection. And the red line there is the five times ten to the sixth, which was our optimal dose of CD34 positive cells. And the red is the second collection and the green is the third.

So for the centers one through three, we only really had a single patient here who didn't reach the optimal dose, and there were two collections performed for that center. A second patient, who was a little bit lower, they did do the third collection, they just didn't do a

third collection for this patient. If they had, it would've probably reached a dose. So clearly, some donors revise better than others. I don't know if anyone knows exactly why that is, but I think that certainly for this center, we could have added one more that reached the target.

And so this is centers four through eight, and again, you can see that the few patients who aren't reaching the dose, here our third collection probably would have done it. In this patient, there were three collections, so the patient just didn't mobilize, or the donor, I'm sorry, just didn't mobilize very well. And again, I think in all the other cases, so we encourage two collections, we allowed three collections if you didn't reach the minimum dose. But certainly, if there had been three collections, I think everyone, except this one donor, would have provided the dose that we were targeting. Does that answer your question?

DR. BISHOP: I mean again, I can't tell, one or two collections, it doesn't tell me what the total starting dose. Again, I can imply that, based upon those two centers, it looks like the collection would have started with a higher starting dose. So was there a minimum criteria that you set? Did you assume a 50 percent efficiency, and therefore asked people to collect at a

minimum of four million CD34 cells per kilogram before processing them?

DR. KEEFER-TAYLOR: No, that wasn't absolutely specified. We do, in general, at least at our center, we considered an estimated at 50 percent recovery, and so we had that. And so based on the first product, we used that to decide whether or not to do a second product even before we had done the selection.

DR. BISHOP: Just kind of getting to my question, as we look for this device, it doesn't appear to be as much as a function of the device, as maybe a poor collection, maybe poor mobilizers, or maybe even the way that, based on volume, based on site or kind that they're collecting. So if you're able to tell me that, well, at all these centers, unfortunately they only gave us three million cells, and even though we had a 60 percent efficiency, therefore that's why they got below four million. That I understand. But then again, if there's variation, if there's just poor recovery, that's another issue. So I can infer from this, but I can't take away any absolutely number.

DR. KEEFER-TAYLOR: So I guess the other assessment, we did look at factors that affected the CD34 recovery, and that would be slide seven for the cell processing data. So here we looked at two factors that we thought might affect the recovery, relative to the device,

and that was the total number of TNC that were loaded onto the device, and the total number of CD34 positive cells that were loaded onto the device. And then, for log T depletion, we also considered TNC and CD3.

So in this assessment, the total number of cells, just nucleated cells, showed no significant correlation with recovery. But we did see a correlation with the number of CD34 loaded. So actually for products that had a higher percent, or actually in this case, it's a higher starting number of CD34 positive cells, we actually had poor recovery.

DR. BISHOP: Well, that actually leads to actually my second question, because that wasn't actually provided in our background materials. And was there a recommendation that only what is the maximum numbers to be loaded into the column?

DR. KEEFER-TAYLOR: So some of these products here at the far end did exceed was recommended, to load onto the tubing set. For the large scale tubing set, it's about one percent of the TNC is the upper limit, with the upper limit of the columns. If the column is one times ten to the ten cells, then it's one times ten to the ninth.

DR. BISHOP: So it's not an absolute number, because you could have a small volume.

DR. KEEFER-TAYLOR: For the tubing set, so

there's the amount of antibody you use, as well as the capacity of the columns. So for the large scale column, you use two vials of antibody to ensure that you get the adequate labeling of the cells. And for the small scale column with the six times ten to the tenth upper limit, you use one bottle. Here's the numbers, so for the standard set, it's .6, so it's 60 times ten to the ninth total cells. And it's .6 times ten to the ninth CD34 positive cells in the same likewise the large. So some of those products, even though the instructions to the centers were to follow the directions in the manual, which these are the directions for the reagent and the manual, some did not. And so, those did have poor recovery.

But even if you excluded those that exceeded the dose at the higher end of the recommended dose, the recovery was somewhat less. But it wasn't night and day. It wasn't that you didn't get a good dose. You're putting more on, you're going to get more back in absolute numbers. So I think that the upper limit that they set is not unreasonable. But the advice would be clearly that you should not exceed that upper limit of CD34.

DR. BISHOP: One final question, and this can go either to Dr. Devine or Dr. O'Reilly. In our background materials, they also provided us immune reconstitution data. And it was stating that chimerism at one year was

100 percent donor chimerism was 43.5 percent. And so, one, what is the cutoff? I assume this is whole blood and not T-cell or myeloid chimerism, and what is the cutoff for defining full, 100 percent chimerism? And I don't know if that's within a five percent discrepancy based upon testing. And then finally, does one assume that you have reached tolerance, or is that an expected finding with a T-cell depletion?

DR. DEVINE: So we have a slide on the chimerism, so maybe you can pull that up. We analyzed chimerism a couple of different ways. We actually just looked at whole marrow samples, and then also did split chimerism on the peripheral blood, as well. Chimerism was the typical definition, which is 95 percent or more donor cell to define full chimerisms. Most of the analyses have a sensitivity of about one to five percent, so 95 percent or greater would be considered full chimerism.

So as you can see, we looked at this at the various time points. And within the marrow, again, the marrow samples were not fractionated, so these were greater than 50 percent donor at all time points measured, and roughly have the patients were 100 percent donor at one year. And in the blood, 43.5 percent were 100 percent donor, particularly in the T-cell. So we found that there were many patients who were mixed chimeras T-cell

department, and yet remained in remission. And so, there didn't seem to be any strong correlation between the degree of T-cell chimerism and freedom from relapse, or any other clinical event in this setting.

I don't know, Dr. O'Reilly has more experience than I do in general in T-cell depleted transplants, and I think he may be able to speak to the issue of chimerism, because in some transplant settings, we think that it may be a predictor of relapse, but it hasn't been in this particular trial. I don't know, Richard, if you wanted to speak to that.

DR. O'REILLY: We introduced the idea of T-cell depletion back in 1980 with the interleukin separated system, which we used initially for children with immune deficiencies. But we have used T-cell depletion from the same point of leukemics since 1981. And as you know, there have been a wide variety of T-cell depletion systems looked at.

I can say that in our initial series that was published by S.E. Papadopoulos, there are significant proportion of those patients who remained mixed kind marrows. These are mixed kind marrows now out through almost 30 years. These patients are, in fact, in doable remission. We have not had a relapse in our AML group after the period of 20 months post-transplant, so these

patients are stable, mixed kind marrows. Usually the mixing in terms of the chimerism is in the T-cell subset rather than the hematopoietic system, which is almost uniformly exclusively known. Does that answer the question?

DR. BISHOP: And was that the case in this situation? I could understand the T-cell chimerism, but the myeloid chimerism, as well?

DR. O'REILLY: Yes, I believe that's the case.

DR. DEVINE: Just to address Dr. Bishop's question. In virtually all circumstances, the mixed chimerism was in the T-cell compartment of the peripheral blood, rather than a myeloid compartment.

DR. HWU: You have an upper limit of CD3 cells at 100,000 per kilogram, and that's to avoid a graft-vs-host disease. And it does look like those rates were lower than expected. But there was a slight increase in the life-threatening infections, and one case of lymphoproliferative disease. And I'm wondering if there might be a lower limit of CD3s as well, that you don't want to go below. In the four patients that, in 303, had the life-threatening infections, as well as the patient with the post-transplant lymphoproliferative disease, what were the post processing counts? Were those patients that had a very low level of CD3s that were in the product?

DR. DEVINE: I'll address both questions. So the first question about what is the lower limit that we should not go below, it's a great question, so I don't have the answer for that. I think it's a great question. In terms of the patients with life-threatening, let's remember first that most of the so-called life-threatening infections were the EBV reaction, so those patients had to get Rituxan. That's considered a life-threatening indication, even if the copy number goes down after the Rituxan.

We don't really have the data on the individual patients to know if they were the ones who got super low T-cell doses, so it's a hypothesis. But there was such variability, and again, all of the patients got very low T-cell doses. And we're talking about seven times ten to the third T-cell per kilogram. So we don't have data with any more granularity. I don't think there would really be a lot of precision to that type of analysis anyway, but it's a great question.

DR. HWU: In a product, do you keep what flows through, in the event a patient in the event a patient does get lymphoproliferative disease, that you could give some donor T-cells back to try to combat that?

DR. DEVINE: Some centers do that. That was not a requirement on this trial.

DR. O'REILLY: With regard to that, the critical

variable here is, as Steve said, if you had reactivation of EBV, these patients did get Rituxan, in so far as they got a therapy intravenously, that is de facto in that category. So that was considered to be a life-threatening infection. We, in doing this trial, have been concerned with regard to all of the systems that have involved T-cell depletion existing to date, that there would be an increased risk of EBV.

I have a slide, I think it's number four. The actual incidence of EBV, however, needs to be also looked at because reactivation of EBV is usually not in any way looked at by individuals getting conventional marrow transplants, because the incidence of EBV lymphoma is usually about one percent. And this basically shows you a review here. This is the R series here, 44 patients. There's an 18 percent incidence of reactivation. But remember, each of these patients were evaluated, both at their local spot and also in a study done in Seattle prospectively to determine the incidence of EBV reactivation.

So this is quite different from the 0101 story, where such monitoring was not in any way required, nor was it done in the vast majority of cases. Any patient who had reactivation would be considered to be a patient with a potentially and lethal infectious complication. I think

most of the differences you're seeing between these two really have to do with the EBV. The incidence of EBV, we had one out of the 18. Most groups with T-cell depletion systems that have been looked at have ranged anywhere from two to six percent. However, if you give Rituximab as a prophylaxis at the time of reactivation, over 90 percent of these patients can be induced into EBV negativity and never develop this complication.

Now, when other groups have actually done prospective analyses to evaluate the incidence of reactivation of EBV -- you can see for example with the campout(?) system, 16 percent of these patients had evidence of EBV reactivation, one percent developed EBV PTLD. In the core blood transplants, where the group in Minnesota looked at this, 23 percent of the patients had activation, six percent developed PTLD. And in a large study that was done in Europe, there were 406 patients prospectively evaluated for EBV reactivation by DNA analysis. Fourteen percent, again, had EBV reactivation, four percent developed PTLD. These patients did not receive immediate treatment with the Rituxan.

So in actuality, whether it's T depleted or conventional, the issue of the incidence of reactivation of EBV can range anywhere from three to, as you can see, up to 14 to 23 percent, depending upon the type of graft. But

these are on modified transplants, administered with classical methotrexate cyclosporine and as you can see, an overall incidence of 14 percent, which I would suggest is not different. Is there a difference in risk of PTLD? The readout that I would have to suggest would be it is, and that's exactly why we did this type of analysis and that's why we would put this in the package insert that's in there, as well. Does that clarify?

DR. GALANIS: I have a question both for Dr. Taylor and Dr. Devine. Looking at the outcome slide, there is variability. In part, it looks to be dependent on the center. I see, for example, great variability in the CD34 percent that's purity for centers five and eight, they were doing pure procedures. And I was wondering, are there any thoughts as to if the number of procedures or the number of patients that the center does might affect the quality and the characteristics of the final product?

DR. KEEVER-TAYLOR: First of all, no, I don't think the quality of the graft, the purity of the graft, has any relationship what so all with the center that's performing. It's actually related to what's in the starting product in some cases. So what we didn't show you, just for interest of time, so just what were the impurities that were in the products. And so I'm showing you the T-cells, P cells and K cells and the monocytes.

And if you look at the medians, you can see they're really down close to nothing. But that's the variability is what is the impurities.

So monocytes tended to be fairly high. And in fact, there was one product, I believe, was like 67 percent purity. That was a product at 22 percent of monocytes, which can nonspecifically adhere to the column. So why that isn't more common, I don't know. But you can see there's quite a few where there's a fair number of monocycles.

P cells likely can be a bit sticky, but these, the axis here is the percent of cells and their product. So the cell number and the product is fairly low, so it's not like you're giving huge numbers. You're giving far fewer of these contaminating, if you want to use that term, subsets than there are the CD34 cells. But this was the major thing that affected the purity.

Occasionally, you can get myeloid cells also, so some grafts I know, for at least one of the products, that had a lower purity that was at my own center, it wasn't any lymphoid cell, it was myeloid cells. And it was one of the donors that had been mobilized with 16 milligrams per kilogram of DCSF and had a really high starting granule content in the product. So does that answer your question?

DR. GALANIS: (Inaudible - off mic) some centers

maybe did not exactly follow the manufacturing or the instructions. So is there a training period? How can someone account and address that, if the device is approved?

DR. KEEFER-TAYLOR: I think I have to defer to the Miltenyi folks for that.

DR. JOHANSEN: It is about training. So prior to running the CliniMACS, we go out. There are specially trained personnel within the clinical group. And they go to the customer's sites and they provide a training, not only on the instrument and how it works, but on the principle of the technology. The training is assessed with a written test to the customer, to make sure they can understand the instructions. It's usually a full day of training, if not more. They run a product through the CliniMACS to make sure they are comfortable with using it. And in addition, we have an emergency hotline that they can call any time during the week, and also they can make arrangements if they have an over the weekend run that they would need assistance with.

DR. BISHOP: That was actually one of my questions. In your briefing materials, you state that they have to take a test. I was just curious if that test is validated in any former matter, in terms of the efficiency of each center.

DR. JOHANSEN: The test wasn't formally validated by Miltenyi. We just went through to make sure that all the key points were captured in the training, and to make sure they completely understand how it's run and what they need to do to get the cell product they desire.

DR. BISHOP: I have one final question, I swear. This goes to either Dr. O'Reilly or Dr. Soiffer or Dr. Devine. The data that you're presenting for potential FDA approval, and again in the proposed indication, and in a myeloablative setting, and as kind of well pointed out in this discussion about EBV as the inclusion of antithymocyte globulin, which I guess to my understanding, is primarily to remove host lymphocytes in order to promote engraftment.

So would the indication necessitate the inclusion of an in vivo T-cell depletion prior to infusion, be it, and again I would assume ATG, but again alemtuzumab in order to make sure this device works the way it's supposed to? I hope I said that right.

DR. SOIFFER: I am going to address your question. We anticipated there might be some question about the use of antithymocyte globulin. So I want to just address a few things, first on the graft-vs-host disease side of things, and then on the engraftment side of things.

So first, as you know, thymoglobulin was used in this trial, and there are a number of published series on

thymoglobulin and allogeneic hematopoietic stem cell transplant. There have been multiple dosing strategies used for thymoglobulin in these trials, and the one that was used here, remember, was 2.5 milligrams per kilogram on day minus four, which is a low dose compared to what's being used elsewhere. As you can see here, the total thymoglobulin doses range from two and a half to 15 in the studies that I'll refer to, usually administered to day minus four and zero.

So in the BMT CTN 0303, as I mentioned, we use one dose of thymoglobulin, two and a half milligrams per kilogram administered on day minus four, just as you suggest for, as Dr. Devine mentioned, engraftment purposes, or promotion of engraftment. That was the thought at the time the study was written.

We can talk about the half life of thymoglobulin. As you can see here, the half life is about 44 hours after one dose of two and a half milligrams per kilogram. It's much longer after repetitive higher dosing regimens, and that's been studied in several manuscripts. And for a dose, you can see here of 1.25 to 1.5 milligrams per kilogram per day for seven to 11 days, the half-life is about 2.3 days. So most of the thymoglobulin in that day minus four is gone by the time the graft is in. Not all of it, but most of it.

So there are a number of publications that have surfaced over the past decade, with the use of the thymoglobulin product in terms of graft-vs-host disease, both after ablative transplants and after reduced intensity transplants. This is an article from Dr. Moti in France, looked at 101 patients who received the transplant in this situation of reduced intensity from HLA identical donors. And in this manuscript, he described several dose levels, the ten milligrams per kilogram and 7.5 milligrams per kilogram that they had been using, and then a reduction to 2.5 milligrams per kilogram what was used here. The dosing in these trials were, in general, over four days, day minus four minus one, and patients received additional cyclosporine as part of graft-vs-host disease prophylaxis.

In this study, in the 2.5 milligrams per kilogram group, the chronic graft-vs-host disease rate was about 70 percent. The acute GVHD rates there are 36 percent. At one year post-transplant, still about 30 percent of the patients were on cyclosporine, and 33 percent of patients required a second line of therapy for immunosuppression. In their study, when they looked at the different doses, actually, I think the 73 percent is all, it's not just the 2.5, I think it's all the doses. In this analysis, they looked at risk factors for acute and chronic graft-vs-host disease. And as you can see, thymoglobulin dose was a

factor in terms of their analysis for acute and chronic graft-vs-host disease.

Dr. Russell in Canada published in BBMT in 2007, articles that you're probably familiar with, in which he looked at the use of thymoglobulin in 54 patients who received match-related donor transplants, and 54 matched pairs from this center who did not receive thymoglobulin. In his center, thymoglobulin was used at a dose of 4.5 milligrams per kilogram, delivered over three days, minus two, minus one and zero. And again, they received additional cyclosporine for GVHD prophylaxis.

And in this trial, you have the table here which looks at the results for ATG, thymoglobulin in this case, and the control, 32 percent versus 19 percent, for grades two to four graft-vs-host disease, grades three to four, thirteen and six percent, for the ATG. And you can see here the chronic graft-vs-host disease, which we really want to emphasize, 55 percent in the patients who got thymoglobulin at 4.5 in his studies, so 55 percent as compared to the 19 percent of someone in our group.

Dr. Bodu Galupo(?), in an unrelated donor population, so a little different than what we're talking about here, as opposed to the last two slides. Published in 2001, thymoglobulin again, looking at 15 milligrams a high dose, seven and a half milligrams, the intermediate or

lower dose in his case, and no ATG. And basically, there was no difference in grades two to four graft-vs-host disease in the two thymoglobulin doses. In the chronic graft-vs-host disease rates, for 7.5 milligrams per kilogram of thymo, it was 38 percent versus 65 percent in the control group, so that's a much higher dose than used here.

Dida Blasé, also from France from Marseilles, published an experimental hematology just this past year, 100 patients undergoing allo transplant. Again, looking at a dose of 2.5 milligrams per kilogram of thymoglobulin on day minus three. And the study results are presented below with 43 percent in grades two to four graft-vs-host disease, and 81 percent chronic graft-vs-host disease at two years.

Now, the question, mostly we've been talking about graft-vs-host disease, but you did make reference to the issue of engraftment, and whether ATG was necessary for engraftment. And the decision to include ATG or thymoglobulin in this study was worked on at Memorial Sloan-Kettering, which Dr. O'Reilly can refer to, in which they did give thymoglobulin, which they thought was necessary to promote engraftment. In our own center, at Dana Farber, when we did murine antibody, we never had used thymoglobulin to promote engraftment, and there was no

issue with engraftment. But from Sloan-Kettering and Dr. O'Reilly's colleagues, and Ann Jacobowsky reported in 2007, another trial of ex vivo T-cell depletion, in which they elected not utilize ATG, and in that study, published in Blood, there was no graft rejection observed in that study.

So this is, just to conclude, a series of summary tables, 0303 compared to the Moti studies, the different doses of thymoglobulin, the Russell study, and we'll just look at the bottom line at the bottom there, with a chronic graft-vs-host disease in the ClinMACS 0303, 19 percent chronic graft-vs-host disease versus 48 for the higher dose of ATG, 73 for the lower dose of thymoglobulin, the one we used here, the Dr. Russell, Canadian publication, 55 percent at 4.5 percent milligrams per kilogram ATG. The Blasé Moti combined study, 81 percent here at 2.5 of milligrams per kilogram. And here the Badu Galupo study, which is an unrelated donor transplants, in which they report there's 38 and 41 percent at the very high doses of ATG.

So in conclusion, we don't feel that the low dose of ATG delivered on day minus four had any impact on the outcome in terms of chronic graft-vs-host disease, given that dose, and as is stated, the Dr. Jack Gobowski paper, 2007, suggests that maybe we don't need that ATG at all for engraftment.

DR. SNYDER: So if the product were to be approved, would you recommend using ATG as part of the protocol, or you would not recommend using it?

DR. O' REILLY: Mike's original question, I think, is the one, why did we include it in the initial protocol. And I can clarify that, because this was based on the protocol we had developed here. When we started to T depleted transplants with leukemia, we and all other centers recognized that either in the context of ex vivo T-cell depletion or even in vivo T-cell depletion, there was a risk of graft rejection. And that graft rejection basis for this, we defined in a series of papers in blood initially in the HLA disparate donor recipient pairing.

Nancy Kernan was able to show that there were residual T-cell after total body radiation in cyclophosphamide that exhibited reactivity directed against a single major alloantigen. And we subsequently had a couple of papers in Blood with Claudio Bordignon and also Nancy Kernan as first authors, which documented again that there were in the HLA matched donor recipient pairing, the persistence of CD8 T-cells of host type, which were capable of reacting against minor alloantigen presented by the donor, which could induce graft rejection.

And then, in the New England Journal of Medicine, we also demonstrated the persistence of T-cells in a donor

recipient pairing, where the only disparity was an allelic alteration in B44, namely B4401 versus B4402. And what we found was the development of T-cells of host type drawn directly from the blood, which exhibited selective cytotoxicity directed against donor type, but not against the host type. So this suggests strongly to us that despite cyclophosphamide and total body radiation, you had residual resistant populations capable of rejecting the transplant which had been depleted of T-cells.

This was depletion with lectin separated marrow grafts. As you well know, there are a lot of these large studies coming from the Perugia Group, where they use the CliniMACS device for peripheral blood stem cells. Using that type of an approach, they're able to give mega doses of CD34 cells, as you've seen today, with very low doses of T-cells. And they've used the TBI regimen with either cyclosporine or fludeurabine.

When we introduced the ATG to TBI and cyclophosphamide, we eliminated immune rejections and primary graft failures in our series. They subsequently did the TBI thyo side or TBI thyo flu. And in that setting, what we observed more recently is the paper that Jacobowsky, published in Blood. And there, when we used the TBI thyo flu with the peripheral blood progenitor cells, these were isolated by Isolex and CD2 depletion, as

opposed to ClinIMACS which all can be done in one. But the key variable again was, in the absence of ATG, we had no problems of graft failure.

So right now, what I can say is that with the specific ablative regimens, in particular immunoablative regimens involving TBI thyo with flu or TBI thyo side, our general sense would be that it in a HLA match donor recipient pairing, AGT might not be required to remove residual host cells. The limitation that we all have as transplanters is that we do not have anything other than antithymocyte globulin to deal with memory T-cells. And unfortunately, some of these cytotoxic memory T-cells are radio resistant. That's a long winded answer, but hopefully that sort of clarifies.

DR. PINKERNELL: Just to address this from the company point of view, at this moment, we do not intend to include ATG as a recommendation in the labeling.

DR. SNYDER: Did anybody else from the sponsor want to weigh in on that ATG? It's a very complete answer.

DR. AHSAN: I have two questions. Actually, one I wanted to reiterate Dr. Galanis' question about this concern about the CD34 purity, and how the variability in that increases for those centers that do very few samples. So the answer was that there was other cell types that are decreasing the CD34 purity. Is there room or

recommendation or the possibility of running the sample through it twice, in order to minimize the non-specific binding of those other phenotypes?

DR. KEEVER-TAYLOR: I don't know that you can run samples through twice. It's certainly not anything that any of us have ever done, or that the company suggests doing. And maybe someone can say what the implications of that might be. I think having a good, highly mononuclear cell enriched starting product would probably help decrease some of the variability and purity. But I would also say, if you looked at the slide, I showed you what the impurities were. The T-cells were the ones that were going to cause problems, and they are uniformly and very completely removed.

Really high numbers in B cells could be concerned, but even if the ones that had eight, ten percent B cells, that's still a very low number of B cells that are being fused. And in case, it might be beneficial, and I don't think there's any reason to believe that monocytes are particularly harmful to be in the product. I don't know that it's something we should really worry about. But as far as running things through the column twice, I can't really answer that.

DR. BETHUE: We do not recommend to run cell product twice on the CliniMACS. This will not improve, so

to say, the purity. Actually, the CliniMACS system runs the cells several times. The magnetic separation cell, they are magnetically purified twice during the operations. We have now worldwide over about 35,000 separations, from several customers who had white cell(?). We have a database and know pretty well what compromise purity and impurity.

As has been presented, reagent consists of a monotone antibody against CD34 cells. So phagocytotic C receptor expressing cells may take up the reagent during labeling procedure. And therefore, they can show up in the final CD34 cell preparation as impurities. Therefore, we commend in our labeling procedure either to use the otologist plasma, meaning the IDG and the otologist plasma is preventing if FC receptor for other cells, and by this, preventing the uptake of the reagent.

It's also very important to keep to the temperatures and to the labeling conditions, which we recommend in our process. This is answering your question?

DR. AHSAN: Yes, it does. And then I also had a second question. I'm sure this afternoon we'll talk a little bit more about this subpopulation and its appropriateness for an HDE. But could you speak to the data in terms of including CR1 and CR2, both in the same subpopulation, considering their disparate response, in

terms of accumulative relapse and disease-free state at year two?

DR. DEVINE: So your question is the differences in the risk of relapse between the two groups. Well, we think that the precision of those estimates is not really there between the two groups. The numbers are small. We didn't really power the study to be able to look separately at the first or the second remission group, so we really want to look at them in aggregate. I think we would need larger numbers. So based on the trial results, I really don't think we can make, from a purely statistical standpoint, any major statement regarding that.

DR. NOGA: It still gets to a certain point I wanted to make. There is a lot of cell therapists in the room, and a lot of us know that in allogeneic transplantation, any manipulation whatsoever has effects down the line in terms of outcome. And here we are, writing a label for transplanters. And we all know, transplanters are so agreeable and actually do everything exactly the same. I actually congratulate them on the CTN and what they've been able to do in getting several groups to actually go through these trials in a very tight manor. But that does bring up a point. When you look at this, the regimen that was used here, a very monoablative, very appropriate regimen when one's looking for using T-cell

depleted grafts and trying to get engraftment.

You're using about 1400 centigrade of radiation, cytoxan, Thiotepa, ATG. And then, you look just as a comparison, even though again it was just a comparison, to the 101 trial, where I believe almost equal amounts of people use the BU/CY regimen versus a radiation based regimen, which again, I don't know how many of those people, and if somebody can tell me, how many of them were actually the regimen that was used here, other than the ATG. I don't think probably a lot.

The point is, when people get out there to use this, are we expecting that they are going to actually follow this regimen? And I heard Miltenyi say they're not going to ask for the ATG to be in there. But are we going to look at people using a straight BU/CY regimen, and then as the label would indicate or supposedly will indicate, that without additional GVHD prophylaxis, are these same people then going to actually put prophylaxis on board afterwards. These are issues, and I know we can't solve a lot of them, but this is going to be one of the problems coming up with this.

DR. O'REILLY: I am not talking for the company, so the company will have to also talk to this. But what you raised is one of the singular issues that we're here. The regimen that was used here was in fact a regimen that

we had developed at Sloan-Kettering. And all aspects of it, including the ATG at the time, was based on the idea that we, as a group in BMT CTN, would in fact now use a protocol which was published, where the result was as published and determined to what degree we could repeat this, using this regimen of T-cell depletion.

I think that the issue that comes up here is what would be immunoablative enough for a T depleted transplant. This regimen is one that works. We have also published, and we are actually conducting a large study, looking at other ablative regimens, immunoablative regimens, namely using Busulfan, Melphalan, Fludarabine, or Clofarabine. In each of these instances, we are in fact getting a consistent engraftment. Other groups have used this type of a system in Europe, using usually a bu/flu or bu/mel/flu type of regimen to getting engraftment.

But I think that these issues of the sort of one thing you can say is with this approach, you do not need any post-transplant prophylaxis. You are quite correct, transplanters do what they jolly well please. Unfortunately, that is a disturbing fact. But I think the idea that this, in fact, is enough to prevent graft-vs-host disease is there, and I think the data will support that. And the other aspect of it is, what would be consistently enough to allow for engraftment. And there are certain

regimens that we now know are adequate, but that's really a part of the aspect of control, that is extended beyond a device modification.

So what we're saying is, with appropriate immunoablation, these transplants can ensure consistent engraftment, and reduce both acute and marketedly choric graft-vs-host disease without post-transplant prophylaxis. That's as far as I think we're seeing it right now. But it is a problem, I agree.

MR. FLATAU: I have a number questions also related to the conditioning regimen. But isn't the intensive conditioning part of the reason that the relapse rate was comparable to the 0101 trial?

DR. DEVINE: So your question is what role does the conditioning regimen play in preventing relapse. And we do think all conditioning regimens play a role. We don't believe that this particular conditioning regimen is absolutely necessary to prevent relapse in the setting, because here could be other reasons why these patients done relapse, including earlier recovery of natural killer cells, etcetera. So we don't believe that fundamentally we have to stick to this one regimen to prevent relapse in the setting. I think the Wagner trial speaks to that as well. That's the lancet trial that looked at T-cell depletion compared to methaotrexate cyclosporine GVHD prophylaxis.

Relapse rates were similar in that setting, as well.

MR. FLATAU: I've got another question on I guess slide 57 of your presentation. It has to do with the rate of relapse, and if I read it correctly.

DR. DEVINE: You want to look at cumulative incidence of --

MR. FLATAU: Fifty-four, I think. So that says, I think, 3.1 percent of the 44 patients relapsed between one year and two years.

DR. DEVINE: I'm sorry, repeat the question, please.

MR. FLATAU: Three point one percent of patients relapsed between one and two years.

DR. DEVINE: Yes.

MR. FLATAU: So that's one and a half patients, 3.1 percent of 44.

DR. DEVINE: It's a cumulative incidence, so there's also competing risks involved with that.

MR. FLATAU: So it's not the 44?

DR. DEVINE: It's not. I don't know, Marcel, if you want to address this, just to clarify.

DR. PASQUINI: So I'd like to pull out a different slide. So this analysis was not included in the data analysis plan. It was performed for the publication, and the reason for that is that we restricted it to the

data analysis plan, the two data collections that were done for both clinical trials. The BMT CTN's structure is after the primary endpoint of any trial. The data collection shifts to the regular CDMTR data collection. So what we incorporated for this longer term analysis was to look at the data reported by these centers to the CDMTR, and expanded to follow up with these patients.

So that, you see, that there was beyond a year difference in relapse. You continue to have events in the 0101 beyond two years. And then, we separated that by remission status. And here, you can see that there is the event that was reported initially the data analysis plan. However, in the 0101, you continue to have relapse events and they are close to three years. They're similar with 48 percent versus 57, which was the same amount that was seen before.

And then, I'm sorry, there was a conditioning regimen, you asked, as well, the committee asked. And regarding the differences between the TBI based condition and the Busulfan based condition, in the busulfan, there was decided by the center and some centers use Busulfan cyclophosphamide, Busulfan fludeurabine combination. And the definition of myelobulation was the standard definition with TBI graded at 1200 centigrade total dose.

MR. FLATAU: So most of the TBI patients in the

0101 got more than 1200?

DR. PASQUINI: Unfortunately I don't have the exact doses of patients of 0101. We know that there was greater than 1200, which is the defined dose for myeloablation. So there could be a variety of different doses in these centers in the 0101 participating, because it was not really stipulated by the protocol, the exact dose of PPI.

DR. O' REILLY: And for our pediatric population, the conditioning units in the 0303 trial would be an appropriate conditioning?

DR. PASQUINI: I would say yes, but I would refer to Dr. O'Reilly who has more experience in the pediatric populations, since I am an adult transplanter.

DR. O' REILLY: In the pediatric group, most of the patients who would be transplanted would be transplanted for acute lymphoblastic leukemia. In that setting, the only agent that really gets effectively into sites such as the CNS is TBI. Using TBI regimens and T-cell depletion system, we are, for example, in very high risk leukemias now in seeing long-term disease-free survival rates in excess of 70 percent in that group.

I should also state that in patients with myeloid malignancies, we would, in this kind of a setting, use BU/MAL/FLU regimen and that has allowed us consistent

engraftment. That spares the issue of radiation in children, that has been associated with extremely good long-term disease-free survival, but it's a small series in our shop, and we have a publication now in for review in this regard.

I don't know that necessarily answers your question. I can't certainly say is a TBI-based regimen appropriate? Yes. Has this regimen been used in children? Yes. This was the hyper fractionated total radiation was introduced by our group in 1978, and it was the basis for the New England Journal of Medicine paper that we had, which was the first to really quite nicely show the potential of transplants in children with AML in second remission. But we are now moving away from the use of radiation-based regimens, except in patients with high-risk AMLs and clearly, for example, BU/MAL/FLU conditioning regimen can allow for consistent engraftment with these types of T-cell depleted grafts in kids up through the age of 22, 24. It can also be done now up to the age of 74 in our adult group, as well.

DR. TERRITO: In that pediatric group, about what percentage are you seeing for chronic GVH and acute GVH?

DR. O'REILLY: With T-cell depleted transplants?

DR. TERRITO: No, with the non-T-cell depleted.

DR. O'REILLY: With non-T-cell depleted

transplants, overall you would see in patients under five an incidence in HLA-matched donor recipient pairings. Under five, the incidence would be somewhere between 20 and 30 percent. If you go above age five in our large series, basically the results are very similar to what you would see in young or older adults. So there, you're getting into the 30 or 40 percent range in HLA-matched donor recipient pairings.

DR. TERRITO: And in chronic?

DR. O'REILLY: Chronic graft-vs-host disease, for all groups, it's at least 30 percent. I think that that holds true, even in the young children, the risk of chronic GVH is there. I have not seen a big difference in that, in the kids.

MR. FLATAU: Dr. Devine in his BBMT paper said that the endpoint of this 0303 trial was chosen to be this early disease-free survival, to allow planning for a follow-up trial, to prepare it for other GVHD prophylaxis strategies. And I'm wondering what the status is of that.

DR. DEVINE: There are a number of reasons, looking at the early time point, we're also interested in some of these concerns we had about higher risk of relapse, graft failure, more inspections that weren't realized, so that was an important part of it. Part of it down the road is we're obviously trying to look through the network for

novel strategies, to try to compare the standard strategies. So this is now under discussion, this trial, as well, is under discussion, as one of the potential strategies to prevent both acute and chronic graft-vs-host disease. Within the network, there's nothing finalized at this point.

MR. FLATAU: This is to do a randomized trial?

DR. DEVINE: One of the discussions is considering that. That has not been finalized, but there is ongoing discussions with the CTN steering committee regarding that.

DR. SNYDER: Dr. Gee?

DR. GEE: I have a question for Dr. Kever-Taylor relating somewhat to the variability that's been discussed recently in the performance of the device. When we have used the device, we have been strongly encouraged by Miltenyi to add thymoglobulin prior to the reagent labeling. Was the thymoglobulin used in the buffers in this trial?

DR. KEEVER-TAYLOR: No.

DR. KELLEY: So I wanted to get back to the issue of the CD34 purity, and it's really more a comment for my fellow committee members. So the purity doesn't really seem to be a problem. You're getting 93 percent purity with a very tight CV. It's the recovery that's more of an

issue, and that's true for all of the centers. And so the centers who are getting some of the better recoveries are the same ones that are getting some of the lower purities. So I don't think there's a correlation there and I don't think it's something that we should be concerned about for those centers who are doing fewer separations.

DR. SNYDER: Just to ask you, do you think that some of the cells that are part of the impurities are actually having some kind of biologic activity, if they're having the better outcomes?

DR. KELLEY: So I think that Dr. Taylor's explanation for the contaminating cells makes sense for getting the poorer recoveries.

DR. SNYDER: I see.

DR. KELLEY: But it doesn't seem to be affecting purity. So getting back to the question of should you put the cells over the column again, that's not really going to add any benefit.

DR. SNYDER: And maybe doing something good rather than bad?

DR. KELLEY: Yes.

DR. COUTURE: I also want to ask a question to anybody that's a sponsor that wants to answer it, about the advice itself and the safety of the advice, particularly in regards to contaminants introduced by the device, magnetic

beads or antibody. And while I think I know what the answer to that question is up front, the question really comes back to training and whatnot, and has the company looked at what the impact of misuse of the product or the device would be on increasing those contaminants and what the problems might be.

DR. JOHANSEN: We didn't perform any use studies, but the CliniMACS has been used worldwide since the late '90s. We did do the magnetic testing to show that it didn't interfere or the sphere around. I think Paul could come up and speak to that a little bit, if necessary. But there was no use study done, it was just the training, the CliniMACS user manual, the hotline to support the use in the clinic.

DR. SNYDER: Okay.

DR. COUTURE: I am sorry, so are you saying you've never looked at what sort of residuals are coming off the column into the final product?

DR. JOHANSEN: Into the product? I'm sorry, I was talking about the training. No, we have.

DR. BETHUE: First of all, I would like to repeat your question to make sure that I understand it correctly. You are asking for extractables off the column of the system?

DR. COUTURE: Yes, and how that's enacted by

misuse of the column. We see from the centers in your study aren't all using the column the way it was defined. And so a broad use of this would be expected to get even a broader array of misuse of the column. So my question is, have you looked at misuse of the column or leachables and residuals and other contaminants of the column, particularly under extreme conditions?

DR. BETHUE: As you might be aware, the system is a device and there are regulations for devices regarding extractable leachables according to the ISO 10993 standards. And we have applied to the methodology of the standard to our tubing set and especially also additionally to our columns, and have measured out for potential leachables, etcetera. The reports are available to the agency and the amount of leachables and the product which are leached very well below under established toxicology limits. This is for the tubing set, but also especially for the columns case.

The column itself consists of three major components. This is the housing, which is a nylon derivative. This is iron shot, but the iron shot in the column is covered with a surface coating lacquer, and that's pretty much it. And the lacquer has the function to prevent unspecific drops of cells towards the column to reduce unspecific binding and to increase often purities.

The columns regarding the use and misuse, the device is labeled as single-use device only. The columns are glued into the tubing set. You cannot remove them easily and put them into another tubing set, etcetera, you would destroy the stellar connections. So these are measures we have undertaken to prevent misuse or secondary use.

DR. SNYDER: Dr. O'Reilly?

DR. O' REILLY: I just wanted to clarify the question in terms of the misuse, because as you've seen, the system is largely a closed system. So there are these issues of exceeding or people exceeding what is recommended on the column. We don't have that paper here, I believe, but there was a study done in Germany that was, I believe, published in the British Journal of Hematology where actually a group did twice as much as what was recommended. They still found the CD34 selection and purity, and they actually, based on that, were recommending quote unquote potentially they could ease on this. The company has not done that.

But I think that this system has, as you saw, the key variable here is the consistency in terms of the T-cell depletion and the consistency of the purity of the T-cells, and the fact that these were uniformly sterile by all criteria required, suggested it's a tight system with the

training system that you have. I think Dr. Kelley is correct, the variations really have to do with the loading, as opposed to anything beyond that.

DR. KEEVER-TAYLOR: The paper to which Dr. O'Reilly referred actually did show that what we showed was that you could overload TNC without consequence to CD34 selection. But that paper also showed that if you overloaded CD34, you got diminishing returns, so that was consistent with our study. So I think it really is that the labeling has to emphasize that you should not go above the recommended loading dose of CD34.

DR. SNYDER: Steve, you had a question?

DR. GOLDMAN: I am still trying to understand how many T-cells are good, and what are the upper and lower limits here, because of course that speaks to the issue of the desirability of purity and what purity means. And so I'm trying to think of how to operationalize the question. So I was looking at some of the data, in terms of the metrics provided, and suggest a couple of questions, I supposed for Dr. O'Reilly and Dr. Devine primarily.

Have the T-cell levels of individual patients been correlated to the incidence or severity of GVH, first of all? And then, looking at the infection data, trying to get a little more granularity out of that, I think it was provided as granular data, but then enough of it was

redacted that now it's hard to make sense of it, in terms of the initial levels of T-cells administered to individual patients, relative to the time course and incidence and type of infection. So can those issues be addressed?

DR. SNYDER: I guess either Rob or Rich, or maybe not.

DR. DEVINE: So Dr. Goldman, I guess what's the sweet spot? It's a great question. What is the number you want to exceed and what is the number that you don't want to go below. And the first, we don't have the answer to that. So we did look at correlating, realizing the study was really not powered to be able to look at correlations between T-cell dose. So we just asked a simpler question, above or below the median, was there any difference in the risk of moderate to severe graft-vs-host disease, and we didn't find that. But we really haven't looked at any more granular detail in terms of exact cut-offs and so forth. Perhaps get below a certain number and the risk is very low. I don't know, Dr. O'Reilly, did you have a comment? You look like you want to make a comment.

DR. O' REILLY: The data for the target dose that we had going into this trial, of ten to the fifth per kilogram, was based on studies that we had conducted in our early studies of T-cell depletion using an elected-base system. And in that circumstance, what we found was that

in HLA-matched donor recipient pairings, there was a clear cutoff at ten to the fifth per kilogram. If you exceeded that, your risk of graft-vs-host disease was significant. Below that, we didn't see acute or chronic graft-vs-host disease as a significant issue at grade two. This was with the interleukin separated group. So the ten to the fifth is based on that. There have been confirmatory studies done in several other studies that have used either interleukin system or even the Miltenyi system. That's the first part.

Now, the next aspect of it is, what's the issue with regard to infection. We do not have that. I think that was a worthwhile question, we can address that. But I can certainly say that again the principle issue with regard to infection here is the issue of the fact that we were, in fact, monitoring EBV. That's the big difference here. I do think it would be very useful, however, to look at another infection that is common in marrow transplant recipients, and this again compilation of data from a series of studies. This is looking at our own series of 118 patients, where they were receiving a CD34 selected. This is with the Isolex, which no longer exists, coupled with a iroset(?) depletion. And in that circumstance, CMD reactivation was 58 percent, and 6.7 percent of patients actually had disease.

If you now look at unmodified marrow transplants, published by Zow(?) again, these groups are using CMV viremia as an indicator of reactivation of CMV. As you can see, a 60 percent incidence of CMV reactivation, the incidence of CMV disease is six percent. The Meyer study with cyclosporine, 205 patients, 26 percent CMV reactivation, 3.4 percent CMV disease, which was lethal in these circumstances. And this was another series, Dr. Kroger, with an unmodified graft where they had ATG in the pregrafting period at high dose, 55 percent incidence of reactivation, 10 percent CMV disease.

Then, if you look at the unmodified grafts again, what you're seeing is consistency in terms of reactivation rates in the 50 percent range in individuals who are CMV sterile positive at the time of transplant. And the overall incidence of CMV infections is no different with our T depleted graft, versus a modified graft given with conventional prophylaxis. The EBV is unique, and the reason for the EBV being unique is as follows. The frequency of CTO precursors, directed against EBV, in normal individuals like 90 percent of the people around this table, is about one in ten to the fourth clonogenic CTL precursors basically more million T-cells that are there.

And if you went to other systems, such as

tetrimers, you can say that as much as .5 up to two to five percent of the circulating T-cells in the average zero positive individual are directed against Epstein Barr virus. The reason for that is because of the fact, as you also all know, we all harbor EBV. And in fact, a member of the FDA, Dr. Tosado did some eloquent studies early on, showing that anywhere between 10 and 30 spontaneous EBV transformants exist per million B cells in the circulation. And because of that, we put a huge amount of immunologic energy to the control of it. The frequency of major allo reactive T-cells in the circulation is again one in about ten to the fourth, exactly the same as EBV.

The reactivity against minor alloantigen is usually one in about ten to the fifth clonogenic T-cells, basically will be directed against minor alloantigen. But there is big variation, and the reason we think we don't see much dose response relationship within this small grouping in terms of HLA matches is that there is an extreme variation in the frequency of minor alloantigen available T-cells.

You would see it more in multiparous women. You do not tend to see it as much in men, and there are big variations in terms of which minor allogens are or are not allogenic. So that's where the complexity comes in. But in terms of granularity of numbers, the frequency of EBV

and the frequency of major alloantigen reactive T-cells in the blood is exactly the same. And I think that's the big reason for the EBV sensitivity.

DR. SNYDER: I think we will probably cut off discussion now. And we'll take a break and we'll meet back here at 11:05, and the FDA will then give their presentation.

(Brief recess)

DR. SNYDER: So we are going to begin the FDA presentation, which will summarize the product review. And kicking off will be Dr. Deborah Hursh, who's a principal investigator at the Office of Cellular Tissue and Gene Therapies at CBER, and she'll be followed by Dr. Bross and Dr. Lin.

Agenda Item: FDA Presentation

DR. HURSH: Good morning. My name is Deborah Hursh and I will introduce the FDA presentations on the CliniMACS CD34 Reagent System. The CliniMACS CD34 Reagent System is under consideration for approval under a humanitarian device exemption for the indication listed on this slide. Miltenyi has already gone through this, so I will not read it. I will give the first presentation on device performance, followed by Dr. Peter Bross, who will describe FDA's considerations concerning safety and probably benefit. He will be followed by Dr. Mary Lin, who

will present the FDA's analysis of statistics of the clinical data. These talks will provide the FDA perspective, and will serve to facilitate the discussion of the questions we have asked the committee to address this afternoon.

The FDA review team for this application is multidisciplinary and collaborative, and I list the review team on the following slides. And I'd like to stress that many features of this device were reviewed, that will not be part of our discussions today.

As discussed by Miltenyi, the CliniMACS CD34 Reagent System is comprised of the instrument with the magnet, the proprietary PBS/EDTA buffer, the tubing set with selection column, and the CD34 reagent, which is a CD34 monoclonal antibody bound paramagnetic beads. The principle of operation is based on the selection of CD34 expressing cells, using a murine monoclonal to CD34, coupled to a paramagnetic nano particle, which allows magnetic selection to the desired cells.

The purpose of the selection is to, one, actively enrich for CD34 positive stem cell population, while secondly passively depleting donor lymphocytes. The removal of donor lymphocytes may obviate the need for immunosuppressive drugs to prevent graft-vs-host disease. However, it may also remove or reduce T-cells that mediate

anti-leukemia or anti-infective effects.

I will outline the selection procedure in a simplified cartoon form in the next few slides. The cells of the apheresis product and the antibody bead complex are depicted here. The antibody bead complex is added to the cells, and will specifically bind to the target cells. This is done prior to putting the cellular material on the Miltenyi instrument. I have provided a schematic representation of the instrument here. Cells from the input bag passed through tubing into a column within the magnetic field. The non-CD34 cells pass into the negative fraction bag, and the CD34 positive cells are retained. These cells are released by moving the magnet and flow into the collection bag.

The magnetic beads are immobilized on the column by the magnetic field, while the other cells flow through. The enriched CD34 cells are released from the column by moving the magnetic field, and the cells are collected, washed and can be used for transplantation. The quality of the cellular graft, and therefore its clinical utility depends on the device performance. Dose recommendations which were set by the clinical protocol focused on the number of CD34 and CD3 cells proportional to patient body weight.

However, the performance of the device largely

focused on the CD34 yield, which is the percentage of input CD34 positive cells that are recovered after the selection procedure, and the purity of those selected CD34 cells, which indicates the percentage of non-target cells found in the CD34 cell fraction after the selection procedure, and the reduction of the amount of CD34 cells. No acceptance criteria were provided for these parameters, and this may leave the end user uncertain as to whether the device has functioned appropriately or has failed.

In their HDE submission, Miltenyi provided the following information to support the ability of an end user to achieve appropriate device function. They provided information on training and technical support, they submitted the users manual, which is provided with a purchase of the instrument, and they provided historical data. For training and tech support, end users are trained by certified Miltenyi employees, and Miltenyi maintains its technical support hotline for end users to report device problems.

In the user manual, the end user is instructed to test cells before and after device use, and the user is instructed to measure the total number of leukocytes, the percentage of CD34 positive cells, the total number of CD34 positive cells and the viability. The user manual does not provide expectations for the CD34 yield, purity or log

reduction of CD3 cells. Each individual institution develops its own standard operating procedures for use of this device. These SOPs display considerable variety.

Miltenyi also provided data for a study called a retrospective process validation of the CliniMACS plus instrument manufacturing and performance evaluation in the field. And this was carried out in conjunction with the BMT CTN trial 0303, which you've heard a lot about this morning, and which was undertaken to support safety and probable benefit of the device, and about which you will hear more in the subsequent clinical talks by Dr. Bross and Dr. Lin. In this analysis, 84 cell selections from 44 patients carried out at eight different sites who were evaluated.

As I have stated previously, the cell dose was a clinical parameter, determined by the BMT CTN 0303 clinical protocol, and the target was greater than five times ten to the sixth CD34 positive cells per kilogram recipient body weight, with a minimum of greater than two times ten to the sixth CD34 positive cells per kilogram recipient body weight, and a target of less than 1.10 to the fifth CD3 T-cells per kilogram recipient body weight. The device performance was not prespecified, but the yield of CD34 cells, the purity of CD34 cells, the depletion of CD3 cells measured in log base 10 were measured, and the results were

analyzed retrospectively.

The performance data, broken out by study site, was provided in the briefing document and also discussed by Dr. Keefer-Taylor this morning. I provide an overall summary of the 84 selections in the table here. The most salient parameters are the mean yield, the mean purity, the mean log depletion and the mean final viability.

The FDA asks the committee to discuss the following question regarding device performance. Miltenyi proposes to supply device users with instructions for use outlined in the CliniMACS user manual, provide training by certified Miltenyi employees, and maintain a technical support hotline as resources pertaining to correct operation of the device. The table shown on the previous slide provided a summary of the data contained in appendix b of the FDA briefing document that depicts the attributes of the CD34 positive enriched hematopoietic progenitor cells obtained after processing donor apheresis with the CliniMACS CD34 Reagent System at clinical sites participating in the BMT CTN 0303 study.

Please discuss the adequacy of the user instructions and device performance data provided to demonstrate end users will be able to use the CliniMACS CD34 Reagent System, if approved, for processing HPC-A collected from an HLA-matched related donor for recipient

hematopoietic reconstitution. And please discuss any recommendations for establishing device performance criteria. So I will now give the podium to Dr. Peter Bross.

DR. BROSS: Thanks, Deb. I am Peter Bross. I'm clinical oncology team leader with the clinical evaluation branch in the FDA CBER Office of Cellular Tissues and Gene Therapies. I will first summarize the regulatory history of the HDE and then discuss clinical studies submitted and supported of the application. Then, Dr. Mary Lin from the CBER Office of Biostatistics and Epidemiology will then present the FDA analysis of probably benefit and safety.

Regulatory history, in May of 2004, a pre-IDE meeting was held with FDA, National Heart, Lung, Blood Institute and Miltenyi in which clinical development of the device was discussed, including requirements for an HDE. In September 2004, an investigational use exemption application was submitted to CBER for the use of the CliniMACS device in treatment of leukemia. In June of 2005, FDA granted humanitarian use designation to Miltenyi as was previously explained. This is a prerequisite for HDE application. In December 2009, in the pre-HDE meeting, FDA encouraged Miltenyi to perform a comparison to matched historical or concurrent control to support the safety of the device. In April of this year, the HDE application was

submitted to FDA.

Dr. Devine has gone into the details of this study 0303. I'll just emphasize the HDE submission includes data from a CTN study 0303, henceforth referred to study 0303. This was a single-arm, open-label, Phase 2 multi-center study of T-cell depleted peripheral blood stem cells isolated by the ClinMACS system. The eligible population included patients with acute myelogenous leukemia in first or second morphologic complete remission, undergoing myeloablative allogeneic stem cell transplant from an HLA-matched sibling donor.

Endpoints included six month disease-free survival, hematopoietic recovery, acute and chronic graft-vs-host disease, transplant-related mortality, disease-free survival, overall survival and achievement of targeted cell doses. The historical control cohort was selected from another BMT CTN study, which was study 0101. This was a Phase 3 randomized double blind multi-center trial, comparing two drugs for the prevention of invasive fungal infections in allogeneic blood and marrow transplant patients. The indicated population was for patients with hematologic malignancies undergoing allogeneic stem cell transplant. Endpoints included fungal-free survival through day 180, frequency of and time to invasive fungal infection, overall survival, duration of antifungal

treatment, time to acute and chronic graft-vs-host disease, and safety.

The two studies differ in key design elements, including objectives, patient diagnosis, donor HLA-matching, type of stem cells, target accrual, etcetera. I'm going to emphasize that study 0303 only included acute myelogenous leukemia in first or second remission. And 0101 included myelodysplastic syndrome and malignant lymphoma. And also, you'll note that study 0101 included related or unrelated HLA-matched or mismatched patients, and these were primary reasons for exclusion of patients from the cohort.

As been previously discussed, there was an imbalance in use of antithymocyte globulin in the two studies. And there were only seven patients who received antithymocyte globulin in study 0101, whereas all of the patients received antithymocyte globulin in study 0303. And I will acknowledge the previous discussion and just say that this is a component of one of the questions that we have to the committee, and I would encourage the committee members to take a sneak peak at our questions, if you haven't already.

Another difference between the two studies is in the follow-up time. The minimum follow-up for study 0303 was two years, and for study 0101 was one year. And I see

the sponsor has presented updated follow-up studies, which we'll be interested in reviewing.

The control cohort is a subset selected from study 0101 population, based on key eligibility criteria used in study 0303. This included diagnosis of acute myelogenous leukemia in first or second complete morphologic remission. Patients between 18 and 65 years of age, and must have had an HDL-matched related donor and peripheral blood stem cell allograft.

Selection of the control cohort from study 0101 was based on the key eligibility criteria, and I'll just emphasize that primary reasons for exclusion included that the stem cell had to be from a related donor, and patients with AML, you'll recall in 0101, included patients with lymphoma and myelodysplastic disease, also in first or second complete remission. The demographics of the two studies were somewhat similar between the cohort selected from the 0101 and the study 0303.

In comparison of the control cohort, there was a greater proportional of females and age trended a little higher in the 0303 subjects. And none of the subjects were less than 18 years of age. The 0303 study enrolled somewhat more patients with unfavorable cytogenetics and worse performance status, although the differences were not statistically significant. The intermediate risk group

accounted for more than 60 percent of the patients in both cohorts. Data on cytogenetic risk factors was missing in seven percent of the study 0303 subjects and three percent of study 0101 subjects. The remainder of the demographic characteristics were largely similar between the two cohorts.

Forty-seven subjects were accrued to study 0303 from October 2005 through December 2008. Three subjects were withdrawn prior to transplant, two subjects relapsed between enrollment and start of therapy, and the third subject was withdrawn due to development of complications from a procedure. The remaining 44 subjects were transplanted and were valuable for the study endpoints. Two year follow-up has not been completed for eight subjects at the time of the submission. Disposition of the subjects is summarized in this table.

This is the summary of the CD4 cell doses administered in study 0303. The sponsor just sent in CD4 cell doses for study 0101, and we haven't had a chance to review this information yet. The CD34 doses for three subjects were missing. Median doses for three subjects were missing, median doses 6.1.

Probable benefit and safety, as you recall, are the requirements for an HDE approval. The function of the device is to exclude T-cells that may cause graft-vs-host

disease, allowing for transplant to proceed without the need for a prophylactic immunosuppressive drug. Therefore, graft-vs-host disease-related endpoints were used as the primary measure of probable benefit. Issues arising from potential loss of hematopoietic stem cells during processing and reduction in T-cells that mediate anti-leukemia and anti-infection effects were primary safety concerns. Therefore, endpoints related to hematopoietic recovery infection, treatment-related mortality, relapse and survival were the focus of the safety evaluation. Now, Dr. Mary Lin will present the FDA's analysis of probable benefit.

DR. LIN: My name is Mary Lin. I am with the Division of Biostatistics of CBERs Office of Biostatistics and Epidemiology. So I will present FDA's statistical analysis results. FDA's analysis methods for the endpoints of acute GVHD and chronic GVHD. The FDA has performed competing risks analysis with both relapse and deaths as to competing risks. For the endpoints of relapse and engraftment, the FDA has performed competing risk analysis with death as the competing risk. The cumulative instance functions were compared using the Gray's method, and the R function CumIncidence was used to calculate the confidence interval, and the cumulative incidence rate at given time point.

For endpoints of disease-free survival and overall survival, the hazard ratios were estimated by the Cox proportional hazard model, with covariates complete remission stage and age group. And FDA has decided to exclude cytogenetic risk factor from the stratified analysis because of missing data and potential empty strata. A stratified log-rank test was used to compare survival curves.

This analysis, although prospectively defined, is still a retrospective comparison of heterogeneous non-randomized to cohorts. And a number of subjects in both cohorts is small. Therefore, P-values for the comparison between the two cohorts, and whereas endpoints should be interpreted with caution. In addition, ATG is the potential confounding factor. ATG is known to reduce GVHD and it was given to enhance engraftment in 100 percent of patients in 0303 and only eight percent in 0101.

Since the function of the device is to exclude cells that may cause GVHD, allowing for transplantation to proceed without a need of immunosuppressive drugs, GVHD-related endpoints were used as FDA's primary measure of probable benefit. This include acute GVHD, GVHD-free survival and chronic GVHD. So this graph shows the cumulative incidence functions of acute GVHD by cohort. The left panel is for grades two to four acute GVHD and the

right panel is for grades three to four. The red line presents cumulative incidence functions of 0101, and blue dotted line represents 0303.

So in comparison to 0101, there was no apparent increase in a cumulative instance of grades three to four, or grades two to four acute GVHD in 0303. So this table summarizes the comparison of acute GVHD between the two cohorts. The incidence rates at day 100 and Gray's test at p-values for the comparison of cumulative incident functions that are listed for both grades two to four GVHD and grades three to four GVHD. So for patients overall, the cumulative incidence rates of two to four GVHD, they are 100, as 22.7 percent for 0303 and 38.1 percent for 0101. And for grades three to four GVHD, the day 100 rate is 4.5 percent for 0303, versus 9.5 percent for 0101.

For the CR1 subgroup, the point estimate for the day 100 GVHD incidence rates are lower in 0303, compared with 0101. However, for the CR2 subgroup, the grades three to four GVHD day 100 rate is slightly higher. However, the sample size of the CR2 sub grouping 0303 is small, 14.3 percent call response to just one subject out of a total of seven.

So this graph shows the Kaplan-Meier curve of GVHD-free survival for the two cohorts. The left panel is grades two to four GVHD-free survival, and the right panel

is for grades three to four, GVHD-free survival. The red line represents 0101 and blue dotted line represents 0303. From the graph, we can see there was no apparent decrease in acute GVHD-free survival in 0303, in comparison to 0101. This table summarizes the comparison of acute GVHD-free survival between the two cohorts for all patients overall and by CR number. The point estimate of hazard ratio of 0303 versus 0101 was less than one, with the only expectation being grades three to four GVHD-free survival in the CR2 subgroup.

And this graph shows that cumulative instance functions of chronic GVHD by cohort. The red line represents 0101 and blue dotted line represents 0303. There was no increase in the cumulative incidence of chronic GVHD in 0303 in comparison to 0101. This table summarizes the comparison of chronic GHVD between the two cohorts. The incidence rates at one year and Gray's test at p-value for the comparison of cumulative incidence functions are listed. For patients overall and by CR number, the point estimates for the cumulative incidence rates at one year are lower in 0303 compared with 0101.

However, the apparent decrease in chronic GVHD must be interpreted with caution. As previously mentioned, ATG administration has been associated with decrease in both acute and chronic GVHD, and all subject in 0303

received ATG as part of conditioning regimen to improve engraftment. However, only eight percent in 0101 received ATG. And a small number of subjects in high relapse relating mortality in the CR2 subgroup preclude a meaningful assessment of chronic GVHD in that subgroup.

So probable benefit is based on a reasonable assurance that GVHD rates can be controlled using the device, to provide T-cell depleted grafts to patients undergoing transplantation without the need for standard GVHD prophylaxis. The GVHD incidence rate at day 100 and day 180 GVHD-free survival rates are similar or better than those in the control population. However, we need to keep in mind that all subjects in study 0303 received ATG to enhance engraftment as part of a conditional regimen. Also, follow-up was not complete on all subjects, and there were no pediatrics enrolled in study 0303.

Safety issues arise from the potential damage to the hematopoietic stem cells during processing and from substantial reduction in the number of cells from the allograft that mediate NT leukemia effects, and prevent or treat infections. Therefore, endpoints related to hematopoietic recovery infection treatment relating mortality relapse and the survival were the primary focus of the evaluation of safety.

This graph shows the cumulative instance

functions of neutrophil and the platelet engraftment. The last panel is for neutrophil engraftment and the right panel is for platelet. The red line represents 0101 and blue dotted line represents 0303. In comparison to 0101, there was no apparent decrease in the cumulative incidence of engraftment of 0303.

This table summarizes the comparison of neutrophil and the platelet engraftment between the two cohorts. The incidence rates at day 30 and Gray's test for p-value for the comparison of cumulative incidence functions are listed. For patients overall and by CR number, engraftment rates are similar or better in the patients who received T-cell depleted grafts, compared with the control cohort. All patients in 0303 reached a neutrophil engraftment before day 30.

So this table summarizes infections within one year after transplantation. Seventy-three percent of subjects in 0303 developed at least one infection, and 39 had a severe or life-threatening infection. These numbers are comparable to 0101. However, the viral infection rates are higher in 0303 compared with the control. Fifty-five percent of subjects in 0303 had virus infection, versus 36 percent in 0101.

This table summarizes the comparison of treatment-related mortality between the two cohorts. The

incidence rates at one year and Gray's test p-values with comparison of cumulative incidence functions are listed. For patients overall and by CR number, the cumulative incidence rates at one year are similar between the two cohorts. The device decreases the number of donor lymphocytes which are responsible for the GVO graft versus leukemia. Therefore, the possibility that relapse was affected by the use of the device was a concern. As shown in this graft, it appears there was no increase in a cumulative incidence of relapse in 0303, in comparison to 0101 for subjects overall.

And this graft shows the cumulative incident functions by CR number. The left panel is for the CR1 subgroup and the right for the CR2 subgroup. It appears the cumulative incidence of relapse is not worse in 0303, compared with 0101 for the CR1 subgroup. But for the CR2 subgroup, the cumulative incidence of relapse seems to be worse in 0303 than in 0101. However, the number of subjects are too small for comparison.

This table summarizes the comparison of relapse between the two cohorts. The incidence rates at one year and Gray's test p-values by comparison of cumulative incidence functions are listed. For patients overall and for the CR1 subgroup, the incidence rate of relapse in one year are similar between 0303 and 0101. However, for the

CR2 subgroup, the incidence rate of relapse at one year appears to be higher for 0303 than for 0101.

This graph shows the Kaplan-Meier curves of disease-free survival for all subjects. Red line represents survival curve for 0101 and blue dotted line for 0303. It appears that disease-free survival in 0303 is not worse than in 0101 for all subjects overall. This graph shows the Kaplan-Meier curves of disease-free survival by CR number. The left panel is for the CR1 subgroup and the right for the CR2 subgroup. It appears that disease-free survival is not worse than in 0303, compared with 0101 for the CR1 subgroup. But we don't observe this for the CR2 subgroup.

This table summarizes the analysis of disease-free survival for all subjects and by CR number. The analysis was stratified by CR number and age group. Disease-free survival was not worse in 0303, in comparison to 0101 for subjects overall or for those in the CR1. But the point is made for the hazard ratio for the CR2 subjects, however, favored 0101.

This graph shows the Kaplan-Meier curves of overall survival for all subjects. Red line represents the survival curve for 0101 and blue dotted line for 0303. It appears that the overall survival is not worse in 0303 compared with 0101 for all subjects overall. And this

graph shows the Kaplan-Meier curve for overall survival by CR number. The left panel is for the CR1 subgroup and the right for the CR2. It appears the overall survival is not worse in 0303 compared with 0101 for the CR1 subgroup. But for the CR2 subgroup, the two curves do not seem to separate.

Similar to disease-free survival, stratifying analysis with stratification of factors of age and CR number were performed for overall survival. Overall survival was not worse in 0303 in comparison to the 0101 in all subjects overall, or for those subjects in CR1 alone. However, similar to disease-free survival, the point is made for the hazard ratio for the CR2 subjects favored 0101.

To summarize, outcomes using the CliniMACS CD34 Reagent System and no standard GVHD prophylaxis are 100 percent neutrophil recovery by day 30. Viral infection in 55 percent of subjects and EBV infection in 18 percent of subjects. One year treatment-related mortality is 13.6 percent, and one year relapsed rate is 20.6 percent. And an incidence of viral infection is higher using CliniMACS than for the standard transplant controls. And the relapse rate for CR2 patients is higher than for the standard transplant controls. And the follow-up is incomplete.

Issues for discussion, first, safety. The major

safety concern is that the depletion of T-cells might cause an increased risk of graft failure, leukemia relapse and infection, and worsening of subsequent long-term outcomes. Whether the risk of viral infection and death due to relapse would affect acceptability of the clinical benefit of the device is for discussion by the otherwise committee.

Second probably benefit, the process for post indication is for processing allogenic HLA-matched HPC-A to obtain a CD34 plus cell enriched population intended for hematopoietic reconstitution following a myeloablative preparative regimen without additional immunosuppression in patients with AML. Whether the study results demonstrated probable benefit is for discussion by the otherwise committee.

Third, the applicant has proposed to include both CR1 and CR2 in the indication for their device. However, for patients in CR2, the relapse rate is higher and the hazard ratio for survival is greater than one for patients in 0303 versus 0101. We are asking the committee to discuss whether the totality of the data provide a reasonable assurance of probable benefit of patients in CR2.

Last, all of the patients in 0303 were adults, and there are no data available regarding the safety of the use of this device for treatment of children with AML.

We're asking the committee to discuss whether there would be any limitations in generalizing the results of 0303 to pediatric population. That's all, thank you.

Agenda Item: Q & A

DR. SNYDER: So we are now open for questions. And as before Dr. D'Agostino, right at the starting gate.

DR. D'AGOSTINO: I have a number of questions regarding the statistician and the statistics. And some of it is to inform me, for example, there's no pediatric subjects in the CSO's. The statistician, I have to say, how can you make an inference about pediatric subjects unless there's some kind of inference one can draw from past experience. Is there any reason why the pediatric subjects are really on the table, in terms of us having some kind of data that would indicate that there's an effect for those subjects? I have a couple of other questions after, but that's the first question.

DR. BROSS: Well, obviously, it is difficult. You can make certain extrapolation to the pediatric population, and we generally require studies be completed in adult population before going to the pediatric population. And we would welcome your input as to whether we should put any restrictions on the label, just due to the mechanism of the action of the device.

DR. D'AGOSTINO: Again, approaching it from the

statistician's point of view, looking at the data, there's no data, so there's nothing you can say about it. And going on to another question, the CR1 versus CR2, we have a small number of subjects in the CR2, and unfortunately the trends occasionally went in the opposite direction. A question like this came up earlier in the morning. And what I'm asking is a question, but I have my opinion, do we take it as the totality of the data? This study is not large enough to split out the effect of the CR1 and CR2. Again, is there some kind of mechanism that we would say that the sample size in the CR2 is so small, that if we see reversals, not significant reversals, but we see reversals in direction that's to be considered reasonable. And in other words, you'll be thinking of the totality of the data.

Again, from a statistics point of view, start splitting things up. I would like to see something on the gender, some kind of analysis on the gender, just to see if the directions are correct. The CR1 CR2 bothers me more than that, though. I think there is something about what's going on with these individuals. And again, I have an opinion, but what's the opinion of the FDA in terms of seeing possible reversals, but not significant reversals in the CR2 versus the CR1.

DR. SNYDER: Dr. Witten, I think you wanted to

address some of these issues.

DR. WITTEN: Well, I wouldn't say I want to address them is exactly as just answer the first question and sort of the second one. So for both of these, I think they're more, as you noted, not really statistical questions. So as far as what we're asking the advisory committee, let's say for pediatrics, is there information based on clinical experience in general with this kind of procedure or with the grafts or with T-cells.

DR. D'AGOSTINO: That's very good, because if they turn to me and Professor Lee here asks us our statistical wisdom and so forth, I think we aren't going to be able to.

DR. WITTEN: Yes, I think you're off the hook, yes. And I would give a similar answer really, although there is something you could say, maybe not much beyond what you've already said. But for the question about the CR1 and CR2, I think again, those questions need to be looked at in light of what's known about the role of T-cells in those diseases. In other words, is there some reason to think that difference is actually explainable biologically and we need to pay attention to what is. You can't really interpret statistically.

DR. D'AGOSTINO: One other question. I've served on BSMBs in dealing with transplants and so forth. And

I've always had this big fight with the clinicians that I know we look at competing risks. We say we're interested in going onto graft and host disease, and we've used mortality as a competing risk. I find mortality to be the most frightening thing that could face a person. And so, I keep arguing that we should be looking at a composite endpoint that has mortality or graft and host disease, for example, so that we get a handle on sort of the bad things that can happen. Did you do that analysis by any chance? Or did you always have mortality as a competing risk? If everybody's dead by the end of the study, I think that says something.

DR. LIN: We did include acute survival into the

--

DR. D'AGOSTINO: But that was just survival. But then what did you do:

DR. LIN: We went with either acute GVHD or this, so both are included.

DR. D'AGOSTINO: So that endpoint does include both?

DR. LIN: Yes.

DR. D'AGOSTINO: Very good.

DR. SNYDER: Dr. O'Reilly, you wanted to make a comment?

DR. O' REILLY: There was in the FDA presentation

the dogmatic statement that since T-cells provide the anti-leukemic effect of a transplant. In fact, there are early data from the T-cell depletion experience in man, that in fact if you T-cell deplete, there is an increase in the incidence of relapse in patients transplanted for CML, which was almost doubling. That's yielded.

However, as you saw from the study that was done in the T10B9 trial, which was using T10B9 antibody as the T-cell depletion that was conducted, there is no difference in incidence relapse. And as you see, in this trial, there's no incidence of relapse. I would posit even further that the data do not exist to show that, in fact, T-cells are a significant component of resistance to acute leukemias, either AML or ALL. The earlier studies of these actually derive from Don Thomas' and Keith Sullivan's early studies, looking at patients who are young with acute lymphoblastic leukemia, and the readout was that in so far as GVH could equal GVL, what we will do is we will give increased doses of lymphocytes to the recipient to overcome the leukemic problem.

And so what they did was to give a series of patients high doses of donor lymphocytes to, in fact, reduce the incidence of relapse. What they achieved was a marked and significant increase in the incidence of acute and incidence of severe acute graft-vs-host disease,

associated with an increased incidence of death due to graft-vs-host disease. It did not, in any way, alter the incidence of relapse. There have been several studies in AML and ALL looking for evidence of the potential of minor allo-antigen specified T-cells to induce remission. In fact, there are really essentially one or two cases where it is implied, but it is not shown.

Most of the data derives from the early studies, comparing transplants for AML, from identical twins versus HLA-matched siblings. And there is no question that there is an allo effect in that the incidence of recurrence of AML is higher in recipients of genotypically twin transplants than HLA-matched donor recipient pairings. However, recent studies dating from the studies of Rojerie(?) and other studies from our group, Kathy Shue and several others, have clearly implicated a principle effector for the anti-leukemic effect of these transplants, be they T depleted or unmodified grafts to be natural killer cells, rather than T-cells.

And again, what I would suggest is there are no clinical data in randomized trials, nor in the studies in which you use T-cell depletion without post-transplant prophylaxis. The T10B9 protocol actually used post-transplant prophylaxis and saw no difference in either AML or ALL. They saw a significant difference in CML. In this

study, we again show a very low incidence of relapse. So to include the dogmatic statement since T-cells are a principle effector of anti-leukemic resistance is just not scientifically supportable.

DR. NOGA: I have two questions. The first is pretty simple. The viruses, do we have a handle on the viruses? Were they just like ADNO, RSV, was it CMV that we saw the higher incidence with?

DR. BROSS: I am sorry, you were asking for specific virus?

DR. NOGA: Right. It said that there was a higher incidence of virus in these patients. The viruses could be something simple, or it could be something devastating like CMV. So I was wondering what were the viruses that they saw higher incidence in, in the 301 trial?

DR. DEVINE: We don't have all the data, but our hypothesis, Steve, is that this is all related to the EBV reactivation. Remember, we think that a lot of it --

DR. NOGA: Eighteen, yes.

DR. DEVINE: Well, versus if you don't check for it, you don't know if you have it. So 0101, routinely those patients do not get surveillance. Remember, only eight percent got the ATG. So we think virtually all of it is due to the EBV.

DR. NOGA: So it's all EBV, okay, all right.

Then the second question, it's a little hypothetical, so let's say that this HD is granted within an indication for CR1. If an IRB approves the use of the device in CR2, 3, 4, 5, 6, does it get used?

DR. WITTEN: It would need a study. It wouldn't be part of the label.

DR. NOGA: They would probably be approving this in line of a clinical trial.

DR. WITTEN: It would need to come through FDA as an IND. It wouldn't be part of the HD approval.

DR. AHSAN: So a couple of things, one is the CR1, CR2, I think as Dr. Witten said, as a non-clinician, it would be really helpful, and I think it would be in the afternoon that we have the actual discussion of what it means biologically, because clearly, statistically, we have limited evaluation of that. So I think both that and the pediatric question, to really get into the biology and the clinicians can help and say what they think is going on and what they think the differences are between those different states. That would be really helpful.

And then the other thing, though, to direct it to the FDA. And I know someone mentioned that they didn't think it was important, but I do actually think it's important, and the FDA pointed it out, as well, which is

about the purity. I understand that whether it's a high level or a low level, there may be a balance of benefit on the biology. But the change in the variability or the increase in the variability between the centers for this process, because of the HDE, is my question. And I think the FDA identified that as there is no acceptance criteria as to when we have gone through this or processed the cells, and we've appropriately processed them.

So part of the question is for the FDA, which is how important do we think that it is to have ranges of acceptability of the cell population post-processing. And part of the question to this sponsor is do they have any metrics of failure to properly enrich the population or to properly treat the population once you go through it. So you run it through the column. The question is how do you know you successfully ran it through the column? Is there any metric to that? So ones for the FDA, ones for the sponsor.

DR. WITTEN: I just want to clarify our question hopefully. Our question is not really about what are acceptance criteria for an individual treatment dose for a particular patient. We think the clinicians understand that as described in the protocol. Our question is more when a transplant center is learning to use this, how do they know that they're using it, not we're talking about

that specific dose, but how do they know that they're able to use it properly, that they're getting the best result that they can get from running that device. So it's more like are there more instructions labeling training that are needed, rather than are there released criteria that need to be put in for what's the specific dose for the patient, because I think that is probably clinically understood already.

DR. AHSAN: Right, and I agree with that. I guess to me the question is whether or not the process has been done correctly, and part of that is could be training, but part of that could be an assessment of a metric. And so, I guess my question is, how do we know?

DR. SOIFFER: I just want to comment on one thing and this relates to that question, a question I think you raised earlier this morning, to this particular number B up here, in terms of the CD34 purity. And a comment was made, I believe by you, but perhaps by somebody else about larger centers and smaller centers, and these five making(?) the small centers. And this four here is actually the larger center. I know that because it's my center. And in fact, we did have quite a range of CD34 purity.

And so we put 18 patients on the trial, and these other centers here put one or two or three maybe and are combined together. So even though this ends up being

statistically significant between one and five difference in terms of CD34 purity, there is no difference statistically between four and five, the largest center and the compilation of the small centers who just do one or two of these. So I wanted to actually mention that earlier this morning, and I think there is no real difference here.

In terms of the sort of release criteria, what we do for a transplant is really what's described in the goals for the device, which was to achieve CD34 count greater than two, hopefully five, because that was an arbitrary target. The sort of accepted minimal target was two times ten to the sixth. And with an appropriate low number of T-cells which we did. In the trial, in which Dr. Devine could comment on, we did have parameters, you didn't discuss this morning. We'll say the device failed, that is there was more than one times ten to the fifth CD3 positive cells per kilogram. We did advise that post-transplant immunosuppression be given to those patients for clinical issues. So that was the response to what happens if the device failed. There wasn't a plan for redoing it, just to go ahead with regular immunosuppression.

DR. AHSAN: So if I can ask just one follow-up, which is so why do you think center one is so tight compared to your center? Is it donor population or is it processing?

DR. SOIFFER: I don't have an explanation for that. There may be variability in CD34 in how folks are actually assaying for CD34 numbers, both before and afterwards. So there can be variability in how that's done, but I have no other explanation to that.

DR. KEEVER-TAYLOR: I also think it's important to point out that the combined centers five through eight were low accruers on this trial. They aren't necessarily centers with less experience with the ClinimACS device because there are, as you heard, a number of other trials. And at least two of those centers, I know, have enrolled a substantial number of patients on other trials that are not inexperienced centers. They just enrolled fewer patients in this study.

And I think the rest of the issues, I hope we tried to address, is that the reason for this lack of purity, it's really just biologic. There are other cell populations that will sometimes show up in the positive fraction. It's not really a function. No one's done anything wrong. It's just a variation that you see. And Rob correctly pointed out, with the numbers, their center versus the group centers, it wasn't significantly different. The tightness of center one, those are the data, it's hard to know without reviewing all of the analysis results, whether their gating was slightly

different. There are, again, some logistical issues in doing the flow assay, not the device, but in doing the flow assay. There just is some variation there. There always has been and there always will be, I think, in analyzing these populations despite our efforts to try to set limits on how things were done and to describe how things should be done. These are clinical flow labs, some of them, and they do things their way and there just are differences.

But I don't think that it's at all biologically relevant. What you really want is a CD34 cell dose in the range that you know is biologically important to get engraftment, and you want a sufficiently low T-cell dose that you know is likely not to cause GVH. So it's the dose you give. Recovery is a nice number, but if you recover 50 percent, but you still have five times ten to the sixth, you've succeeded. But the T-cell doses is probably the bigger consideration, and viability with some variation, but they were all well above what FDA genuinely considers as an acceptable product to infuse, which is the 70 percent of viable cells.

DR. SNYDER: Steve, did you want to comment specifically on this issue?

DR. NOGA: I just want to make a comment on it. The thing is, and this was said this morning, this is a biologic product. And even with starting from where the

device is, there are so many steps that go before the device, exactly how the mobilization is done. Yes, this was laid out in the protocol, but there are differences. There are differences in the apheresis, even though again it's spelled out. There are differences in how one collects the product. And as such, you can have a lot of variables before you get to the product. So, of course, once you get there, then we see the data. Even with that variability, we see the data that actually they're able to obtain, so it's interesting.

DR. AHSAN: I'd make the point that, that's exactly why you need tighter controls on those things that you don't understand.

DR. NOGA: Right, but some of that is not going to happen.

DR. AHSAN: Well, some of it is not going to happen. The question is you have to pick which ones are most salient, and if you can argue that something is less important. But you have to hear the argument first, before you can say that it's acceptable to not regard that purity value as important and move forward. Because the biology is complex and we still don't really understand graft-vs-host disease manifests itself.

DR. SNYDER: But let me point out that a lot of these issues are going to be dealt with when the committee

has their dialogue in the afternoon. So what we'll try to do is get as many of the questions out to the sponsors in the FDA as possible before lunch. Dr. Lee?

DR. LEE: I would just like to clarify. We have several discussions, comparing the acute graft-vs-host disease. On page 40, 41, 42, we compare grade two to four GVHD versus grade three to four GVHD. Are the patient in grades three to four GVHD included also in grade two to four? It's different. So maybe I understand this definition incorrectly.

DR. O'REILLY: Grade two to four would include two, three and four. And then, grade three to four is a subset of that.

DR. LEE: Right, so why are we comparing this way, a bigger set versus a small set, because the number is smaller?

DR. O'REILLY: Because grade two graft-vs-host disease is severe enough to require significant high dose immunosuppression in an attempt to eliminate it. Grade three to four, despite treatment, more often than not does not respond to any immunosuppressive agent. So grade three to four, grade four is very often lethal, grade three is oftentimes irreversible.

DR. LEE: Yes, it's just so we don't see the number counting, we only see the percent, so you'll be good

to see the number. Thank you.

DR. SNYDER: Rich, did you have a comment on the prior issue?

DR. O'REILLY: I just wanted to again get at the issue with regard to biological fractionation, and just remember that what you're talking about as you start with this bag of leukapheresis is approximately 10^{10} to 10^{11} cells. And what you are in the end now, as a result of this, you are able to capture as you saw very high proportion of the CD34 cells at also a very high frequency. Those cells exist in that leukapheresis, again at very, very low frequencies.

And most importantly, from the standpoint of the T-cell doses you're given, you're giving somewhere usually in the range of two times 10^8 to 10^9 T-cells per kilogram. The average 70 kilogram, what you're talking about is a system that is producing these massive eliminations of all cells extraneous to the stem cell. So the variations that you see are a very, very small fraction of the 10^{10} to 10^{11} that you're actually starting off with. It's still an extraordinarily efficient system.

DR. CURT: This is a request for clarification from the agency and their response to Dr. Noga's question. If this device is approved in CR1, a clinician could use it in CR2, 3, and 4, or potentially in other disease settings

in the absent of a protocol. Isn't that true?

DR. WITTEN: This is an HDE and so they would need a protocol. Under HDE approval, they have to get IRB approval. And if they want to use it for intended uses other than their regulatory requirements, they would need an IMD or IDE. But they could contact our office for information about that, but they would need to do it under a study.

MR. FLATAU: So this is different than a regular marketing that can just do what they want off-label or whatever. HD is different idea.

DR. WITTEN: Yes, this is different approval than a regular approval. Just start with the fact that you need IRB oversight for this.

DR. CURT: How would the agency monitor that?

DR. WITTEN: I don't know, I can't tell you exactly the details of how the mechanism. But the sponsor needs to report something about how many are used or something about the use. So we do hear about the use and that's something that we look at.

DR. HURSH: Miltenyi will have to report to us the number of units of the CD34 reagent that are used per year, and that number will have to be in the vicinity of what would be appropriate for 4000 patients. So we will know how much it's being used.

DR. CURT: Does the granularity of the data you collect dig down below CR1, CR2 for an AML diagnosis? Or if somebody says I have a patient with AML and they're CR3, and they use it, is there any way that you know it's being used off-label?

DR. WITTEN: I don't know how much detail we get about that. I'm not sure how much concern. We look at each individual thing. We wouldn't ask for submission of patient charts or that kind of thing, if that's what you're asking.

DR. SNYDER: Dr. Bishop, you had a question or comment. Dr. Galanis?

DR. GALANIS: If I may come briefly back to the issue of the viral infection, because it's one of the questions we'll be discussing this afternoon. The possible explanation is the frequency of EBV testing. So are there data from studies where T-cell depletion is not used where the frequency of EBV testing for EBV is as frequent as in this trial, same as this trial? I thought the CMV data? That would be helpful.

DR. O'REILLY: What we did was we to review the literature, looking at groups who were doing allogeneic transplants, who were also monitoring for EBV viremia by analysis for DNA, and this is what we show here. This is our trial, in 44 patients. There were 18 percent who

showed evidence of EBV reactivation, and we had one patient with a PTLD. This is the alimtusimab(?) -- there were major concerns about this particular realm. And 111 patients, 16 percent EBV reactivation, one percent of the PTLD. But now, if you look at these studies here and this study here, this is a large study looking at 406 patients who received unmodified nerve wraps with cyclosporine methotrexate post-transplant prophylaxis, but they were monitored for EBV. And 14 percent incidence of reactivation.

They did have four percent EBV PTLD, but these were individuals who did not get Rituximab shortly after evidence of EBV reactivity. But as you can see, looking at the different percentages, these different approaches, the incidence of reactivation is much more common, both in the T-depleted, as well as the unmodified. Then, I think many recognize. But the corner we had was that, in fact as I stated before, when you eliminate the T-cells down to this level, you are potentially at risk for EBV lymphomas. We think the EBV lymphoma risk is definitely higher with T-depleted transplants, but these are the actual results that we find.

DR. COUTURE: One of the problems I'm having with all this is whether what's being discussed is whether T-cell depleted transplants are safe, or whether this device

can produce a safe T-cell depleted product. And maybe right along with this particular, clearly there's a long experience with T-cell depleted studies. And in addition to just virus expression, I'm wondering if the sponsors have any thoughts on how engraftment, long-term survival, particularly perhaps after a CR2, compares in this study to those studies. I guess I would've expected the sponsor to have submitted a trial comparing this T-cell depleted product with another T-cell depleted trial. Now, I realize that's not easy to do and that's not what I expect you to do. But there's historical data out there, and can you make some comparison between this trial and those trials?

DR. DEVINE: So there's the answer from a statistical standpoint, which is we can't. And in terms of the method of T-cell depletion, are we talking about ex vivo versus in vivo T-cell depletion? In terms of ex vivo, currently this is the system for ex vivo T-cell depletion. Now, the Wagner study that we cited used a less efficient method or two less efficient methods for T-cell depletion, and showed more graft-vs-host disease than the one we had with a more efficient T-cell depletion.

My argument would be, in terms of you asked about long-term survival. We feel this idea of a composite, so being alive, free of disease and free of graft-vs-host disease is really most important. And we think that we've

achieved this in a large number of these patients. And so, we think that's probably what's most important, comparison of the historical data from other T-cell depletion trials. But I'm not sure what we would include as the gold standard, possibly ATG at this point, but there really is no other gold standard for T-cell depletion.

DR. BISHOP: For the panels, just realize these are all unrelated donors there, so it's semi apples and oranges, because we're talking about sibling. Our trials had the data that we presented as today are matched-sibling donors. And the Wagner trial, those are matched unrelated donors, and not to the degree of potential matching that was performed with matched-sibling donors. So those were six of six matches, unrelated donors with not necessarily high resolution typing. So to try to extrapolate that back and forth, and I'm not saying positively or negatively, I just want the panel to know that.

DR. SOIFFER: I am just going to just speak to your question about T-cell depletion in general. The reason the trial was done is that there is no FDA-approved T-cell depletion process. Prior studies, and there have been many, I've used many different T-cell depletion methods, which deplete varied amounts of T-cells, lead different cells behind, some trials with immune suppression, some trials with not. So the goal of the

trial is really to do the same thing in a uniform way in multiple centers.

I don't think that we are going all the way to make the claim of we're trying to approve T-cell depletion versus not T-cell depletion. What I think we're talking about is T-cell depletion using the CD34 device that we described here today generates a product that is reproducible, and that the survival is comparable to a non T-cell depleted group with dramatically lower incidence of chronic graft-vs-host disease. And that's the major reason to compare to a non-T-cell depleted cohort is because the incidence of chronic graft-vs-host disease, we sort of lost that. You put the slide up in the beginning. Bad chronic graft-vs-host disease is not just bad, it's awful. And to be able to have a product that does that with CD34 selection T-cell depletion, that's where we are on moving ahead with this.

DR. SNYDER: Are there any questions in particular to be posed, either to the FDA or to the sponsors before we entertain any possible comments from the audience? A lot of the discussion will continue this afternoon among ourselves.

DR. GALANIS: Going back maybe to follow up to the prior question. When HDE is granted, is there a specific indication for the device that the IRBs have to

take into consideration when allowing use? One scenario that comes to mind, can someone, a doctor, who would want to use this device for unrelated transplants, for example? Or the indications of this approval will then dictate what kind of protocol can locally be approved.

DR. WITTEN: Under the HDE approval, a physician has to obtain IRB approval to use the device at the facility. And the IRBs have our approval about what the approval is for. So if somebody wants to do a study that is not within the labeled indication, we would recommend that they get an IND or IDE. I think in general the IRBs take that into account. Obviously, there are emergency situations where the physician's may not have time to get approval from anybody, and there's special exceptions in FDA policy, but I don't think that's what you're asking about.

So the short answer is, if somebody wants to do a study and it's for an indication other than what the approval is for, then they would go to their IRB. The IRB would look at the indication, we would recommend that they do a study. And there's also, like I mentioned, some requirement for the sponsor to report back to us what they know about the use and so forth. So in practical terms, they would need another study from FDA.

DR. GALANIS: Also, the marketing aspect of it,

does that mean that if someone used it in a separate center under IRB approval, the patient now will have to actually pay for use of the device, because it's not an investigational device anymore?

DR. WITTEN: Well, first, I think for investigational, I don't know about the patient paying. Our regulations relate to charging. And for investigational devices, I think there's some charge, if they're HDEs. And if they're HDEs, there's some other requirements. I'm not sure, maybe the sponsor could answer.

DR. BROSS: I know you can charge for investigational devices, also. There's a mechanism by that.

DR. STEVENS: Reimbursement and charging are two separate things, for one thing. If there is an approved investigational device exemption application, then cost recovery is pretty much automatic for an IDE. So they could charge under an IDE, just not make a profit. So whether the patient pays or not, is really not part of the equation. For the HDE, they can charge an amount that doesn't exceed the cost of manufacturing and distribution. For an IDE, they can also build in the R&D costs. That's not part of the HDE or the conduct of the study. It can also be reimbursed for an IDE. But since there's no study

for an HDE, that's not part of the equation for profit.

DR. SNYDER: Steve, you wanted to make one last comment?

DR. NOGA: Just to FDA, I just want to make sure I have this right. So if this is approved under a certain label, the physician wants to go to their IRB, they don't need an IND or an IDE to use it under the humanitarian device exemption. They just need the IRB to approve, not necessarily a study, but they just need to approve the use of this humanitarian device, that's it? They won't need to actually submit a clinical trial. They can just submit a document under whatever standards we have these documents. But they can submit that and then they can use this?

DR. WITTEN: Yes, and as Mr. Stevens had said in his presentation, to use it, it is up to the IRB whether that approval is in general or patient by patient. So it could be a general approval, or it could be patient by patient. That would be an IRB determination.

DR. SNYDER: Is there anybody in the audience who would like to make a statement or address the committee? Now would be the time to do it. Seeing that there are no comments from the audience to the committee, I think what we can do is adjourn for lunch, meet back here at 1:30 and we'll discuss the questions and vote on two of them, and discuss things like probable benefit, safety and the label.

Thank you.

(Recess for lunch)

**Agenda Item: Committee Discussion of Questions
and Vote**

DR. SNYDER: So basically let me just give a quick overview of what the afternoon is going to look like. We have three major areas that we're going to be discussing. The first two of which, we actually will vote on after discussion, and then the last will be simply discussion. So the first topic that we'll be discussing and voting on deals with safety. Then, after that, there will be a discussion and a vote on probable benefit. And then, after that, there will be three questions dealing with various aspects of labeling. This will be purely discussion, not a vote, but it will deal with some of the issues that were raised in the morning. For example, patient indications, CR1 and or CR2, age groups, pediatrics, not pediatrics, and then training and instructions. So that will be in the last group of questions that we deal with.

So the first group of questions will deal with safety. What I'm going to do is read exactly the question. I'll read the long introduction and then I'll read precisely the question, and particularly I'll read the question that's going to be discussed. And Dr. Bishop will

be the first discussant, and then it will be open to everybody. So the question reads as follows, or this is a preamble to all of the questions, in fact.

An HDE application must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices, or alternative forms of treatment. The applicant has proposed that its device can be used for processing HPC-A, that's hematopoietic progenitor cells apheresed, from an HLA-matched related donor for hematopoietic reconstitution following a myeloablative preparative regimen without the need for additional GVHD prophylaxis for treatment of patients with AML in first or second complete remission.

The applicant has provided data from a single-arm prospective clinical trial of its device, and that's the 0303 study that we've heard about, and from a retrospective comparison of the outcomes of this single-arm trial, to a control cohort from the study that was called 0101, which dealt with the fungal infection, receiving unmanipulated HPC-A from an HLA-matched related donor using standard immunosuppressive drugs to prevent GVHD.

With regard to safety, the major safety concern regarding allogeneic transplantation using CD4 (sic) selected HPC-A in patients with AML is that the depletion of T-cells might impart an increased risk of graft failure, leukemia relapse and infection, and worsening of subsequent long-term outcomes. The results of the outcomes for the CD34-selected transplant recipients, 0303, and the control cohort, 0101, are summarized in a table. You probably have a copy of the table or it might get projected. Please note that the follow-up is incomplete for eight subjects on BMT in the 0303 study, and follow-up for the control cohort is limited to one year.

So the first discussion question is as follows. Please discuss the safety of transplantation using CD34-selected HPC-A using the CliniMACS CD34 Reagent System, especially related to graft failure, relapse, infections and treatment-related mortality at one year. And we're going to kick off the discussion with Dr. Bishop. But then, it would be good if everybody could weigh in at some level what your thoughts are going to be, and maybe even indicate how you're leaning towards voting. And after we do the voting, then we actually will go around and you'll articulate the reasons why you voted as you did. But let's kick off the discussion first with Dr. Bishop.

DR. BISHOP: So I'll try to actually make my

comments brief. Putting this in a relative perspective, and part of the discussion today is we're looking at a T-cell depleted product, as compared to a, and I'll use the term, T-cell replete program in matched sibling. So I actually think this is a very good control population, because one would assume that the incidence of graft failure and the relapse infection would be higher. Now, relative to treatment-related mortality, that's a different issue. But in regards to graft failure, the data were very clear. There were no graft failures in this.

And matter of fact, in the control arm, there were actually three graft failures, which I actually found to be a relatively higher incidence than what one would generally assume to be in a general transplant, a T-cell replete transplant setting. I'm going to skip relapse and infection, and go to treatment-related mortality at one year. Actually, the incidence of treatment-related mortality was lower. And the concern would be, it would be equal or more and treatment-related mortality was less. In regard to relapse, relapse in CR1 was comparable. And one would have predicted, based on past evidences that CR1 relapse would have been greater. However, what is unique in this population is that they did not use transplant immunosuppression, which may have provided an advantage relative in regard to relapse.

And then comes the issues, with the exception of CR2, and I actually would like to hear from our biostatistic experts. I actually think you can't make anything out of this. Even though there was an increased hazard ratio, we're looking at such small numbers and the confidence intervals were so long. And the other important thing to remember, this only has one year of follow-up data. And so I really think the CR2 issue, you either have to throw it completely out potentially as a discussion point.

And in regard to infections, infections are higher. However, coming back to treatment-related mortality, the way that we treat infections today is so markedly different than what we have before. We can monitor for them better, we can treat them better, and it really didn't correlate, even though it was a higher incidence of infections, particularly viral infections, it did not necessarily translate into a higher degree of mortality. And so I turn to my colleagues and ask their thoughts in regard to that.

DR. D'AGOSTINO: In terms of looking at the control population, I'm always concerned that these historical control studies fool you, that there's something going on that you're not seeing. And I was asking the sponsor, how come you started with such a large group and

ended up with only 80 some odd subjects. But the FDA presentation takes us through the different steps, where you see what they ended up with was pretty much the right way, correct me if I'm wrong, to call out the sample. So I have some comfort with the historical controls endorsement, where I think you were saying.

And as far as the CR2, I just think it's too small for a statistic statement, for exactly the reasons that were just mentioned. It would have to appeal more to the sort of notion what would you expect worse and what would you expect happening in the CR2 subset that the CR1 isn't giving you any information on. And I obviously can't contribute to that conversation. But they ended up approximately the right ratio of individuals with CR2 in both groups. The confidence intervals are very wide, they aren't conclusive. They are in some cases the opposite direction from the CR1, so it does raise some concern.

And I really think that one would really be stepping out on a limb to draw a statistics inference from it, so I think we'd have to appeal more to the clinical mechanisms and what have you, and ask the question do they have a study. They can get an overall result, should we really be dicing things down. And if the CR2 is something dramatic, then I think that one does have a point, one does have a thing of discussion. And the statistics really

isn't going to clarify or solve the issues.

DR. CURT: I think we actually can say something about CR1 and CR2 from the data at hand, because if you look at the language for humanitarian use, you have to have safety and probable benefit, which is probably the adverse of what a judge would call a reasonable doubt. And I think that the figures we have here certainly don't show probable benefit, if the numbers are going in the right direction. So I agree, Ralph, that it's not statistically answerable.

But I think in terms of reasonable doubt or probable benefit, I think we can say that it's unlikely that there's probable benefit there.

DR. D'AGOSTINO: And we're really discussing this now, this safety issue, which is probably even less so of a concern.

MR. FLATAU: First of all, I would like to say that talking about safety in this setting is pretty odd, because very little is safe in this setting. I think that the two groups, the conditioning regimens are completely different in the 01 versus 03. The follow-up is not adequate. We haven't talked at all about late effects and whether they might be different, either because of the conditioning or because of the use of the device or something. So I think at best, you can always say that it's probably safe in this setting. And we don't have even

a two-year follow-up on all of the 0303 people. And in the absence of doing a randomized study, it's hard to pick out how to compare them.

DR. D'AGOSTINO: In a study of this nature, how long would follow-up in a clinical trial usually be? It's nice to have long-term follow-up, but quite often the trials that I've been involved in, dealing with 100 days, 180 days, two years.

MR. FLATAU: I'd like to see ten years, but I don't think that's -- but I think two years is at least a minimum.

DR. BISHOP: The only thing I'll say is, and again having just spent a large amount of time, and really two years were very fair for all of these outcomes. Ninety percent of relapse, 90 percent of treatment-related mortality and engraftment is defined as generally within a year, the risk of late graft or after 12 months is quite short. So in terms of defining the safety, and again, relative to what do we do with acute myeloid leukemia and CR1, that might be a much more fair question.

But in terms of defining safety of transplantation, almost all of these events occur within two years, and 75 percent of them occur within the first year. So I don't think that, when trying to judge these endpoints, I don't think it's necessarily unfair, relative

to the question at hand.

MR. FLATAU: For safety, though, I think the risk of secondary cancers is outside generally of two years, and I think we have no idea, for instance, how these would compare. And that's a safety issue.

DR. BISHOP: But again, secondary cancer, when you look at allogeneic stem cell transplantation, and just reviewing the causes of death after transplantation, and we're looking at maybe one, possibly two percent that do. It's just very rare. In the autologous setting, that's a more fair question. But in the allogeneic setting, that's just not a regular cause of death. The number one cause of death is recurrent disease, and then followed by infections and graft-vs-host disease.

DR. SNYDER: Dr. Witten, you wanted to make a comment?

DR. WITTEN: I just wanted to comment that actually the 0303 cohort, which is the patients with the sponsor's device, did have two-year follow-up. And the reason that the comparisons are at a year, aside from the fact that many of the comparisons are done this way for the reasons that have been mentioned, is that the control only had one year. So I think the sponsor could probably ask the question about what additional events in these categories they saw at two years, if that was wanted. I

don't know if they have the data off-hand.

DR. BISHOP: But the difficulty there is, again that's using CIBMTR follow-up data, which I think the CIBMTR, it's just not 100 percent, as opposed to on this study where on 0101, it was followed. They were mandated to follow for 12 months. And then, the additional follow-up data is retrospective analysis, based upon CIBMTR reporting. Dr. Pasquini, is that correct?

DR. PASQUINI: That is correct, Dr. Bishop. I would like to pull the slides to show additional information. Even though these are a collection through the CIBMTR, we knew where these patients were. We knew the IDs. We went back to centers and asked specifically what happened with these patients.

This is the additional follow-up. We did beyond one year for this patient population. We can see that there are additional events of relapse occurring beyond one year in the 0101 population. And then the last slide is again the slide comparing by CR2 and CR1. And I've shown this to the committee before, but again, there is two years, 39 percent maintaining a 57 at the three years with no additional events. And these were done by going back to the centers and asking if these patients had relapse or not.

But I agree with Dr. Bishop that we are including

another database, but we use that database to help us identify where the patient is and asked the transplant center what had happened with that patient.

DR. GALANIS: I agree with the sentiment expressed that this trend of CR2 is worrisome, but at the same time, I agree we cannot read the wrong conclusions out of seven patients treated with product derived through the device. One question I wanted to ask the FDA is, would it be possible that assuming this application is approved to then ask the sponsor to come back with additional data when more patients in CR2 are treated to make sure that truly there is no difference down the road?

DR. WITTEN: I think we'd like you to make your recommendation about the data in hand. Whether or not we ask for any kind of additional data collection post approval is something you can suggest. But we're asking for your recommendation for these two questions, based on the data that we have in-hand.

DR. BISHOP: Can I ask the chair and the FDA together? So when we do vote, are we voting on the very specific indications which you read in the preamble? Are we voting in AML in first and second complete remission, as part of the indication? Or do we get to suggest potential modifications of that indication, or is that possible?

DR. SNYDER: Correct me if I am wrong, but what

you'll be voting on is one question that pretty much includes the reasonable safety for the indication, as specified by the sponsor. However, it's important to realize these are recommendations. This is recommendations to the FDA. So what we'll do is, everybody will give their opinion now, what they're thinking. Then even after one casts a vote, we'll go around the table and everybody will then articulate why they voted as they did, and you can put in all your caveats, and the FDA will take that into consideration. And they'll realize that even if you give a yes vote, it was with X or Y qualifications. So these are advisory, but this is to allow you to actually have to step up to the plate.

DR. GALANIS: Are you asking if the question should be separated to CR1 versus CR2, is that what you're asking?

DR. SNYDER: Yes, where that may come up is in the non-voting last set of questions about the labeling. We specifically talk about whether it is or is not wise to specify the labeling as being CR1 and or CR2. So that will be an area of discussion, and the FDA will listen to what we think.

DR. HWU: I think it is challenging to talk about safety in isolation, especially with cancer patients. We always have to weigh the potential risk with the potential

benefits. And while there might be a slight increase in viral infection, EBV infection, and you may even expect that because a job of a T-cell is to fight viruses. It seems to be that, if you grant the limitations of historical controls, it seems to be a significant decrease in graft-vs-host disease. And so that, I think, far outweighs any potential safety concern with the infection in my opinion.

And as for the CR1 versus CR2, I think the numbers are just way too small to make any sort of conclusion at all. And I think it's dangerous to try to interpret CR1 versus CR2 with those numbers.

DR. BROSS: I was just going to say what you say, that there was a discussion question about CR1 and CR2.

DR. SNYDER: Other comments? I'd particularly like to hear just from anybody who's really not had a chance yet to speak. You'll all have an opportunity after you vote, because then we will go around the table and you'll indicate why you voted as you did. So what I'll do is I'll read the question, and then if you look at your microphones, you'll see that there's a plus, a zero and a negative sign. So, the plus sign will be yes, the zero will be abstain, and the negative will be no.

And these will be activated for a period of time, and then after that, it will be locked and they'll record

the votes. And then Gail will then read the votes based on the member into the record, and then we'll go around the room, and you simply indicate why you voted as you did. And this is where you can throw in all your caveats. Again, these are recommendations. This does not have the force of law, so don't worry about it.

Voting question number one, is there reasonable assurance that the CliniMACS CD34 Reagent System is safe for use in order to obtain a CD34 positive cell-enriched population intended for hematopoietic reconstitution following a myeloablative preparative regimen without the need for additional graft-vs-host disease prophylaxis in patients with acute myeloid leukemia in first or second morphologic complete remission? So you simply now just vote yes or no or abstain.

DR. DAPOLITO: For the record, there are a total of 15 voting members. Yes votes were 13, no votes two, abstentions zero, for a total of 15. And I'm sorry, I can't see that, I have bad eyes. So I should read, for the record, Dr. Bishop, yes, Dr. Kelley, yes, Dr. Noga, yes, Dr. D'Agostino, yes, Dr. Lee, no, Dr. Dahlgren, yes, Dr. Ahsan, yes, Dr. Snyder, yes, Dr. Galanis, yes, Dr. Goldman, yes, Dr. Couture, yes, Dr. Hwu, yes, Mr. Flatau, no, Dr. Territo, yes, Dr. G, yes. Dr. Curt is non-voting.

DR. SNYDER: So now we will actually go around

the room and just briefly articulate why you voted as you did. If somebody prior before you has given precisely what you're saying reasoning, you can simply say that you agree with the sentiments or the reasons stated before. And even though Dr. Curt was non-voting, we'll start there for you to simply indicate what your thoughts were, and then we'll go around the room in a counterclockwise fashion.

DR. CURT: I would have voted yes. I think this is a tried and true device that my colleagues here feel comfortable with. And I would be guided by their expertise in this area. But obviously, it's been in practice and it's given results as good as you might get with non-depleted. And giving chronic immunosuppression is not necessarily a cakewalk.

DR. GEE: I agree with the previous comments. I felt that it fulfilled its requirements in regards to the design of the clinical trial and the goals of the clinical trial. I have some concern about the CR2 patients, but I feel the numbers are far too small to make any final decision based upon that small number of patients.

DR. TERRITO: So I agree with statements that have been made, that it looks like it's a procedure that can be done safely with at least as safe an outcome as in the control populations.

MR. FLATAU: I voted no. I stated the reasons

before, but I think that there's too small numbers, and the differences between the treatments that were given to both patients make it hard to draw conclusions on safety, and there's no long-term follow-up.

DR. HWU: I think what the data has shown is that, while we can't always be certain, the benefits appear to far outweigh any potential safety concerns.

DR. COUTURE: I keep trying to divorce the issue of whether T-cell depleted products are safe in patients, versus whether this device can produce a safe T-cell depleted product. I think the data kind of overwhelmingly, to me, suggests that the T-cell depleted approach probably has value and probably is safe. And I think there's no evidence that the device itself produces anything less than a safe T-cell depleted product.

DR. GOLDMAN: I would agree with that sentiment. I don't have additional concerns still in terms of the increased infection incidence, but as Dr. Bishop pointed out, most of these risks are manageable. We still have too little information to go on, in terms of what the optimal T-cell numbers are in this type of procedure. But that's not necessarily an issue referable back to the device.

DR. GALANIS: I would agree the overall overwhelming majority of the data supports safety.

DR. SNYDER: I am going to skip, because I'll

summarize the discussion afterwards.

DR. AHSAN: I agree with what's been said. I think the conversation about infection was useful, the conversation about CR1 versus CR2 was useful. But in the end, I think it is safe enough to move forward.

DR. DAHLGREN: I agree with what's already been said.

DR. LEE: I am not against the use of this medicine. I think it's helpful for the patient. I voted no just because I still have concern about the overall safety. I think it still needs to be maybe after about a year of follow-up and more data to confirm. So I'm not against the medicine.

DR. D'AGOSTINO: We do have conflict of interest as a statement. Have you made statements or have you done things that would create conflict of interest. I've lived through historical control trials, and they raise problems. I think they did a good job in terms of justifying it, and I think the numbers indicate that there is a good, reasonable safety margin. I understand the need for a longer follow-up, but my sense, and again with things that I've seen, that the follow-ups we have here are often times what is presented for us to make decisions. And I feel comfortable saying it's safe.

DR. NOGA: I essentially agree with Dr. Bishop

and his comments. And from a personal note, I will also say that having used all these devices in the past on different clinical trials, including being tortured by red blood cell rosettes and staying up all night, I definitely can see the safety here, and that's why I voted yes.

DR. KELLEY: I, too, agree that data looked compelling for chronic graft-vs-host disease and the device seems to make a safe, effective product.

DR. BISHOP: I concur with all the other comments, especially Dr. Noga's latter thing about use of device, with the only caveat that I think that the CR2 data is non-interpretable.

DR. SNYDER: So just to summarize the sense of the meeting, with regard question one, regarding safety. Those who voted yes in support of safety felt that the data presented fulfilled the demands of the clinical trial, that the T-cell depletion approach appears to be effective and probably safe. And that in terms of the concerns of safety, with regard to graft failure, there seemed to be no evidence of that.

There seemed to be less transplant-related mortality, that relapse was not an issue with CR1, did raise some concern with CR2, but most voters felt that there was just enough data to be able to come down on one side or the other, though that could be some concern later

on. But most were willing to say that they could not make a decision one way or the other, with regard to CR2, and that while infection was increased, this was a manageable and maybe even preventable type of complication, and that the major causes of death seem to have been averted, and that recurrent disease, infection and GVHD. Those that voted no seem to feel that the numbers were simply too small, and that the follow was not long enough. Does the FDA have any questions, anything else you want us to address regarding this?

DR. WITTEN: No, thank you.

DR. SNYDER: We are moving on to the second question. And this is one with regard to probable benefit, and I'll also read that aspect of the question. The function of the device is to deplete cells that may cause GVHD, allowing for transplantation to proceed without the need for immunosuppressive drugs. GVHD-related endpoints were therefore assessed as the primary measure of probable benefit. All patients in 0303 received a myeloablative preparative regimen that included Rabbit antithymocyte globulin at 2.5 milligrams per kilogram as a single IV-dose prior to transplant to improve engraftment. However, prophylactic immunosuppression was not given after transplantation. All patients in study 0101 received a myeloablative preparative regimen with prophylaxis

immunosuppression. However, ATG was administered in the preparative regimen to only eight percent.

The discussion question in particular, with regard to probable benefit is as follows. And Dr. Territo will be the primary discussant after I read the question. Considering the limitations of the data, please discuss whether these data support a finding of probable benefit for use of the CliniMACS CD34 Reagent System for processing allogeneic HLA-matched hematopoietic progenitor cells aphaeretic from a related donor to obtain CD34 positive cell-enriched populations intended for hematopoietic reconstitution, following a myeloablative preparative regimen in patients with acute myeloid leukemia. Dr. Territo?

DR. TERRITO: I think the data do show that there's improvement in acute graft-vs-host disease, at least no worse graft-vs-host disease. And the advantage is that you don't need to use prolonged immune suppression, which is a major advantage for the acute issue. The chronic graft-vs-host disease data, as I think even more impressive, and that it seems like it is very beneficial for chronic. The issue of getting the rabbit ATG, it was a single low-dose, and all, or at least most of the studies that showed an effect of just ATG on graft-vs-host decreases had subsequent immune suppression. So I think in

this group, where immunosuppression was used, that T-cell depletion is the primary reason for the decrease in the graft-vs-host disease. So overall, I think that it does come down to a positive result in this regard.

DR. CURT: I think the vote may be confounded if you keep CD1 and CD2 in there, because some people may read it as if they don't think CD2 is worthwhile, that they'll vote no, if they think that CD1 is worthwhile. So that may force people to vote one way or the other. It's all or none as it's written now.

DR. SNYDER: Other people want to comment on this particular question of probable benefit.

DR. TERRITO: I think this issue is the same as when we're talking about the safety, because overall safety, if you have more deaths from relapse also goes along with it. And I think for all of this, that the two different ones are.

DR. SNYDER: It is a little bit separatable, but probably benefit means more likely than not, like a civil suit.

MR. FLATAU: I think to me this is a kind of a funny thing. This approach to T-cell depletion has been around, as Dr. Ali said. They've been doing it for 30 years and it's not in widespread use. I think in the 0101 trial, altogether four percent of the patients had a T-cell

depleted transplant. And so now, we're talking about lowering the bar considerably over, making this FDA-approved procedure, and allowing that, when it seems like after that long experience and not being put into practice, the bar should be raised a lot, or at least somewhat because of the vast experience we've had with it

And so it just surprises me that we're sort of talking about it when I think the 0303 study was a great study, but it basically pointed the way that we needed to do further investigation and do a randomized trial, and see how the two studies compare. I think it's pretty clear that there's probably a benefit in terms of graft-vs-host disease or chronic graft-vs-host disease, but how do you compare the other outcomes. How do you compare the relapse rate, how do you compare infectious deaths, PTLD and all these other variables that are going to differ between the two groups? And so we just need to do a randomized trial.

DR. HWU: I just want to make a comment regarding that I've been in cancer research for a long time, and I can tell you the money is tight, it's challenging to do clinical trials. And I'd love to have data and a randomized trial for every single question that comes along, but it's just not practical. There are many other questions in trying to increase efficacy that may need to be addressed, such as NK cell infusion and other things

that will be expensive and challenging to do. I just think it's not practical to require a randomized study for every single question, especially when you have a device that's been used for a number of years and data that does appear that it's of benefit.

DR. GOLDMAN: Just to say a legalistic point, so in regards to the voting, and I, too, have concerns about the CR2 data, which is interpretable. And so the question wording includes first or second morphologic complete remission. How do we deal with that? So in other words, if folks said agreeing with the proposition that the probable benefit was demonstrated on initial and first remission, but not necessarily so on second. It's the ors and and.

DR. SNYDER: Because it's an or, you can vote, and then later, for the labeling, qualify that. Please notice that a non-voting discussion question after we do this is the labeling, and that's where all the qualifications and concerns can come out, and that can be the recommendation, as well.

DR. D'AGOSTINO: I think in a way, I don't get this in terms of voting, it's not the typical approval that we're being asked for. It is the probable benefit, it hasn't gone through the usual device route and things of that nature, with the standard trials. I think that's very

important, for me, in terms of trying to make sense out of this here that we're not being asked to hold the same standard. And I also have the question of the one versus two and I'll bring it up in the comments. But I think that we're talking about an overall test procedure, again the historical control, and we have overall results. If we start pulling out the CR1 versus CR2, it actually would enhance some of these results if we focus on the CR1. And I think we have opportunity to discuss that as we go later on.

MR. FLATAU: As a patient, I think it doesn't matter whether it's an HD or not. Here's a would-be device that's FDA-approved and there's no other device that's FDA-approved in this setting. So I think that would be a significant difference. It doesn't matter if it's HDE or a regular approval or an accelerated approval to the patient. There's one that's approved and nothing else that's approved.

DR. BISHOP: I think your points you make are quite valid. I guess I'm looking at this quite differently. I don't think we are trying to lower the bar. This isn't a question that's been brought up before. Are we trying to answer the question of T-cell depletion versus non-T-cell depletion. That question has been asked since I was a fellow. And I think there's different ways to

achieve the same results.

And there's people who believe in T-cell depletion and there's different ways to treat cancer. And if you get the same result, and if we look at overall survival for CR1, this is not powered to be a non-inferiority study, but that's kind of the question we're asking. Do patients in CR1 go to transplant and derive benefit from this? And the answer is yes, and the alternative would be to do a T-cell replete. And are those results as good? Do the patients derive benefit? If we saw this and we compared it to 3030 and we saw that the overall survival that all the patients were dead, then you'd say, no, they didn't derive benefit. But those patients did derive benefit and in a comparable patient population.

And again, where are the patients who qualify for this study for transplantation and CR1, transplantation was considered the appropriate, if not the treatment of choice in most situations. And therefore, how I look at it again, is kind of like a non-inferiority. And the major thing being is finally now this is a way, a relatively standardized way to do it, so that's from a different perspective, but I appreciate what you said.

MR. FLATAU: I guess there is two points. One is we talked about standardized. Initially, there's a saying

that the thing about standards is there are so many of them to choose from. But we talked about there's different standards and different people. And I guess probable benefit to me would be a little bit stronger than not inferior, right? Probable benefit should be at least likely to be better than the existing treatment. I think a lot depends on what the definition of follow-up.

DR. BISHOP: This is not a question of existing treatment. This is not a comparison for superiority.

MR. FLATAU: I thought the presentations early on then HD thing said it should be probable benefit.

DR. BISHOP: It should derive benefit, not superiority.

MR. FLATAU: I thought it said probable benefit.

DR. BISHOP: It's probability of deriving benefit.

MR. FLATAU: Right, including over existing treatments.

DR. BISHOP: I'll turn to the FDA on that.

DR. WITTEN: The question we are asking is from the use of the device, is there probable benefit that would occur to the patient? So is there probable benefit? In other words, the patient could have unmodified cells, so they could have cells modified with the use of the device, and does that use of the device provide probable benefit to

the patient, which I think that is what you're understanding. That's what I was trying to explain. Is that clear?

DR. SNYDER: I think also, as you've been beating into my head that probable benefit is not the same as efficacy. This is a completely different question. Efficacy might be what you're talking about, and that has a statistical definition in all of that. This, again, is more likely than not, based on the available data in hand.

MR. FLATAU: I guess I would call it probable efficacy then, right? Isn't that what we're talking about?

DR. HWU: So it does look like there's less graft-vs-host disease, but I think the probable comes in because it's historical controls. As Ralph said, there are always caveats with that. But I think that's where the probable comes in versus a randomized study.

DR. GOLDMAN: I had been looking at it as probable benefit for the patient, not probable efficacy and not probable superiority over other treatments, for example, that have exactly the same outcome as a unmanipulated graft. But a patient not having to take prophylactic therapy for GVH would be a benefit to the patient. So it doesn't have to have better outcomes, it has to have just some upside for the patient. I think that's the bar, if I'm not mistaken. I think that's the

bar, not better than existing therapy, some benefit to the patient.

DR. WITTEN: That is it in some respect.

MR. FLATAU: An alternative is chemotherapy, which I think is inferior. But some patients would benefit because they wouldn't have a transplant and they wouldn't relapse. Is that probable benefit, too?

DR. WITTEN: Well, this is a device, so I'm not sure that term is used. I'm not sure how to answer that. I think in this case, a patient's going to get a transplant, is using the device to manipulate the cells they're going to get provide probable benefit to them? So that's what it is looking at. It's not looking at this treatment compared to other kinds of treatment. Just the use of the device in this setting, a patient is going to get a transplant, does the use of the device provide probable benefit? So it's not comparing it, if what you're asking is it supposed to compare this to the universe of other treatments out there. That's not really the question.

DR. BISHOP: And if this is a poor analogy, I'll turn to my colleagues about this. If somebody has colon cancer, let's say stage three colon cancer, and you give infusional 5FU and you have the opportunity to give oral Cepacaine and you get the same outcome, but yet you can

take a pill instead of taking an infusion. I don't know if that's the same analogy, but that's kind of how I look at it. I can tell you there's multiple people in this room that would love to see the T-cell depleted just significantly, everybody would love to see that.

But I do see this as an outstanding platform, potentially to build on and to know that if I would give my patient this approach, that I can feel comfortable knowing that I will have as good as outcome as the T-cell replete transplant, and knowing that it's under some degree of regulation. As Dr. Noga said, having not as much as Dr. O'Reilly, but messed with red blood cells, trying to T-cell deplete a graft before.

MR. FLATAU: I just would like to say I'm one of those who'd like to see it kick ass.

DR. D'AGOSTINO: When I was asking the FDA questions, that third line in the table there is, to me, where you actually have looked at the graft and host disease, plus you've tied it into mortality. And unlike the other three numbers in that table, the first column, those are incident rates. This is basically how many people are still around and having witnessed a death or graft and host disease, and I think it's pretty impressive. And if you look at the graph, although my copy is not great, it sort of hangs in there. They have 180 days, but

this hangs in there, going up to a year and longer.

And if you just look at the ones and twos, or twos and threes or what have you, you end up getting a .09 for a p-value. You don't get a .05 and so forth, but you're ruling out something like a 10 percent increase. And given the things about the nature of the device and what it offers you, I think that this is very promising, but it's not statistics proof. And in order to say yes to it, moving, sliding off that, is it a p-value or a .05 for fixed end point.

DR. SNYDER: Steve, did you want to make a comment?

DR. NOGA: Mostly everything has been already said. You talk about probable benefit, 30 years of looking at probably that same picture of chronic graft-vs-host disease might be the same one, I don't know. It's horrible. And any time you can see a study that decreases that terrible morbidity and mortality, I think you have probable benefit for that patient.

DR. SNYDER: Anybody want to make any comments before we vote?

MR. FLATAU: I think that this is a promising approach. But I guess the question to me is, is it ready for primetime or is this just an indication that we should study this further. And to me, I don't see the data that

says this should be FDA approved. And I think this was a nice study and we should do a further study.

DR. LEE: I just would like to make a point. In order to label the medical device safe, it should have a higher bar and statistical significance. But we explained so that when a doctor tells your patient that there is this possible treatment that it may have probable benefit. But whether to tell the patient it is safe, that's a different thing, because probable benefit is something. That depends. Right now, we don't have this personalized medicine, but it's probable benefit. I think that's a different kind of bars.

DR. SNYDER: Does anybody want to make any comments before we vote?

DR. WITTEN: I just have a question regarding whether there are any other comments about the role of ATG in the findings for the study, if anyone else has a comment. I'd be interested to hear it before you vote.

DR. BISHOP: When Dr. Soiffer was making his presentation, I thought it was important to show the half life. The dose is small, and by the half life, by the time the graft would be infused, there would be calculated to be six percent ATG. Whether or not that would make a significant difference on the T-cell population, I think would be unlikely. And so, that's how I interpret it.

Now, the argument could be made whether you need that in the preparative regimen in facilitating graftment. I still think it's unlikely, based upon the data that was presented by Dr. O'Reilly. But I do agree that there's a high degree of heterogeneity within the preparative regimen, but that's my personal opinion. I thought it was an important issue to discuss, but my personal opinion, I don't think it makes that big a difference.

DR. SNYDER: Any other comments or questions before vote? We're going to be voting on question number two and I'll state it for the record. Is there reasonable assurance that the CliniMACS CD34 Reagent System provides probable benefit by obtaining a CD34 positive cell-enriched population for patients with acute myeloid leukemia in first or second morphologic complete remission undergoing a myeloablative preparative regimen. So you can vote now.

So as we did before, we'll go around the room and just briefly articulate why you voted as you did. And we'll start with Dr. Curt, even though he was non-voting.

DR. CURT: I would have voted yes for the all the reasons that were stated during the discussion and your opening comments.

DR. GEE: Yes, I'd agree and I'd add the fact that there were no failures into engraft, which is an associated risk with T-cell depletion. So I think those

two combined.

DR. TERRITO: I think I already stated my feelings and I voted yes.

MR. FLATAU: I voted no and I think I've taken enough time giving my opinion about that.

DR. HWU: I think Steve said it best that graft-vs-host disease is a horrible clinical complication and anything we can do to try to decrease that is important. And if we had infinite time and resources, yes, we could do a randomized study for everything. But how many more patients are going to have to get graft-vs-host disease before we let that happen? I think the benefit is very clear.

DR. COUTURE: I voted yes, because I think both not only was probable benefit shown, but I think there was also some evidence of efficacy, which I think is just sort of icing on the cake.

DR. GOLDMAN: I agree with the likely demonstration of efficacy. I thought the data in regards to suppression of chronic GVH was especially compelling. And the historic controls are recognizing their deficiencies and also if they were sufficient for the purpose here.

DR. GALANIS: I also voted yes for the reasons we discussed. I do share the concerns that other people have

expressed regarding the inappropriate data for CR2. But I will address the thing as far as the label discussion.

DR. SNYDER: I will do a summary at the end.

DR. AHSAN: So I voted yes and I think the word probable is fuzzy. I think the word benefit is arguably even more fuzzy. And so between the data and the comments from the clinicians that have firsthand experience with this disease, I think it swayed me to say yes, there is probable benefit.

DR. DAHLGREN: I don't really have anything new to add.

DR. LEE: I can see, it's clear there are probable benefits, although it may not be significantly differences. But that's my stand on, although this is probably benefit, but to claim it is safe for the device, it might need another year of data to confirm that.

DR. D'AGOSTINO: I've stated my views, I think, fairly clearly in the previous discussion. I do think that we're not following a P of .05 here. We're looking at the trends and the data, the sense of the data, the complications and so forth, and I think there is a probable benefit.

DR. NOGA: And I agree with what's already been said in terms of probable benefit.

DR. KELLEY: Same, I agree with my colleagues.

DR. BISHOP: I agree with my colleagues.

DR. SNYDER: Before I do a summary, Gail will simply read the final tally for the record.

DR. DAPOLITO: There were 15 voting members, 14 yes, one no, zero abstention, thank you.

DR. SNYDER: So with regard to probable benefit and question number two, the sense of the meeting I think is for those voting yes, they were persuaded by just how horrible a disease chronic GVHD can be, particularly chronic GVHD. And despite all the limitation to the historical controls, that there was probable benefit specifically to the patient in that certainly there was no worsening of GVHD, probably an improvement, and certainly an advantage of not needing chronic immunosuppressive therapy afterwards. That those voting no felt that perhaps a randomized trial should be performed, comparing various methods of T-cell depletion. Those voting yes felt that T-cell depletion has been around for a long time, that it's probably accepted and that it may simply not be practical or cost effective to do a randomized controlled trial on methods of T-cell depletion.

With regard to whether ATG was a cofounder, most of those commenting on this felt that it was a single low dose of ATG prior to the transplant with no follow-up, and that that probably did not play a confounding role in

interpreting the data. And there still remains some concern about how to interpret use of this even for probable benefit for CR2. Is that a pretty accurate summary of what we did?

So we're moving along pretty well. Now, I think we'll move on. The next three questions, and these are the remaining three questions, are non-voting questions. They're just for discussion. And it concerns the labeling and it will break up the labeling into some of the component parts that have been the topic of conversation pretty much all day.

So what I'll do is I'll read the preamble, and then I'll break them up into the three following questions, and each question has a discussant. And just to give you a sense of where the questions are going, question number three will discuss CR2 with regard to the label, question number four will deal with applicability to kids and question number five will deal with advice on how practitioners should be trained or instructed and assessed.

So the preamble is this. Please consider the issues surrounding labeling for safe use of the device. The labeling must define which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize clinical benefit and minimize adverse events.

Please address the following questions regarding product labeling.

The applicant has proposed the following indications for use, so this is the proposal for the label as it stands right now. CliniMACS CD34 Reagent System is indicated for processing allogenic HLA-matched hematopoietic progenitor cells-apheresis from a related donor to obtain a CD34 cell enriched population intended for hematopoietic reconstitution following a myeloablative preparative regimen, without the need for additional graft-vs-host disease prophylaxis in patients with acute myeloid leukemia in first or second morphologic complete remission.

The first question with regard to this is as follows. An analysis of outcomes for patients by remission status is show on the table that I think may be projected. Only seven of the 44 patients in study 0303 were in CR2 at the time of transplantation. For this very small population, although the GVHD-related outcomes favor 0303 patients, the relapse rate appears to be high and the hazard rates for disease-free survival and overall survival for the CR2 patients favor the control cohort.

The applicant has proposed to include both CR1 and CR2 in the indication for their device. However, the patients in CR2, the relapse rate is higher and the hazard rate for survival is greater, for patients in 0303 versus

0101. Please discuss whether the totality of the data support a reasonable assurance of probable benefit for patients in both CR1 and CR2, or if the label indication should be restricted to patients in CR1. And Dr. Noga is going to lead the discussion on this.

DR. NOGA: 303, 101, these two trials. If I were submitting these to the NIH as a grant, I might be looking for a new place to work, because you have your one study and you're comparing it against another study that is totally disparate. And eventually, they did work out a group of patients who fit the criteria they wanted. But I think this is going to confuse a lot of people as it did here. We're so used to looking at clinical trials, where you actually have a randomized comparison, and that it's hard to look at this as just another trial sitting there for you to look at as a comparison. It's just as easy to look at the whole literature and use that as a comparison. And I think this is what's causing a lot of problems.

I'll quickly dispense with the CR2 business. This is totally underpowered, and it wasn't meant to be powered in this way. It's a very small study. And as such, I don't put a lot into the CR2 data at all. But when you look at this trial, to me, it's really a trial or a study of the multi-center use of a selection column in allogeneic transplant. An allogeneic transplant is truly

translational medicine, and they want to use platforms that are standardized to get to the next level. And in this case, this can be that platform.

And I'm bringing that up because, yes, the GVHD rate is lower and that's very good. Is the relapse rate lower? Hard to say right now. But there again, transplanters just don't have a patient that relapses and then they go, I'm sorry, you've relapsed. They have other protocols, other trials, other graft manipulation, other things they do in addition to this, but they have to get the patient to survive and in good quality until they get to the next step.

So the reason I bring all this up is because I'm not too sure why this was separated into CR1 and CR2 to begin with. Why wasn't it just AML and CR? Because I think what's going to happen, this is why I asked some of the other questions earlier to the FDA. I think that what's going to happen is this gets out as saying CR1 and CR2, or it gets out as only CR1 as the indication. A lot of people are going to be trying to get around that, not in a bad way, but trying to get around it legally, to actually use this because you've finally got the first platform that you can actually use in this regard as the humanitarian device exemption.

So the way I look at this is that the CR2 data

doesn't bother me. What might bother me is how it's labeled in that if it's too restrictive, they're going to go around it anyway, and this is going to create more of a problem in the end.

DR. D'AGOSTINO: I don't think the data gives us comfort in terms of the probable benefit. But I do think that can't they handle this in the labeling that you describe what the data show, in fact, that the CR2 was at a very small number of subjects in this study, and the results are completely inconclusive. Certainly any kind of statistical manipulation interaction test and what have you just aren't going to be able to show us anything. So the way I feel in this area, you do exactly what Dr. Noga just said, that you talk about the trial, you talk about its success, and then, because we have the data in front of us, we have to sort out the CR1 and CR2, and the data in CR2 is very small and inconclusive in terms of its conclusions.

MR. FLATAU: So I guess I'm not quite understanding. Are you saying that we have so few patients in CR2 that we should let the label say it's indicated for CR2?

DR. D'AGOSTINO: No, I am saying I'm used to labels that describe studies and this would be described in the labeling that the CR2, the study with such and such, the CR2 has a very small number of subjects, and the

results are inconclusive.

MR. FLATAU: It seems to me that doctors will probably try to get around this and that would be good because they'll have to, all I know is what was here, get a device exemption or whatever and do another trial, and we'll get more data, because their numbers are so small in CR2, so we can get data on patients who are beyond CR1, and try to hopefully make more sense of it.

DR. D'AGOSTINO: Well, hopefully the FDA is going to ask the sponsor to follow the patients and have a database in terms of who's using the drugs, are using the device. I'm assuming that's going to be the case.

MR. FLATAU: (Inaudible)

DR. D'AGOSTINO: Well, again, this is a study that's before us and I was asking can somebody tell me, because it's obviously not my expertise that is CR2 so biologically different and what have you, are the subjects so compromised that you would expect a different result, and I haven't heard anybody give any sort of biological explanation for the results.

DR. NOGA: Actually, that's what I was going to comment on. CR2 patients can scare you. It depends on how they got to CR2. If they had a lot of therapy before that and relapsed, or they relapsed early, these can be really poor risk patients. You're allowed one thing to go wrong,

and one thing can go wrong and maybe you can get through it. But more than one thing goes wrong, and then you've got a major problem. And that's why a patient getting significant graft-vs-host disease really sets them up because they have a lot of other toxicities coming into the transplant from whatever they had before that.

CR2s are not like CR1s in many cases, so that's what's bad about them. That's just one reason why you see so many CR1s here. They made a decision to actually transplant patients in CR1 when they used to wait, because their outcome is better. So we already know CR2 outcomes. I don't want to label that for everybody, but in general, a lot of CR2 outcomes are worse.

MR. FLATAU: I was beyond CR1 when I was transplanted, so I realize that. I guess my point is not that they shouldn't be transplanted, but if they were transplanted on a trial, then we will get better data on their outcomes, and that would be a better way to inform what the decision should be made as far as this is a reasonable approach for CR2 or not, because the numbers, as you say, are just too small as they exist right now.

DR. BISHOP: You are not going to ask us to vote on this question? I would say the label should be restricted to CR1 based upon the data that was available to us for review.

DR. GALANIS: And I would echo this, I would second this, because at the end of the day, as Dr. Witten said, we have to comment on the data we have. No idea why data on seven patients were presented. But at the end of the day, looking at that, as underpowered as this, it comes down to do not harm. And it might be there there's more patients is going to show that this difference does not exist. It might be that it's going to show because the biology of the disease and the stage is completely different, that actually is going to prove true. But looking at this data, I simply cannot tell, and based on that, I would not be sure that I'm not harming a patient by giving them this option at CR2.

DR. HWU: As an immunologist, as Ralph said, is there any biological reason that it's going to be different in CR1 and CR2, CR3? I've been thinking, I can't really even hypothesis why one would be different than the other in terms of the need for peripheral T-cells and NK cells mixed into your graft, compared to having a more purified CD34 population. I don't know, I guess anything's possible, but I can't imagine that biologically or physiologically, there's going to be a difference.

I agree with Steve. I think that we should have made the label more granular than we had the data for. And so, really you can't interpret CR1 versus CR2, so I think

we should just not even mention it and just say CR.

DR. AHSAN: So maybe, just so I can better understand, can we flip the question, which is you can always opt not to use it for CR2. So the question is, are there people who do this routinely who would want to have the option to use it for CR2 patients, because by specifying CR1, we eliminate that possibility.

By including both, we leave it up to, and these are run of the mill physicians that are using this therapy to begin with. So they're fairly educated in the entire process, so we leave it to their discretion. I know that's not the way we need to make the decisions for the FDA, but just so I can better understand the status. So if a clinician could pipe in, as to whether or not they would want to have it as available to them for a CR2 patient.

MR. FLATAU: Two points, and one, I don't know anything about biology, but obviously patients in CR2 have had more treatment in this conditioning regimen and uses more intense, and so that maybe a reason for poorer outcomes. Of course, we have no idea because the numbers are so small. And second, I think it is good to have that option, but I guess my point is as I understand if, they do in CR2 and it's only indicated for CR1, it has to be on a trial, then we're sure to get the data collected and hopefully get published and we can get the answers.

Whereas if it's just up to the physician's discretion, well, maybe it gets reported, maybe it doesn't. And it's, I think, not as a sure path of getting it reported.

DR. SNYDER: Anybody else want to weigh in, make a comment?

DR. D'AGOSTINO: Isn't the FDA going to require pretty detailed follow-up on the patients, or is that not the case?

DR. WITTEN: There is no requirement. You mean any patient that receives the device?

DR. D'AGOSTINO: Well, some kind. I'm used to sort of an accelerated approval, and then you go on to more clinical here. So I'm trying to draw analogies there where you do want to know what's happening to this device in practice, and what kind of patients are getting it. The FDA is not going to have any requirement of that nature?

DR. WITTEN: Well, I can't tell you what we would or wouldn't do, but there's no requirement for HDEs that you do that. We, of course, always encourage sponsors who have HDE, if they want to work towards getting the full approval and getting additional data, we would do that.

DR. D'AGOSTINO: Because I think that Arthur's making that you do want to know how well this is working in that group.

DR. WITTEN: But I think really the original

comment that I made, which is we want a recommendation based on your best understanding of the data, probably is the best recommendation I can make. If something is or is not labeled, the effect that would or wouldn't have on getting future data. I think there are so many things that go into that, including the size of the population, what the sponsor or the clinical or academic community wants to do, what kind of study would get supported. There are just so many things that go into, that's why I just said I think what would help us the best is not to have a recommendation based on what might happen if we do one thing or another. But what do we know and what recommendation does that lead you to make? Although, I do completely recognize, appreciate and believe in the goal of getting more data for these kinds of situations. I think it's important.

DR. D'AGOSTINO: I do want to just also point, say for example, the last two entries on the table. We're looking at the 1.45 and the 1.352 as the hazard ratios. Those numbers are consistent with the device being twice as good as the control and up to four times worse. The competence intervals are just monstrous. They're very uninformative.

DR. SNYDER: Go ahead, Larry, and then we'll do Dr. Hwu and Dr. Territo.

DR. COUTURE: So it's my view that the purpose of

an HDE is to make a device available to physicians and clinicians who are treating patients who have very few of their options or want the option. And I see, as Angela said, it's a platform technology. There's no doubt that a lot of transplanners are going to want to use in this setting. And I think as we already heard, transplanners are going to use it in a setting, they want to. However, by hook or by crook, they're going to get around a CR2 limitation if they feel it needs to be used in CR2 or if it has potential, has promise in their own experience in their own hands in CR2. I think it's going to happen.

And I think putting additional restrictions on it just doesn't make a lot of sense, and just seems to be very difficult to enforce. And it makes more sense just to ignore that whole issue, put it out there for CR1 and CR2, or just indicate it as an NCR was a suggestion. But I do think that since it's an HDE, that the label should be very clear on what the basis was for having approved that HDE. And in this particular case, it was reasonable data that suggests was probable overall benefit, but that that data is kind of not so definitive for CR2. That's not the words you would use, but the idea is to put some caution in the label, so that clinicians know that it's not just a black and white issue for CR2 and they should think about it very carefully in terms of what other options are available for

the patient. But I would give them the ability to use this device as a platform for both CR1 and CR2.

DR. HWU: Arthur brought up an interesting hypothesis that possibly a stronger conditioning regimen is not as well tolerated in CR2 or CR3, compared to CR1 patient. But I just want to make it clear, this is for the device approval, and people can use any conditioning regimen they want with this. It's not linked to the conditioning regimen in 303, is that correct?

DR. TERRITO: I just wanted to make a point that we've been looking at the results separately for the CR2, but I think it's the risk and the benefit that has to be looked at in the CR2 and that the numbers are so small that it's hard to put a definite benefit and risk number on it. So I would have problems approving it for the CR2.

MR. FLATAU: So I guess I don't understand this labeling concept. This is a device that the patient is never going to see. And so, if the label is on the device, they're never going to see the label. How is the information going to get to the patient?

DR. WITTEN: Well, the label will provide information to the physician, who hopefully does speak to their patient. And I think generally there are patient information books. Mr. Stevens, maybe you can comment on that. I know we've put out a summary of safety and

probable benefit on the web. But I think often, there are specific patient labeling, and that is something you could recommend. And there is a brochure that gets handed out.

DR. STEVENS: It is typical for devices, in addition to the package insert and the user manual, it's certainly a possibility to have a patient label or a patient brochure.

MR. FLATAU: I guess I don't know what other devices are out there, but it seems unusual for a device that a patient is never actually going to see, maybe the donor sees. And I think I would strongly urge that there be a brochure for patients, and I don't know what FDA can do about it.

DR. WITTEN: That is something that we could specifically request.

DR. SNYDER: Probably something like that could be included in patient information about how they get treated for their leukemia or something like that. A lot of things that patients never see have labels. I think label is maybe a misnomer. It's not literally a label that goes on there, it's the booklet that goes along with the machinery or the drug or something like that.

DR. NOGA: That is kind of what I was going to say, is if you come into a hospital and you have different procedures done, you name it, including pacemakers and

everything else, all of those have labels and things that the patient never sees. They may be a booklet explaining, be good to your pacemaker or whatever, and it goes through the different things, and they get their serial number for their pacemaker and stuff like that.

But they actually are never sat down and the studies are reviewed or anything else. Not saying right or wrong, but I think that's the kind of thing we're dealing with here. This is a device and they generate this official label. But then, there may be other ancillary things that go along with it or might be planned to go along with it.

DR. SNYDER: Any other comments or points to make about this particular question concerning the labeling for CR2? Let me try to summarize the sense of the meeting, with regard to this particular question. There was a sense that the label should actually indicate the rationale for this device being an HDE. And that a lot of the concern concerning CR2 was based on comparing studies 0303 with study 0101, which was viewed like comparing bananas with coffee. And that this was no better than a historical control that was underpowered with small numbers for CR2, and that probably no better than actually looking at the literature, what seemed to be evident was that the rate of GVHD was lower and we're unable to know whether the relapse

rate was really lower, that potentially that the quality of the survival may have been better.

There was some concern that maybe there was no real rationale, including a biologic rationale for dividing CR into CR1 and CR2, and that maybe the label should actually not make that distinction, and simply talk about CR. That if one makes the labeling too restrictive, it could eliminate patients or physicians who wish to use it and may do so unnecessarily. That the label could say something, if one does elect to divide CR into CR1 and CR2, which some members felt was unnecessary. But if one elected to do that, it could say something like of probable benefit and safety in CR1, and inconclusive for CR2, if that distinction is to be made at all.

But that it maybe better to simply use CR and leave the decision up to the physician and the patient, so that they at least have this as an available option. There was a lot of feeling that there should be, no matter what is decided, that they should be very careful follow-up going forward, if the device receives HDE designation. Is that a fair summary?

DR. GALANIS: I think that that does not capture the thought that a number of members felt that the indication should be restricted to CR1. Because the committee was in some ways divided.

DR. SNYDER: What about having the label saying something like, as Dr. D'Agostino and Dr. Nago proposed that, if one does make the distinction between CR1 and CR2, that you assert that there is probable benefit and safety in CR1, and inconclusive for CR2, or not even mention CR2 simply?

DR. NOGA: That would be their preview of course. The FDA makes the final decision.

DR. SNYDER: The next question for which the lead discussant will be Dr. Territo is as follows. All of the patients in study 3030 (sic) were adults, and there are no data available regarding the safety of the use of this advice for treatment of children with AML. Please discuss whether there would be any limitations in generalizing the results of study 0303 to a pediatric population.

DR. TERRITO: Well, I think the main conclusion is going to be that we don't have any data to tell us one way or the other. I think it's unlikely that there would be increased risks as far as engraftment in children. However, the overall risk of GVH is a little lower, and so I think it would be unclear as far as the risk-benefit ratio in children. And I think with the data we have here, that we really can't make recommendations for children.

DR. SNYDER: How do you think the label should read then, just the way you stated it or actually preclude

children?

DR. TERRITO: Well, I think since we don't have any data in children, that we would have to preclude children.

DR. HWU: I think if we don't have data in children, we should just leave it out, because we don't have data in children. We don't have data maybe in Asians, we should leave out Asians. I would hope not. So I think that if we don't have the data, that we should leave it out and not mention it. And I think physiologically, I'm trying to think about T-cells and the CD34 cell has to go to the thymus to develop into a peripheral T-cell. If anything, a child would have a better thymus and a better ability to take a stem cell and make it into a T-cell and not really require any peripheral T-cells to fight infections. So if anything, it might be better tolerated in a child. Rob Gress has some data, looking at T-cell recapitulation in children versus adults in looking at age, that would suggest that. So I think if anything, it might be better, but we don't know, so I think we shouldn't mention it.

DR. SNYDER: So not mention it or simply say there was no data available on children? Not even mention the word pediatrics one way or the other, or just say no data available in children and Asians?

DR. HWU: We don't have any data in children. Maybe we should say we don't have any data in Asians.

DR. SY: Well, it brings up the interesting thing, as I recall, there was an over-representation of females compared to males in the same study, as I recall. So I guess it gets to the point where you're mentioning that we should simply say, where our area of ignorance is, no data on kids, period.

DR. HWU: That would be reasonable.

MR. FLATAU: I agree with Dr. Territo that we should preclude children. I think AML is treated differently in children versus adults, so we have no data, so we can't say what the results are. In general, the recommendations for transplants are somewhat different in pediatric AML patients versus adult AML patients. I think unlike Asians, Asians are treated the same as everyone else, as far as I know.

DR. O'REILLY: As a pediatrician, I have to say that in regards to what you were saying, you are correct. If a patient has a sibling in a kid circumstance, the child would receive the transplant, period. There is no question about the child receiving the transplant. Number two, the incidence of chronic graft-vs-host disease in children is as bad as it is in adults after the age of five. And it is a really horrific disorder. And so to deny children would

be inappropriate.

I think the idea that Evan suggested, mainly saying we do not have data in children is fine. But to preclude the use of this device in children, yes, I would fine to be somewhat abhorrent. Just to also be sure everybody recognizes, T-cell depletion was initially applied to children, not to adults. It was applied to children with severe combined immune deficiency in 1980 when we did that. And I have a useful thing to report to the group in all of that series, since that time, we've done over 100 and we're now reviewing over 600 kids done nationally who have received T-cell depleted transplant from a mother or father across the haplotype. And at the present time, over 70 percent of the people who received that are still alive and doing well. And also, the incidence of GVH in that population has been extraordinarily low.

So the idea that the T-cell depletion has quote unquote been around, never caught on, I'm reminded of the great song of Paul Simon where he talks about these are the days of miracles and wonders, the boy in the bubble. Because of T-cell depletion, there are no boys in the bubble. It has not existed since 1980. So that is a national, multiple trial that's now being conducted by a study in a consortium through the NIAID.

The last thing I would just give as a vignette, and I recognize it's unfair, but a child with AML who was six years old received a transplant for AML in a secondary remission. This child got a secondary graft because of the fact that he quote unquote relapse. He did relapse and he got an unmodified marrow graft. He then went on to develop severe chronic graft-vs-host disease, which left him unable to move and unable to eat, except through a tube. And his remark to his doctor was very clear. I recognize that I once had leukemia, I'd rather have my leukemia than my chronic graft-vs-host disease. I understand that that's unfair, but I also feel that it's horribly unfair if kids are denied this possibility, just based on the idea of no data. That's all.

DR. GALANIS: I will agree with you on that there are data in children, which is inconsistent with the labeling for a lot of drugs and other things we do in oncology.

DR. LEE: I always read all the medicine my doctor prescribed to me. I look at all the clinical trial information. So I think this should be a scientific statement, right, that the study was based on a clinical trial on adult and it shows probable benefit. And just say no study was done on children. But that does to preclude the use to children. This is a scientific, not a

sentimental statement.

DR. TERRITO: I would like to rescind my original, and I agree that I would just limit it and say that there's no data in the children.

DR. SNYDER: I can just add as a neonatologist, there's not a single drug that we use in the newborn intensive care that indicates that it can be used in a pediatric population, certainly less than a year of age. Not a single drug, but that's how we function.

DR. NOGA: I would just add that really the NIH, FDA, we're all under mandate actually to try to get kids and pregnant women and other groups like this on studies, because they're not. They're usually excluded, especially as drugs are coming on the market and things. And in this case, I might be wrong here, you can tell me because you're pediatricians and that. But if I remember correctly in the United States, which is what we're talking about now, almost all children with leukemia or whatever are actually going on clinical trial, so that this would not be done without capturing the data. It's not like it would be done by a pediatrician in the community. It would be done at a transplant center that's experienced with pediatric oncology. And so, these would be done on a clinical trial, as far as I know. So that does make a difference.

DR. SNYDER: Does anybody else want to weigh in

on this particular question before I summarize it? With regard to how the label should deal with the pediatric population. The fact is, there is no data on kids. There was a discussion as to how to broach that fact in the labeling. There was a sense that to deny kids would really be unacceptable given how bad GHVD is, and that T-cell depletion was actually first developed in the pediatric population. And it may be best to simply be honest and say there is simply no data on children, but not actively preclude kids in the labeling. Is that a pretty fair representation?

We're moving into the last question. And for this, we have two discussants, first, Dr. Kelley and then Dr. Gee. And I'll read the question, and this maybe gets to a little bit of Steve was alluding to about who actually will be doing this.

So Miltenyi proposes to supply device users with the instructions for use outlined in the ClinIMACS user manual, provide training by certified Miltenyi employees, and maintain a technical support hotline as resources pertaining to correct operation of the device. The table that I think is in your handout, and also maybe projected, provides a summary of the data contained in appendix B of the FDA briefing document, that depicts the attributes of CD34 plus enriched hematopoietic progenitor cells obtained

after processing donor apheresis with the CliniMACS CD34 Reagent System at clinical sites participating in study 0303.

The questions being posed are the following two, and we'll take the two questions together in terms of discussion. Please discuss the adequacy of the user instructions and device performance data provided to demonstrate end users will be able to use the CliniMACS CD34 Reagent System, if approved, for processing HPC-A collected from an HLA-matched related donor for recipient hematopoietic reconstitution. Please discuss any recommendations for establishing device performance criteria. So is the training adequate, and then how do we follow performance? Dr. Kelley?

DR. KELLEY: So regarding the adequacy of the user instructions, I find them to be sufficiently comprehensive to give the end user the instructions that they need to perform a successful selection. Regarding the device performance data, I think that we have evidence that the sufficient CD34 dose can be obtained from two apheresis products, which is very reasonable. And that the final product has excellent purity. I think that the percent yield is very variable, and it's up to hopefully centers as they move forward to evaluate what in their center may be affecting that. Is it their mobilization regimen, is it

the amount of blood volume that's processed, more understanding of what the individual and combined contaminants, so to speak, in the products are and how they may affect the yield. However, I don't think that the fact that it's so variable at this point would be a confusing element to the end user.

My recommendations moving forward to evaluate the device performance would be that, first of all, not only is there onsite training by the Miltenyi personnel, but that that training would include using a bona fide, mobilized, apheresis product, so that the end user can go through the whole process and feel confident that they got a good CD34 selection. And who pays for that? I don't know. It's an expensive product to buy.

And also, one would think that this is going to be done in academic transplant centers, in laboratories that are accredited and are following good laboratory practices with good quality plans, and that the machines aren't going to show up in doctor's offices in North Dakota. So I think that we can assume that under those circumstances, that there would be additional validation done at the center. So it wouldn't just be training when the Miltenyi folks come, but the laboratory director and the quality assurance team would insist that the procedure be validated to show reproducibility. So those are my

comments.

DR. GEE: In general, I agree with what Dr. Kelley has said. I do have a couple of comments about the instruction manual in general. There are two points specifically that I think need to be reemphasized. One is that the instructions for handling the material that comes off the device are fairly basic in that they tell you to remove the cells from the device and to introduce certain assays on them. About 30 pages head of that, it tells you that the cells are not to be infused in the buffer in which they are collected off the machine. So I believe that that should be repeated at the time that the cells come off the machine, that the instructions should be to transfer them into a new feasible grade buffer.

The second thing which I raised slightly earlier, is that there as has been pointed out some variability in the yield. And you saw in the trial that one of the yields was as low as 29.9 percent. And in our hands, using this device, we have seen a considerable variation in the yield from the device, related to a lot of the points that Dr. Keever-Taylor has raised. And that is why I raised the point about the gamma globulin in the buffer. That does block a lot of non-specific binding, and I think it does improve the yields on the machine and the reproducibility.

And the instruction manual points this out, but

again, it is pointed out at a point that is divorced from the instructions on the use of the machine. It indicates that if you have problems with purity and yield, you should have at least 30 percent analogous plasma in the collection, or that you should supplement it with gamma globulin. And I think that needs to be moved closer to the point where you're instructing the person how to use the machine, not in the troubleshooting section.

There were certain other points in the manual where there were things that were difficult to read, and I realize this is only a draft. But I would encourage the things like the screen shots are almost impossible to read in some of the things, and I think that needs to be addressed.

There was also the issue about the use of the number of reagent kits, depending on the size of the apheresis product. And I think that is in there, but it needs to be almost emphasized more strongly, right in the middle of the instructions as opposed to in a box to one side of the instructions. So those are little things.

I think the manufacturers now have enough experience in using this to give the end user some indication of what the yield and what the purity should be. I think that, as has been said today, most people feel that the purity is about 50 percent and the yield is in excess

of 70 percent, but that is not stated in the manual, and I think there's enough experience to give some indication as to what those expected values should be, so that you know when the machine has not performed up to expectations.

And then I think finally, the other point is in this particular indication, you're being told to do preimposed leukocytes counts, CD34 and I think the analysis on the negative fraction is important in order to account for all of the cells and to be able to show that the numbers add up. And then, secondly, we've talked about T-cell depletion and it isn't recommended that you do the T-cell content of the final product. And if it's going to be used in this indication, that is one of the indicated uses is to possibly reduce T-cells. So I would recommend that in applications where T-cell numbers are important, they need to be part of the evaluation and the instruction manual.

DR. SNYDER: Dr. Bishop?

DR. BISHOP: I just want to echo a lot of what was said. But I also think it's important, the data that we reviewed today was based upon a clinical trial which mandated a minimum of 2 million CD34 cells and then less than one times ten to the fifth CD3 cells. But in order to obtain that minimum value, which promotes engraftment, you have to have a starting product. And I don't think it's

part of my questioning of Dr. Taylor, is I think you need to have a recommendation that you start with either, and I was going to suggest 5 million cells pre-depletion, because again, based upon a mean value of 66 percent with a standard deviation of 20. And again, as Dr. Gee pointed out, that variability all the way down to 30, assuming at a minimum of 40 percent yield, that 5 million cells preselection would generate 2 million CD34 cells. I don't know how they're going to feel about that, but that's how I would set up my SOP at my institution.

DR. SNYDER: Others want to comment on this? Is everybody running out of steam, I guess? Yes, Dr. Kelley?

DR. KELLEY: What would be the fate of that product that was collected, that had less? Perhaps hold it over and do another collection the second day and pool them?

DR. BISHOP: That is an excellent question. What about the patients who you achieve less than 2 million cells, and I think they have to be a recommendation for additional apheresis on the patient. Either that or if the patient couldn't be collected any further, due to institutional guidelines, I think I would be reluctant, unless it's determined that the patient has already gone through the conditioning regimen and you're waiting for the cells. Now that the various scenarios are playing out in

my head, but again, I would sit for a target level of over that amount. It would depend upon the clinical situation. I'm used to freezing everything, to make sure I don't have that problem. But there's people who infuse fresh, so I understand.

DR. KELLEY: I think the efficiency of the selection is much better on a fresh product than a frozen product.

DR. SNYDER: Is anybody else going to make a comment on this question? I guess just to summarize the scent of the meeting with regard to both training backup and assaying performance. I think there was a sense that basically the instructions, training and the backup provided by the sponsor is adequate, though there was a sense that, as part of the actual face-to-face training and tutorial, it might be useful to really pinpoint particular aspects that could be pitfalls and not just simply troubleshoot. And that might be how to actually reconstitute the preparation before giving it.

There was even a sense that maybe providing users with a test batch first, so that they could see what the gold standard is, might be useful. That this equipment, this device, should only be used by those that are experienced in bone marrow transplantation, and do this routinely, not just a doctor's office in North Dakota.

And then, it would be good to follow various performance criteria. And although it appears that the observed variability were not really a problem, it still would be good to keep track from center to center a degree of mobilization, starting blood volumes, particularly so that one doesn't overload the system going in, the amount of blood volume processed, the degree of purity, the identity of contaminants, not only preimposed lymphocyte counts, but also analyzing the negative fractions to see what that population is, so that all cell types are accounted for, and just have a really good sense of both the blood product that is going into the patient and that which is being actively excluded from the patient. Did I miss anything, or anything else we should add?

DR. KELLEY: You said something about reconstitution before starting, and I wasn't sure what that was.

DR. SNYDER: I was just reflecting what you were saying about adding plasma.

DR. KELLEY: Okay. So providing something to inhibit non-specific binding?

DR. GEE: It is in there, in the troubleshooting. It just needs to be, I think, moved into the actual instruction section.

DR. SNYDER: I think that Dr. Gee was thinking

that being proactive, and in terms of showing users how to use this, rather than simply troubleshoot in retrospect.

DR. KELLEY: And then just one other clarification, you said to limit the blood volume that goes onto the machine that should be the cell count.

DR. SNYDER: That's what I meant, yes, sorry.

Anything else that we can provide for you, Dr.

Witten?

DR. WITTEN: No, I'd like to thank the committee for this discussion today.

DR. SNYDER: I guess we did our jobs, thank you very much. We're adjourned.

(Whereupon, the meeting was adjourned)