



FDA BRIEFING DOCUMENT
Cellular, Tissue, and Gene Therapies Advisory Committee

September 23, 2011

BH110018
CliniMACS[®] CD34 Reagent System
APPLICANT: Miltenyi Biotec

***Disclaimer:** The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the CliniMACS[®] CD34 Reagent System application to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation; instead, it is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.*

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AABB	American Association of Blood Banks
7-AAD	7-Aminoactinomycin D
AML	Acute Myeloid Leukemia
ATG	Antithymocyte Immunoglobulin
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
CI	Confidence Interval
CIF	Cumulative Incidence Function
CNS	Central Nervous System
CR 1 or 2	Complete Response First or Second
DFS	Disease-Free Survival
EBV	Epstein-Barr Virus
EMBT	European Group for Blood and Marrow Transplantation
FACT	Foundation of Accreditation of Cellular Therapy
GVHD	Graft-vs.-Host-Disease
GVL	Graft-vs.-Leukemia
HDE	Humanitarian Device Exemption
HLA	Human Leukocyte Antigen
HPC-A	Hematopoietic Progenitor Cells-Apheresis
HPC-C	Hematopoietic Progenitor Cells-Cord
HPC-M	Hematopoietic Progenitor Cells-Marrow
HUD	Humanitarian Use Device
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
ISCT	International Society for Cellular Therapy
ISHAGE	International Society of Hematotherapy and Graft Engineering
JACIE	Joint Accreditation Committee-ISCT and EBMT
NHLBI	National Heart Lung and Blood Institute
NK	Natural Killer
OS	Overall Survival
PMA	Premarket Approval Application
PTLD	Post Transplant Lymphoproliferative Disorder
SOP(s)	Standard Operating Procedure(s)
TCD	T-Cell Depletion
TMOP	Technical Manual of Procedures
TRM	Transplant-Related Mortality
WBCs	White Blood Cells

1. INTRODUCTION

Miltenyi Biotec (hereafter referred to as “Miltenyi” or the “applicant”) has applied for a Humanitarian Device Exemption (HDE) to market its CliniMACS® CD34 Reagent System. The application (BH110018) is being reviewed by the Office of Cellular, Tissue and Gene Therapies within the Center for Biologics Evaluation and Research of the Food and Drug Administration. This application is the subject of the advisory committee meeting of September 23, 2011.

A humanitarian use device (HUD) is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. A device manufacturer’s research and development costs could exceed its market returns for diseases or conditions affecting such small patient populations, and the HUD provision of the regulations provides an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations.

An HDE is the means of obtaining marketing approval for an HUD. An HDE application is similar in both form and content to a premarket approval (PMA) application, but the applicant is exempt from the requirement to demonstrate effectiveness at the level of evidence required for a PMA. Specifically, an HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, 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.

2. PURPOSE OF THE MEETING

The applicant has proposed the following indication for use of its device:

“Humanitarian Device: Authorized by U.S. Federal law for processing allogeneic HLA-matched

hematopoietic progenitor cells-apheresis (HPC-A) 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 (GVHD) prophylaxis in patients with acute myeloid leukemia (AML) in first or second morphologic complete remission.”

HPC-A is a heterogeneous population of cells that includes the purported stem cell, as measured by CD34 expression, that is responsible for hematopoietic reconstitution as well as repopulation of lymphocytes that may mediate cellular immune reactions. In the setting of allogeneic related HPC-transplantation, mature lymphocytes derived from the donor may provide the recipient some protection from opportunistic infection and may also be responsible in part for eradication of the recipient’s leukemia, a phenomenon known as the graft-vs-leukemia (GVL) effect.

Donor lymphocytes may also recognize recipient tissues as foreign, and the resulting reaction to the recipient antigens is manifested as GVHD, a potentially fatal disorder presenting as skin rash, enteritis and hyperbilirubinemia. To prevent GVHD from occurring, recipients of allogeneic HPC-A also receive immunosuppressive drugs which themselves are associated with additional toxicities and risks for infection.

The CliniMACS[®] CD34 Reagent System is a cell selection device used to obtain a CD34+ cell enriched population intended for hematopoietic reconstitution. The process of CD34+ cell selection results in simultaneous passive depletion of donor lymphocytes, potentially obviating the need for immunosuppressive drugs to prevent GVHD. At the same time, excessive depletion of donor lymphocytes from the HPC-A, could trigger an increase in the risk of infection and leukemia relapse in the patient. Reliability of device performance with respect to positive selection of CD34+ cells in conjunction with passive depletion of CD3+ donor lymphocytes is important to the recipient’s clinical course. Inadequate device performance resulting in damage to CD34+ cells or their poor recovery following HPC-A processing could impair hematopoietic reconstitution in the recipient. Further, there may be additional risks posed to the donor when added apheresis collection procedures are necessary to compensate for poor device performance

in order to ensure an adequate CD34+ cell dose is available for transplantation. It is also possible problems with device performance that compromise overall depletion of CD3+ donor lymphocytes could place the recipient at increased risk for developing GVHD.

This briefing document summarizes information FDA believes will prepare the committee to give advice regarding interpretation of the results of a clinical trial using the CliniMACS[®] CD34 Reagent System to process HPC-A from related donors for recipients being treated for acute myelogenous leukemia. The advice of the committee will assist the Agency in determining whether or not the data support a reasonable assurance of safety and probable benefit derived from use of the device.

3. REGULATORY HISTORY

3.1 PRIOR MARKETING HISTORY

The CliniMACS[®] CD34 Reagent System has not been previously approved for marketing in the US. In Europe the components of the CliniMACS[®] system are CE-marked medical devices. According to information provided from Miltenyi, approval for CE marking of the CliniMACS[®] CD34 Reagent System for Europe was granted by TÜV Product Services of Munich, Germany for CE marking of the CliniMACS[®] CD34 Reagent System for Europe in 1997. Since that time the CliniMACS[®] CD34 Reagent System has been approved and marketed in over 16 other countries worldwide.

3.2 CLINICAL INVESTIGATIONS

Data from a Phase 2 clinical study, BMT CTN 0303, conducted by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) are provided in support of this HDE application. The study was performed under Investigational Device Exemption (IDE) BB-IDE 11965, sponsored by the National Heart Lung and Blood Institute (NHLBI). The IDE submission was received by FDA on October 1, 2004.

During an IDE pre-submission teleconference involving FDA, NHLBI and Miltenyi representatives conducted May 12, 2004, Miltenyi expressed its intention to use data collected from the proposed Phase 2 study carried out under IDE 11965 to support filing of an HDE application. The CliniMACS[®] CD34 Reagent System received HUD Designation (HUD Request #04-0146) on June 24, 2005.

The IDE clinical study, BMT CTN 0303 “*Magnetic-Activated Cell Sorter (CliniMACS, Miltenyi) for CD34+ Selection of Granulocyte Colony-Stimulating Factor Mobilized Allogeneic-Related Peripheral Blood Stem Cells; Total Body Irradiation, Chemotherapy, Anti-thymocyte Globulin (Rabbit)*” is a single-arm, open-label Phase 2, multicenter study designed to determine the feasibility of measuring outcomes for a T-cell depleted transplant arm in a planned prospective randomized trial comparing CD34+ cell selection and passive T- cell depletion versus unmodified peripheral blood hematopoietic allografts obtained from healthy HLA-matched sibling donors. The results of the study were submitted to support an indication for treatment of acute myeloid leukemia (AML) in first or second morphologic remission.

Upon accrual of a total of 47 patients to BMT CTN 0303, Miltenyi requested a Type B/Pre-HDE meeting with FDA which was conducted December 18, 2009. During that meeting, FDA suggested that Miltenyi propose a comparison between results from the BMT CTN 0303 study with results from a similar study that did not involve CD34+ selection and passive T-Cell depletion (TCD). A study was selected, BMT CTN 0101, that provided a contemporaneous patient cohort for comparison. Miltenyi drafted DAP 1001-34, a data analysis plan for comparing data from the two studies, and submitted the plan to FDA for review. Data analysis was performed in accordance with DAP 1001-34 and the results have been submitted in support of Miltenyi’s HDE application[†].

The Miltenyi HDE application, BH110018, was filed by FDA on April 21, 2011.

[†] The investigators have submitted the clinical outcome results and cell processing data from these studies for publication. The former are currently under review for publication. The latter are pending publication in *Biology of Blood and Marrow Transplantation* (in press).

In addition to patients enrolled in the BMT CTN 0303 clinical study conducted under BB-IDE 11965, approximately 2850 CliniMACS[®] CD34 Reagent Kits have been used to treat patients enrolled in FDA-sanctioned clinical studies for various indications being carried out under either IDE or Investigational New Drug (IND) applications.

4. DEVICE DESCRIPTION

4.1 OVERVIEW OF THE CLINIMACS[®] CD34 REAGENT SYSTEM

The Miltenyi CliniMACS[®] CD34 Reagent System used in the clinical study conducted under BB-IDE 11965 is designed to select CD34 antigen positive hematopoietic cells from a heterogeneous leukapheresis product. The isolation process uses a magnetic bead coated with an anti-CD34 monoclonal antibody together with microprocessor-controlled Magnetically Activated Cell Sorting (MACS) to isolate CD34 antigen expressing cells from the starting leukapheresis product. The reagent system is comprised of 4 critical components:

- CliniMACS[®] CD34 Reagent
- CliniMACS^{®plus} Instrument
- CliniMACS[®] Tubing Set / Tubing Set LS
- CliniMACS[®] PBS/EDTA Buffer

These 4 critical components are packaged separately, and are not configured into a finished device assembly until reaching the ultimate end user at the cell processing laboratory associated with the clinical transplant center. It should be noted that the instrument, tubing sets and buffer are not dedicated solely for use with the CliniMACS[®] CD34 Reagent System. In the US, end users are using the instrumentation and disposable components in conjunction with other Miltenyi proprietary monoclonal antibody-based selection systems under INDs or IDEs.

In the Phase 2 BMT CTN 0303 clinical study conducted under BB-IDE 11965, the CliniMACS[®] CD34 Reagent System was used at eight participating clinical centers for processing donor HPC-

A products to enrich for CD34+ hematopoietic progenitor cell content and passively deplete allo-reactive CD3+ T-cells. To substantiate its position that consistent performance may be expected with respect to processing of donor HPC-A, Miltenyi submitted to the HDE information on instructions for use outlined in the CliniMACS[®] user manual, training of end users provided by certified Miltenyi employees, and the data collected for HPC-A products processed at the clinical sites participating in the BMT CTN 0303 clinical study. The device performance data from the clinical study, evaluated as the reproducibility and consistency observed in characteristics of the cells obtained following HPC-A processing with the CliniMACS[®] CD34 Reagent System, will be addressed in section 4.4. First, we provide an overview of the instructions and training provided by Miltenyi to users of the device (sections 4.2 and 4.3).

4.2 INSTRUCTIONS FOR USE

Instructions provided in the CliniMACS[®] User Manual describe the process for performing CD34 cell selection of a donor leukapheresis product using the CliniMACS[®] CD34 Reagent System ([Appendix A](#)). Details supplied in the user manual focus primarily on technical aspects of device operation. The instructions for use provide limited guidelines and recommendations concerning assessment of the pre-selection leukapheresis product leaving these decisions to the discretion of the end user cell processing laboratory. With respect to the initial leukapheresis product, the user manual states that the following parameters must be determined:

- Total number of leukocytes (Normal Scale Reagent: 60×10^9 WBCs / Large Scale Reagent: 120×10^9 WBCs)
- Percentage of CD34 positive cells
- Total number of CD3 positive cells
- Viability

The user manual does not include recommended values or ranges of values for the percentage of CD34 positive cells, total number of CD34 positive cells, and viability of cells in the starting

leukapheresis product. Miltenyi states in the user manual that other tests might be required depending on the intended use of the cells, such as T-cell enumeration, however, once again this is left to the discretion of the end user. Despite stating the need to evaluate initial leukapheresis products for the parameters listed above, the user manual does not provide specific instruction as to how these assessments and their results impact operation of the device and overall cell selection performance. Establishing criteria for determining whether or not a donor leukapheresis product is suitable for selection using the CliniMACS[®] CD34 Reagent System is the responsibility of the cell processing lab.

The CD34 cell selection performed using the CliniMACS[®] CD34 Reagent System involves two phases: cell labeling of antigen positive cells (Phase I) with a primary capture antibody and the automated cell selection process (Phase II). Step by step instructions are provided for each of these processes, which are summarized briefly below.

Phase I - Magnetic Labeling

This step involves combining the CliniMACS[®] CD34 Reagent with cells collected from the donor by apheresis. The CliniMACS[®] CD34 Reagent is an antibody conjugate of a Class II murine IgG1 monoclonal antibody (mAb) to human CD34 antigen (AC101 Ab) that is covalently linked (chemically conjugated) to dextran beads that have an iron oxide/hydroxide core (iron-dextran complex; about 50-100 nm in diameter) and are superparamagnetic.

For the magnetic labeling step, the apheresis product is incubated with the CliniMACS[®] CD34 Reagent during which time the CliniMACS[®] Reagent antibody selectively binds to cells expressing the target cell surface antigen, CD34. The mixture is then washed in CliniMACS[®] PBS/EDTA Buffer supplemented with human serum albumin which is provided by the user. Following centrifugation, the resulting cell pellet is re-suspended in the CliniMACS[®] PBS/EDTA Buffer and the antibody-labeled cells are ready for selection.

Phase II – CliniMACS® Run

Following incubation with the CliniMACS® CD34 Reagent, the bag containing the cell suspension is attached to a sterile CliniMACS® Tubing Set. Following a series of automated priming steps, the cell suspension is passed sequentially through a blood filter to remove any aggregated cells and then through the first CliniMACS® Column, which serves as a pre-column separation step to eliminate cells that bind non-specifically. The labeled cell suspension then moves through another CliniMACS® Column of the CliniMACS® Tubing Set positioned within the magnetic field of the CliniMACS® Plus Instrument. The antigen-expressing cells, to which the CliniMACS® CD34 Reagent has been bound, are retained within the column matrix in an automated, continuous flow separation system by the CliniMACS® Plus Instrument. All other cells (i.e. those that are not bound to the magnetic bead-Ab conjugate) flow through the column and are collected in the CliniMACS® Tubing Set “Negative Fraction Bag”. The CliniMACS® Column, in which the antigen-expressing cells are retained, is automatically washed with the CliniMACS® PBS/EDTA Buffer. The magnetic field is withdrawn from the column and the antigen positive cells are eluted into the “Cell Collection Bag”.

With respect to the population of cells collected post-processing with the CliniMACS CD34 Reagent System, the user manual states target cells must be examined for the following parameters:

- Total number of leukocytes
- Viability and total number of CD34 positive cells
- Purity and recovery of CD34 positive cells.

The user manual also recommends that the total number of leukocytes and the viability of the non-target cell fraction be determined. We note that this latter value was not included in the cell processing data collected during the BMT CTN 0303 clinical trial. Miltenyi emphasizes that the above panel of tests serves as a representative example of testing to be performed, and stipulates other tests should be conducted based on the intended use for the processed cells.

Although Miltenyi cautions against giving the patient too few CD34+ cells or too many CD3+ T-cells, the user manual does not provide recommended values or ranges of values that define the expectations a user should have for how the device will alter the properties of the starting cellular material. The end user is left to determine what constitutes appropriate device performance with respect to completion of a successful cell selection procedure using the device. No guidance is provided as to what the user should expect in terms of recovery and purity of CD34+ cells, degree of passive depletion of CD3+ T-cells or other pertinent parameters.

With limited instructions pertaining to the expected results for the quality of the CD34+ cells selected and overall performance of the device for any given run, the end user is left to determine independently whether or not the device performed as expected.

4.3 TRAINING OF END USERS

End user training is important to ensure device operation and performance consistency. The CliniMACS[®] CD34 Reagent System is intended to be used by healthcare professionals operating within a healthcare facility under normal laboratory conditions. Miltenyi requires end users to provide verification of accreditation, and be in good standing with the Foundation of Accreditation of Cellular Therapy (FACT-JACIE) or American Association of Blood Banks (AABB), and document Institutional Review Board (IRB) oversight in writing. Initial instrument setup includes installation, operation and performance qualification conducted by Miltenyi. Certified Miltenyi employees provide end user training using the Training Checklist, a Miltenyi corporate document, to ensure that all areas of training have been covered. Upon completion of instruction, a training assessment and CliniMACS[®] Training Certificate are provided to each training participant for inclusion in their personnel training records. Emergency technical support is available via a call center Hotline. The CliniMACS[®] Plus Instrument Users Manual is subject to document control by Miltenyi, and Miltenyi maintains records for all reports of device complaints and malfunctions.

4.4 DEVICE PERFORMANCE EVALUATION: BMT CTN 0303

Performance of the CliniMACS CD34 Reagent System in BMT CTN 0303 was assessed by secondary endpoint analysis of CD34+ and CD3+ cell doses. The ability of each participating study site to uniformly meet CD34+ and CD3+ cell doses targeted by the clinical protocol using the CliniMACS CD34 Reagent System for processing donor leukapheresis products was an important element of the clinical study. Minimally, participating clinical sites were expected to provide cellular grafts for transplantation that met the following criteria post HPC-A processing using the CliniMACS® CD34 Reagent System:

- CD34+ Cells: $> 5 \times 10^6$ /Kg recipient body weight for CD34+ cells (minimum target of $> 2 \times 10^6$ CD34+ cells/Kg specified)
- CD3+ T-Cells: $< 1 \times 10^5$ /Kg recipient body weight

As a precaution, if the minimum target number of $> 2 \times 10^6$ CD34+ cells/Kg recipient body weight could not be met, even after multiple donor aphereses, the study required cellular grafts contain at least 1×10^6 CD34+ cells/Kg recipient body weight. It was not necessary to implement this contingency as all patients enrolled and treated on BMT CTN 0303 received at least the targeted minimum CD34+ cell dose of $> 2 \times 10^6$ cells/Kg recipient body weight. There was no upper limit to the number of CD34+ cells that could be administered.

Results provided indicate that cell processing laboratories across clinical sites were able to provide cellular grafts meeting pre-specified target CD34+ and CD3+ cell doses on a routine basis using the CliniMACS® CD34 Reagent System. The majority of patients (86%) received the targeted CD34+ cell dose of $> 5 \times 10^6$ /Kg recipient body weight and no patient received $> 1.0 \times 10^5$ CD3+ T-cells/Kg recipient body weight. The remaining 14% of patients not receiving the targeted CD34+ cell dose of $> 5 \times 10^6$ /Kg recipient body weight, were infused with the minimum target dose of $> 2 \times 10^6$ CD34+ cells/Kg recipient body weight. In total, 91% (40/44)

of the TCD grafts achieved either the target CD34+ cell dose ($> 5 \times 10^6$ /Kg recipient body weight, n=36) or the minimum CD34+ cell dose ($> 2 \times 10^6$ cells/Kg recipient body weight, n=4) after a maximum of 2 donor leukaphereses. For the other 4 patients, 3 donor leukapheresis procedures were performed. In one instance, the target CD34+ cell dose was achieved ($> 5 \times 10^6$ /Kg recipient body weight) while for the remaining patients, 3 leukaphereses were necessary in order to achieve the minimum target CD34+ cell dose ($> 2 \times 10^6$ cells/Kg recipient body weight).

Although these results indicate qualified, trained technicians operating in the controlled environment of a cell processing laboratory were able to routinely produce CD34+-enriched cellular grafts meeting pre-specified values for CD34+ and CD3+ cell doses, they provide limited information regarding the consistency of expected run-to-run CliniMACS[®] CD34 Reagent System performance. To this end, performance consistency in the hands of multiple end users operating in different cell processing laboratories was assessed by retrospective evaluation of a more comprehensive set of cell processing data collected in clinical study BMT CTN 0303 conducted under BB-IDE 11965.

The Technical Manual of Procedures (TMOP) developed by the Graft Characterization Committee for clinical study BMT CTN 0303 recommended participating clinical sites follow procedures for graft assessment that are in agreement with those of the Foundation of Accreditation of Cellular Therapy and Joint Accreditation Committee-ISCT and EBMT (FACT-JACIE). The TMOP outlined graft characterization procedures, but deferred to each institution's Standard Operating Procedures (SOPs) for processing of HPC-A, thereby allowing each center to use its own protocols for performing CD34+ cell selection, outside of operation of the CliniMACS[®] CD34 Reagent System which was controlled by following the CliniMACS[®] Users Manual. Characterization of the cellular grafts obtained post-processing using the CliniMACS[®] CD34 Reagent System generally included (but was not limited to) the following:

- Determination of total nucleated cell count (WBC/mL) using either hemacytometer or particle counter cell counts.
- Cell viability differential cell staining determined according to institutional SOPs.

- Determination of hematopoietic stem cell content of the product, using CD34 expression as detected by flow cytometry to identify stem cells within the WBC component of the cell preparation. The CD34+ cell determination performed was to be in accordance with the ISHAGE guidelines.¹ Non-viable cells were excluded from the analysis by co-staining with 7-AAD or Propidium Iodide. If a participating center did not use the ISHAGE guidelines methodology, the institutional SOP used was reviewed by the Graft Processing Technical committee.
- Determination of lymphocyte content including T-cells, B-cells, and NK-cells of allogeneic donor products using CD3, CD4, CD8, CD19, CD56 expression as detected by flow cytometry.

Assessment of post-processed cells for CD34+ cell yield, CD34 cell purity, and CD3+ T-cell log reduction can serve as indicators of expected CliniMACS[®] CD34 Reagent System cell processing performance. Neither Miltenyi nor the BMT CTN cell processing laboratories participating in clinical study 0303 established prospective criteria for any of the aforementioned cellular graft characteristics prior to initiation of the study.

Results, broken out by participating study site, were provided for post-selection characterization of the allogeneic CD34+ cell grafts prepared for each patient using the CliniMACS[®] CD34 Reagent System to process matched donor HPC-A. Cell processing data from 44-evaluable patients accrued at eight different clinical sites in the US were compiled. The data comprised 84-CD34+ cell selections performed using the CliniMACS[®] CD34 Reagent System. The discrepancy between the number of evaluable patients and number of cell selection procedures performed is due to the fact that multiple apheresis products were collected and processed as needed to obtain the protocol-specified target CD34+ cell dose. Results summarizing mean cell processing performance characteristics achieved at each individual study site participating in the BMT CTN 0303 study as well as an overall summary of cell processing data collected for all participating study sites are provided in [Appendix B](#). The data shown have been reproduced

from tables included in Miltenyi's HDE submission and have not been adjudicated by FDA. Analysis of the results is confounded, to some extent, by the lack of prospectively established criteria for each of the parameters measured as well as the degree of flexibility afforded to each of the participating study sites with respect to SOPs followed for processing HPC-A using the CliniMACS[®] CD34 Reagent System and testing of the cellular preparation post-selection.

4.5 SUMMARY OF DEVICE PERFORMANCE

It is expected that the CliniMACS[®] CD34 Reagent System will be used by end users in a variety of different environments. A key issue is the reliability of device performance in terms of the consistency of the cellular graft obtained post-processing using the CliniMACS[®] CD34 Reagent System. Currently, it is expected that each site where the CliniMACS[®] CD34 Reagent System is used will establish criteria for determining when donor cells collected by apheresis are suitable for processing with the CliniMACS[®] CD34 Reagent System as well as set criteria intended to be indicative of cell selection consistency. Miltenyi will supply a user manual that contains instructions for operational use and provide end user training, and has submitted to the HDE a retrospective analysis of cell processing data collected in clinical study BMT CTN 0303 to provide evidence of the consistency of device performance. Presented with this information, the committee will be asked to discuss the topic of CliniMACS[®] CD34 Reagent System performance and to offer recommendations deemed necessary to assure end users that the device performs as expected when processing donor HPC-A given Miltenyi does not provide specific recommendations with respect to expected performance.

5. SUPPORTING CLINICAL DATA

5.1 SOURCES OF DATA

The clinical studies used to support safety and probable benefit include one single-arm prospective clinical trial using the CliniMACS[®] CD34 Reagent System (BMT CTN 0303) and a retrospective cohort comparison (DAP 1001-34) of the results in BMT CTN 0303 to historical controls selected from the clinical trial BMT CTN 0101.

5.1.1 BMT CTN 0303

BMT CTN 0303 is a single-arm, multicenter phase 2 trial of transplants of HLA-identical, CD34+ enriched, T-cell depleted peripheral blood stem cells isolated by the CliniMACS[®] CD34 Reagent System in the treatment of patients with AML in first or second morphologic complete remission.² The trial was designed to assess the efficacy of transplantation of HPC-A allografts processed using the CliniMACS[®] CD34 Reagent System specifically in patients conditioned with a myeloablative preparative regimen. The primary endpoint was 6-month disease-free survival (DFS). Secondary endpoints included measures of hematopoietic recovery, acute and chronic GVHD, transplant-related mortality (TRM), long-term DFS, overall survival (OS), and achievement of the targeted cell doses. A complete protocol synopsis is provided in [Appendix C](#), and key design elements are listed in Table 1 below. The analyses in this briefing document are based on an interim report, as some of the subjects have not completed follow-up and a final study report has not been submitted.

5.1.2 BMT CTN 0101

BMT CTN 0101 (source of control cohort) is a randomized, double-blind, multicenter trial comparing fluconazole vs. voriconazole for the prevention of invasive fungal infection in allogeneic blood and marrow transplant patients.³ The purpose of the trial was to compare the efficacy of two antifungal drugs given prophylactically to a large but heterogeneous population of hematopoietic stem cell transplant recipients who had received a myeloablative preparative

regimen. The primary endpoint was fungal-free survival through Day 180. Secondary endpoints included frequency of and time to invasive fungal infection, OS, duration of antifungal treatment, time to and severity of acute and chronic GVHD, and safety. A complete protocol synopsis is provided in [Appendix D](#), and key design elements are listed in Table 1 below.

Table 1: Comparison of Key Design Elements of BMT CTN Protocols 0101 and 0303

		0303	0101
Design		Phase 2 single-arm	Phase 3 randomized
Eligibility	Age	18-65 yrs	>2 yrs
	Diagnosis	Acute myelogenous leukemia in 1st or 2nd remission	Leukemia, myelodysplastic syndrome, malignant lymphoma
	Donor	HLA-identical	Related or unrelated, HLA-matched or mismatched
Preparative Regimen		Myeloablative	Myeloablative
Stem Cells		HPC-A	HPC-A, M or C
Cell Processing		CD34-Selection (CliniMACS)	(4% had T-cell depletion)
Minimum Follow-up		Two yrs	One yr
Target Accrual		45	600

The two protocols differed substantially in key eligibility criteria, the source and processing of the stem cells, and the duration of follow-up. For the cohort comparison, DAP 1001-34 described in Section 6.1.3, the subset of subjects from BMT CTN 0101 was chosen on the basis of the key eligibility criteria in BMT CTN 0303.

5.1.3 DAP 1001-34

DAP 1001-34 is a retrospective comparison of the results of BMT CTN 0303 to an external control dataset from BMT CTN 0101. A preliminary report has been published.⁴ The focus of this analysis was to support the hypothesis that TCD via CD34 selection as the sole form of immune suppression is safe compared to transplantation using conventional GVHD prophylaxis. The treatment group includes all transplanted subjects from BMT CTN 0303. The control group was selected from BMT CTN 0101 on the basis of 1) diagnosis of AML in 1st or 2nd remission,

2) age 18-65 years, 3) HLA-matched related donor, and 4) PBSC allograft. The DAP 1001-34 study endpoints include measures of hematopoietic recovery, acute and chronic GVHD, TRM, relapse, DFS and OS. A complete protocol synopsis for DAP 1001-34 is provided in [Appendix E](#).

Interpretation of the endpoints from BMT CTN 0303, the single-arm trial, was confounded by the heterogeneity of the subjects. The cohort comparison, DAP 1001-34, was offered to provide perspective for the transplantation endpoints and to facilitate interpretation of the single-arm trial. Although the analyses were prespecified in the protocol, DAP 1001-34 is a retrospective study of nonrandomized populations. As such, DAP 1001-34 would not be an acceptable design for approval of a PMA. In addition, due to the small number of subjects, the study power is not sufficient for the detection of some clinically meaningful differences between groups, and significance values (p-values) should be interpreted with caution.

The results presented in the following sections represent the FDA analysis of the data submitted by the applicant. Differences between these results and those reported by the applicant reflect changes resulting from FDA adjudication of the endpoints. These differences are minor and did not affect the conclusions. For the endpoints of acute GVHD and chronic GVDH the FDA has performed competing risk analyses with relapse and death as the competing risks. For the endpoints of relapse and engraftment, the FDA has performed competing risk analyses with death as the competing risk. The cumulative incidence functions were compared using Gray's method.⁵ The R function CumIncidence⁶ was used to calculate the cumulative incidence rates and 95% confidence intervals.

5.2 SUBJECTS

5.2.1 Subject Accrual and Selection

Forty-seven subjects were accrued to BMT CTN 0303 from October, 2005 through December, 2008. Three subjects were withdrawn prior to transplantation; two subjects relapsed between

enrollment and start of therapy, and the third subject was withdrawn due to development of complications from a procedure performed between enrollment and start of therapy. The remaining 44 subjects were transplanted and are evaluable for the study endpoints. Two-year follow-up has not been completed for eight subjects. Disposition of the subjects is summarized in Table 2.

Table 2: BMT CTN 0303 – Disposition of Subjects

		Number (%)
Enrolled		47 (100%)
Off study prior to transplantation	Relapse	2 (4.3%)
	Ineligible	1 (2.1%)
Transplanted	Died	17 (36.2%)
	Completed	19 (40.4%)
	Ongoing	8 (17.0%)

Six hundred subjects were accrued to BMT CTN 0101 from November, 2003 through September, 2006. Selection of the subset for the control cohort is summarized in Table 3. Eighty-four subjects from BMT CTN 0101 fulfilled the selection criteria.

Table 3: Selection of Controls from BMT CTN 0101

Criterion	Resulting Sample Size	Excluded
All enrolled subjects	600	0
Subjects transplanted	599	1
HPC-A from related donor	236	363
HLA-matched donor	233	3
Subjects age 18-65 years	231	2
Subjects with AML	96	135
First or second remission	85	11
Allograft not T cell depleted	84	1

5.2.2 Subject Demographics

Table 4 shows the demographics of the 44 subjects transplanted on BMT CTN 0303 and the 84 subjects selected from BMT CTN 0101 for the control cohort. The population from BMT CTN

0303 was largely representative of the US patients with AML in the relevant age group, except for the preponderance of females and the lack of minorities.

Table 4: Demographics of Subjects Used in the Analyses

		All Subjects			First CR			Second CR		
		0303	0101	p	0303	0101	p	0303	0101	p
Number		44	84		37	65		7	19	
Gender	Female	63.3%	44.0%	0.04	62.2%	44.6%	0.09	71.4%	42.1%	0.38
	Male	36.4%	56.0%		37.8%	55.4%		28.6%	57.9%	
Median Age (Range)		49 yrs (21-60)	45 yrs (20-63)	0.14	48 yrs (21-60)	43 yrs (20-63)	0.09	49 yrs (26-58)	48 yrs (25-63)	0.89
Age Group	≤50 yrs	56.8%	67.9%	0.22	56.8%	69.2%	0.21	57.1%	63.2%	1.00
	>50 yrs	43.2%	32.1%		43.2%	30.8%		42.9%	36.8%	
Race	White	95.5%	85.7%	0.51	94.6%	90.8%	0.44	100%	68.3%	0.58
	Asian	2.3%	2.4%		2.7%	1.5%		0	5.5%	
	Black	0	2.4%		0	1.5%		0	5.5%	
	Other	2.3%	3.6%		2.7%	3.1%		0	5.3%	
	Unknown	0	6.0%		0	3.1%		0	15.9%	
Ethnicity	Hispanic	6.8%	11.9%	0.13	8.1%	7.7%	0.31	0	26.3%	0.17
	Not Hispanic	84.1%	77.4%		81.1%	81.5%		100%	63.4%	
	Unknown	9.1%	10.7%		10.8%	10.8%		0	10.4%	
Performance Status	90-100	77.3%	81.0%	0.62	78.3%	80.0%	0.85	71.4%	84.3%	0.46
	70-80	22.7%	19.0%		21.6%	20.0%		28.6%	15.8%	
Cytogenetic Risk Group	Favorable	4.5%	10.7%	0.34	0	6.2%	0.18	28.6%	26.3%	0.53
	Intermediate	63.6%	65.5%		67.6%	66.2%		42.9%	63.2%	
	Unfavorable	25.0%	14.3%		27.0%	16.9%		14.3%	5.3%	
	Unknown	6.8%	9.5%		5.4%	10.8%		14.3%	5.3%	

In comparison to the control cohort, there was a greater proportion of females, and age trended higher in the BMT CTN 0303 subjects. The remainder of the demographic characteristics were largely comparable between the two cohorts. None of the subjects were less than 18 years of age.

All subjects on BMT CTN 0303 received ATG in the preparative regimen compared with only 8% in BMT CTN 0101. ATG was used in BMT CTN 0303 to prevent graft rejection in recipients of CD34-selected allografts.⁷ Inclusion of ATG in the preparative regimen has been associated with a reduction in acute and chronic GVHD, and it may delay immune reconstitution after transplantation, thereby increasing the risk of infectious complications.^{8, 9, 10} The difference in ATG administration between studies could therefore potentially confound interpretation of results.

5.2.3 Summary of Exposure

The actual cell doses administered in BMT CTN 0303 are summarized in Table 5. CD34+ cell dose for BMT CTN 0101 are not available.

Table 5: Median (range) Cell Doses Administered

	BMT CTN 0303		
	N	CD34 (x 10 ⁶ /kg)	CD3 (x 10 ⁵ /kg)
All	84	7.9 (2.4-30.4)	0.07 (0.01-0.83)
CR1	65	7.4 (2.4-30.4)	0.07 (0.01-0.63)
CR2	19	8.0 (7.4-22.8)	0.07 (0.03-0.83)

5.3 PROBABLE BENEFIT

Since the function of the device is to exclude cells that may cause GVHD, allowing for transplantation to proceed without the need for immunosuppressive drugs, GVHD-related endpoints were used as the primary measure of probable benefit.

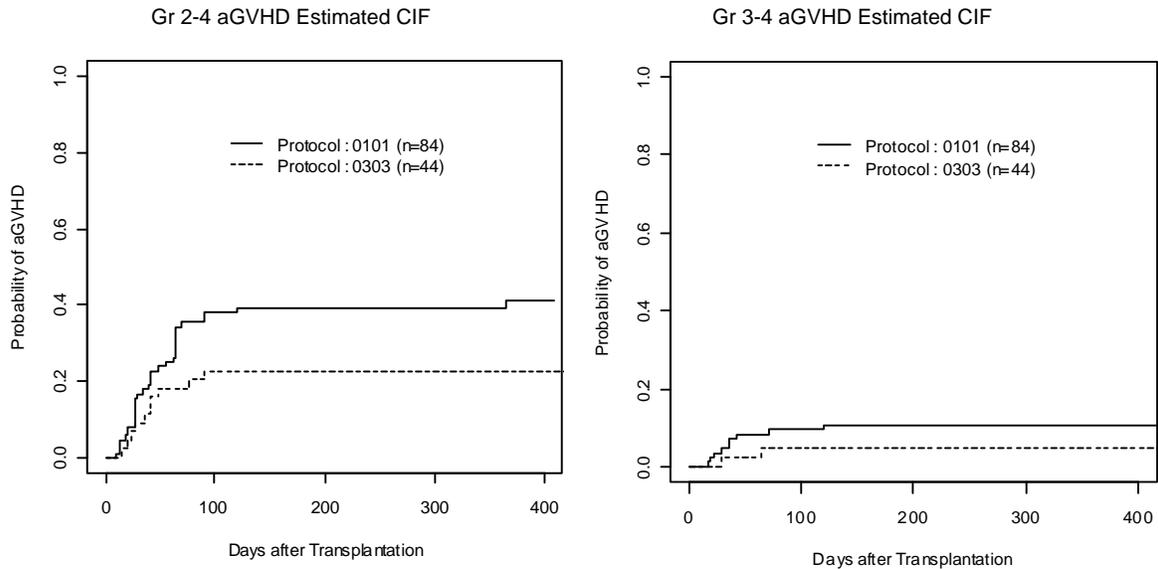
Ten subjects in BMT CTN 0303 developed moderate-to-severe acute GVHD by Day 100 after receiving CD34-selected allografts. Eight subjects had Grade 2 GVHD and 3 had grade 3 GVHD. The cumulative incidence of grades 2-4 GVHD at Day 100 is 22.7% (95% CI, 11.6-36.0%), and that for grades 3-4 GVHD is 4.5% (95% CI, 0.8-13.7%) in BMT CTN 303. The target limit for grades 3-4 GVHD prespecified in BMT CTN 0303 is 20%. Thus, the actual cumulative incidence met the prespecified limit.

In comparison to the control cohort in BMT CTN 0101, there was no apparent increase in the cumulative incidence of grades 2-4 or grades 3-4 acute GVHD in the BMT CTN 0303 population as a whole (Figure 1) or when assessed within the CR1 or CR2 populations separately (Table 6).

Table 6: Comparison of Day-100 Acute GVHD

			Gr 2-4 GVHD		Gr 3-4 GVHD	
Group	Protocol	N	Incidence rate at Day 100 (95%CI)	p-value (Gray's test)	Incidence rate at Day 100 (95%CI)	p-value (Gray's test)
All	0101	84	38.1% (27.7-48.4)	0.05	9.5% (4.4-17.0)	0.24
	0303	44	22.7% (11.6-36.0)		4.5% (0.8-13.7)	
CR1	0101	65	35.4% (23.9-47.0)	0.15	9.2% (3.7-17.8)	0.15
	0303	37	24.3% (11.9-39.1)		2.7% (0.2-12.3)	
CR2	0101	19	47.4% (23.6-67.9)	0.14	10.5% (1.7-29.0)	0.82
	0303	7	14.3% (0.5-49.1)		14.3% (0.5-49.1)	

Figure 1: Cumulative Incidence Function (CIF) of Acute GVHD



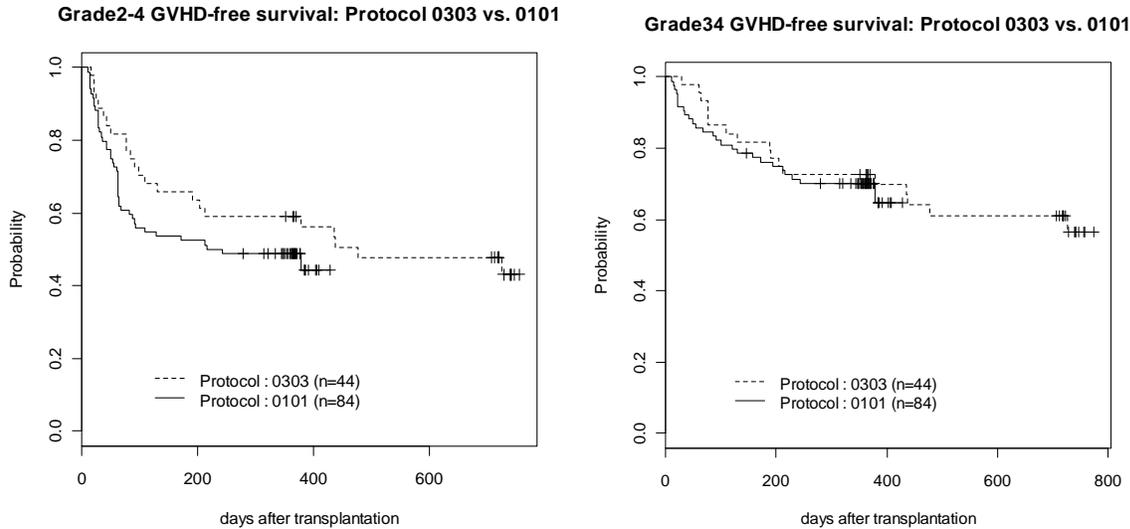
GVHD-free survival was also assessed by FDA (Table 7 and Figure 2, below). FDA analysis confirmed that there was no apparent decrease in acute GVHD-free survival in the BMT CTN 0303 population in comparison to the BMT CTN 0101 population.

Table 7: Comparison of GVHD-Free Survival

			Gr 2-4 GVHD-Free Survival		Gr 3-4 GVHD-Free Survival	
Group	Protocol	N	Hazard Ratio (95%CI) (0303 vs. 0101)	Log-rank test* p-value	Hazard Ratio (95%CI) (0303 vs. 0101)	Log-rank test* p-value
All	0101	84	0.617 * (0.356, 1.069)	0.09*	0.778 * (0.390, 1.552)	0.56*
	0303	44				
CR1	0101	65	0.631 (0.338, 1.177)	0.14	0.682 (0.299, 1.558)	0.36
	0303	37				
CR2	0101	19	0.634 (0.202, 1.988)	0.41	1.261 (0.374, 4.252)	0.70
	0303	7				

*Stratified by remission number

Figure 2: Comparison of Acute GVHD-Free Survival

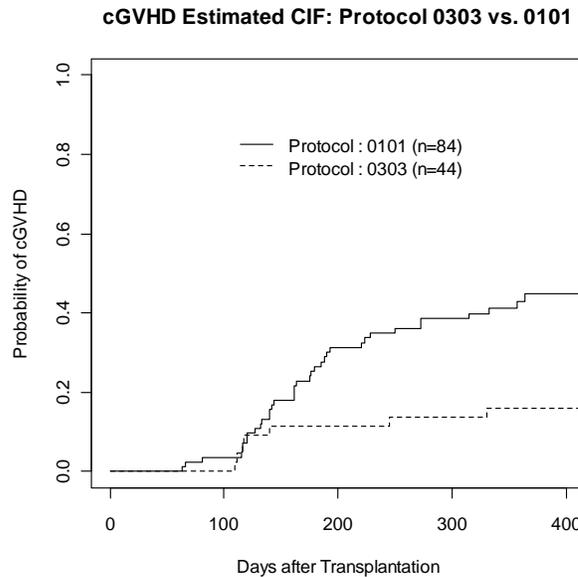


An assessment of chronic GVHD was also performed, and results are summarized in Table 8 and Figure 3 below. FDA analysis confirmed the applicant’s conclusion, that there was no significant increase in the cumulative incidence of chronic GVHD in the BMT CTN 0303 population in comparison to the BMT CTN 0101 population.

Table 8: Comparison of Chronic GVHD at 1 year

Group	Protocol	N	Incidence rate at 1 year (95%CI)	p-value (Gray’s test)
All	0101	84	44.9% (33.4-55.8)	0.002
	0303	44	15.9% (6.9-28.3)	
CR1	0101	65	46.9% (33.5-59.2)	0.010
	0303	37	18.9% (8.2-33.0)	
CR2	0101	19	36.8% (15.4-58.7)	0.087
	0303	7	0	

Figure 3: Comparison of Chronic GVHD



The apparent decrease in GVHD in subjects receiving CD34-selected allografts, especially striking in the chronic GVHD analysis, must be interpreted with caution. As previously mentioned, ATG administration has been associated with a decrease in both acute and chronic GVHD. All subjects in the BMT CTN 0303 study received ATG as part of the conditioning regimen (to improve engraftment); however, only 8% of the selected subjects in Study 101 received ATG. In addition, follow-up for subjects on BMT CTN 0101 is 1 year, and since follow-up on BMT CTN 0303 is ongoing, follow-up for a proportion of those subjects is also limited to 1 year. The small numbers of subjects and the high relapse-related mortality in the CR2 population precludes a meaningful assessment of chronic GVHD in that subgroup.

In summary, for the subjects who received CD34-selected HPC-A on BMT CTN 0303, the rates of acute GVHD, acute GVHD-free survival and chronic GVHD are numerically not worse than those for the historical controls. Whether these results support the probable benefit that the device allows transplantation to proceed without the need for immunosuppressive drugs to prevent GVHD is for consideration by the advisory committee.

5.4 SAFETY

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 anti-leukemia effects and prevent or treat infections. Therefore, endpoints related to hematopoietic recovery, infection, treatment-related mortality, relapse, and survival were the primary focus for the evaluation of safety.

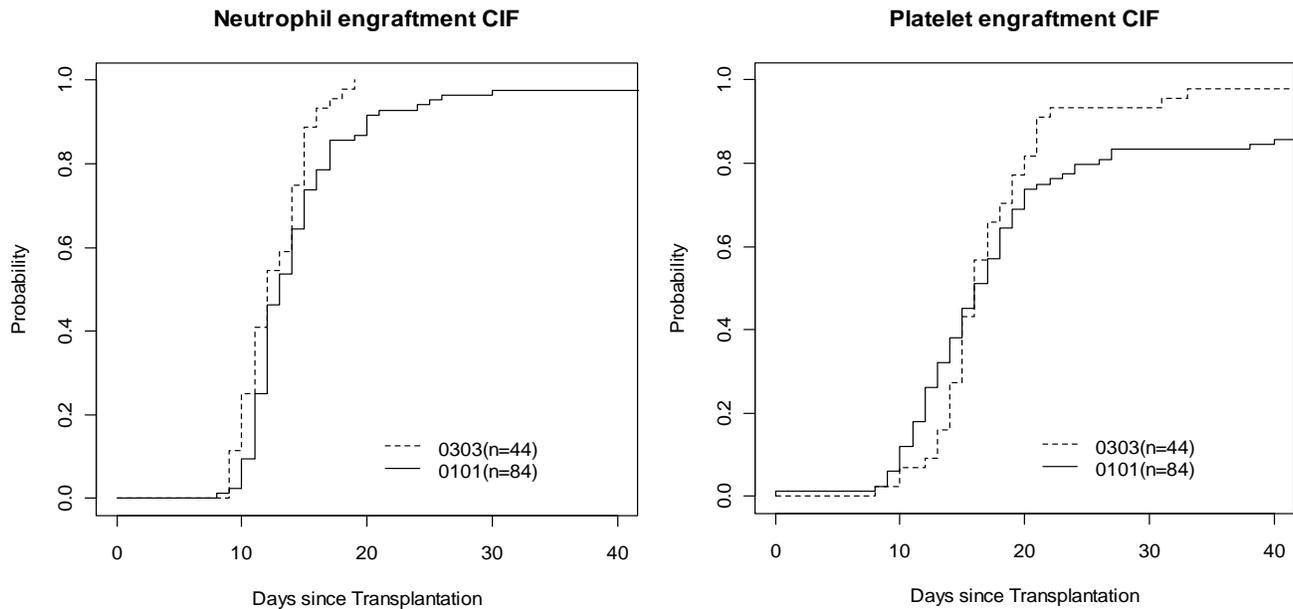
5.4.1 Engraftment

Three subjects experienced primary graft failure on BMT CTN 0101 compared to no subjects on BMT CTN 0303. Secondary graft failure was reported for one subject on each study. Comparison of neutrophil recovery and platelet recovery by cumulative incidence showed no delay in the subjects from BMT CTN 0303 in comparison to the controls from BMT CTN 0101. The lack of impairment of hematopoietic recovery was true for the CR1 and CR2 subgroups as well (Table 9 and Figure 4, below). How differences in CD34 cell dose may have impacted hematopoietic recovery cannot be determined, since the CD34 cell dose information is not available for BMT CTN 0101.

Table 9: Comparison of Hematopoietic Recovery (Cumulative Incidence)

Group	Protocol	N	ANC \geq 500 % at Day 30 (95%CI)	Gray's test p- value	Platelets >20,000 % at Day 30 (95%CI)	Gray's test p- value
All	0101	84	96.4% (88.3-99.0)	0.002	83.3% (73.2-89.9)	0.23
	0303	44	100.0%		93.2% (78.6-98.0)	
CR1	0101	65	95.4% (85.1-98.6)	0.004	83.1% (71.2-90.4)	0.26
	0303	37	100%		91.9% (75.0-97.6)	
CR2	0101	19	100%	0.57	84.2% (55.1-95.2)	0.51
	0303	7	100%		100%	

Figure 4: Comparison of Hematopoietic Recovery



5.4.2 Infection

Immune reconstitution was also examined in subjects on BMT CTN 0303. Immunoglobulin levels were not reported. Peripheral blood was tested at various intervals for lymphocyte subset recovery by flow cytometry. The median time to a CD4 count >200 was 1 year. The cumulative incidence of CD4 count >200 was 58% (95% CI, 37-80%) at 1 year and 71% (95% CI, 46-96%) at 2 years after transplantation.

Nearly three quarters of subjects on BMT CTN 0303 developed an infection, and 39% of subjects had a severe or life-threatening infection (Table 10). However, the proportion of subjects with infection or with severe or life-threatening infection in BMT CTN 0303 was not significantly greater than for subjects in BMT CTN 0101. There was also no increase in the proportion of subjects with bacterial, fungal, protozoal or other infection in BMT CTN 0303 compared to BMT CTN 0101, but there was a trend toward more viral infections in BMT CTN 0303 (p=0.06).

EBV infection was diagnosed in 8 subjects on BMT CTN 0303. The median time to diagnosis was 3 months (range, 1 – 11.5 months). A new EBV infection was not diagnosed later than 1 year after transplantation. The 1-year cumulative incidence of EBV infection is 18.2% (95% CI, 6.6-29.7%). Rituximab was administered for treatment of EBV infection. Only one subject on BMT CTN 0303 developed post-transplant lymphoproliferative disorder (PTLD), and this case of PTLD was fatal.

Table 10: Infections Within 1 Year After Transplantation

	0101 (n=84)	0303 (n=44)	p
Subjects with any infection	57 (68%)	32 (73%)	0.69
Maximum Severity: None	28 (33%)	12 (27%)	0.57
Moderate	30 (36%)	15 (34%)	
Severe	23 (27%)	13 (30%)	
Life Threatening/Fatal	3 (4%)	4 (9%)	
Subjects with : no infection	28 (33%)	12 (27%)	0.60
1-4 infections	49 (58%)	26 (59%)	
≥5 infections	8 (10%)	6 (14%)	
Subjects with infection due to: Bacteria	48 (57%)	25 (57%)	1.00
Virus	30 (36%)	24 (55%)	0.06
Fungus	9 (11%)	5 (11%)	1.00
Protozoa	0 (0%)	1 (2%)	0.34
Other	3 (4%)	0 (0%)	0.55
Total Infectious Events	162	112	
Total Infections due to: Bacteria	103 (64%)	62 (55%)	
Virus	46 (28%)	41 (37%)	
Fungus	9 (6%)	8 (7%)	
Protozoa	0 (0%)	1 (1%)	
Other	4 (2%)	0 (0%)	

5.4.3 Treatment-Related Mortality (TRM)

There was no significant difference in TRM in the BMT CTN 0303 population in comparison to the BMT CTN 0101 population for all subjects overall or for those in CR1 alone by Gray's test (Table 11).

Table 11: Comparison of Cumulative Incidence of Treatment-Related Mortality

Group	Protocol	N	Incidence rate at 1 year (95%CI)	Gray's test p-value
All	0101	84	15.7% (8.8-24.3)	0.52
	0303	44	13.6% (5.5-25.5)	
CR1	0101	65	15.6% (7.9- 25.6)	0.76
	0303	37	13.5% (4.9-26.6)	
CR2	0101	19	15.8% (3.7-35.6)	0.68
	0303	7	14.3% (0.5- 49.6)	

5.4.4 Relapse

Since the device decreases the number of donor lymphocytes responsible for the GVL effect, whether relapse was affected by use of the device was a concern. As shown in Table 12 and Figure 5, there was no increase in the relapse rate in the BMT CTN 0303 population in comparison to the BMT CTN 0101 population for all subjects overall or for those in CR1.

Figure 5: Comparison of Cumulative Incidence Function (CIF) of Relapse

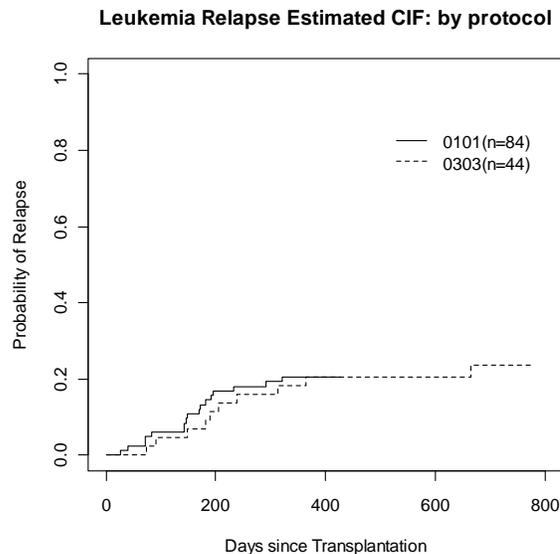
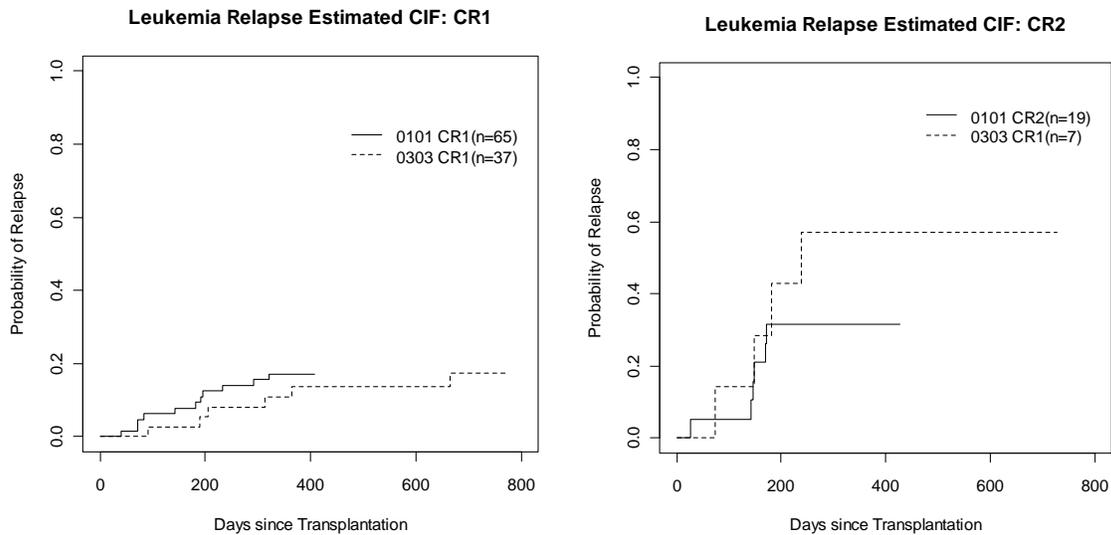


Table 12: Comparison of Cumulative Incidence of Relapse

Group	Protocol	N	Incidence rate at 1 year (95%CI)	Gray's test p-value
All	0101	84	20.5% (12.6-29.9)	0.88
	0303	44	20.6% (10.1-33.8)	
CR1	0101	65	17.3% (9.1-27.5)	0.54
	0303	37	13.7% (4.9-27.0)	
CR2	0101	19	31.6% (12.3-53.0)	0.33
	0303	7	57.1% (12.1-86.2)	

The risk of relapse appears to be higher in BMT CTN 0303 for subjects in CR2, although the numbers of subjects are too small for a definitive comparison (Figure 6).

Figure 6: Comparison of Relapse by CR



5.4.5 Disease-Free Survival (DFS)

Analysis of DFS was stratified by remission number and age (≤ 50 or > 50 years), but not by cytogenetic risk group. A single cytogenetic risk group accounts for more than 60% of subjects in both studies (Intermediate risk group: 65.5% (Study 101); 63.6% (Study 0303)). In addition,

there is an "unknown" risk group, which accounts for 9.5% for BMT CTN 0101 and 6.8% for BMT CTN 0303. Because of the imbalance in the sizes of the cytogenetic risk groups, some strata are empty or have only one patient (e.g., no CR1 patient in BMT CTN 0303 is in the “favorable” cytogenetic risk group; only one CR2 patient in BMT CTN 0101 is in the unfavorable risk group). Considering these imbalances, FDA decided to exclude cytogenetic risk factor from the stratified analysis, although it had been included as a stratification factor in the applicant’s pre-specified analysis plan. The results show that DFS was not lower in the BMT CTN 0303 population in comparison to the BMT CTN 0101 population for all subjects overall or for those in CR1 alone (Table 13 and Figures 7-8). The hazard ratio for the CR2 subjects, however, favored the BMT CTN 0101 cohort. These results are consistent with the applicant’s non-stratified analysis results.

Figure 7: Comparison of Disease-Free Survival

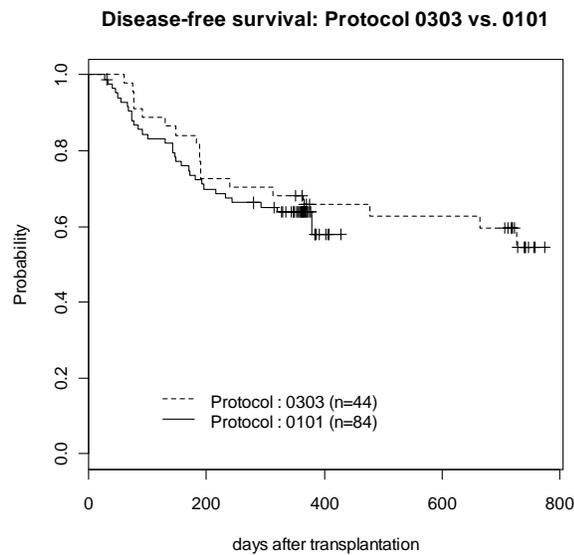


Figure 8: Comparison of Disease-Free Survival by CR

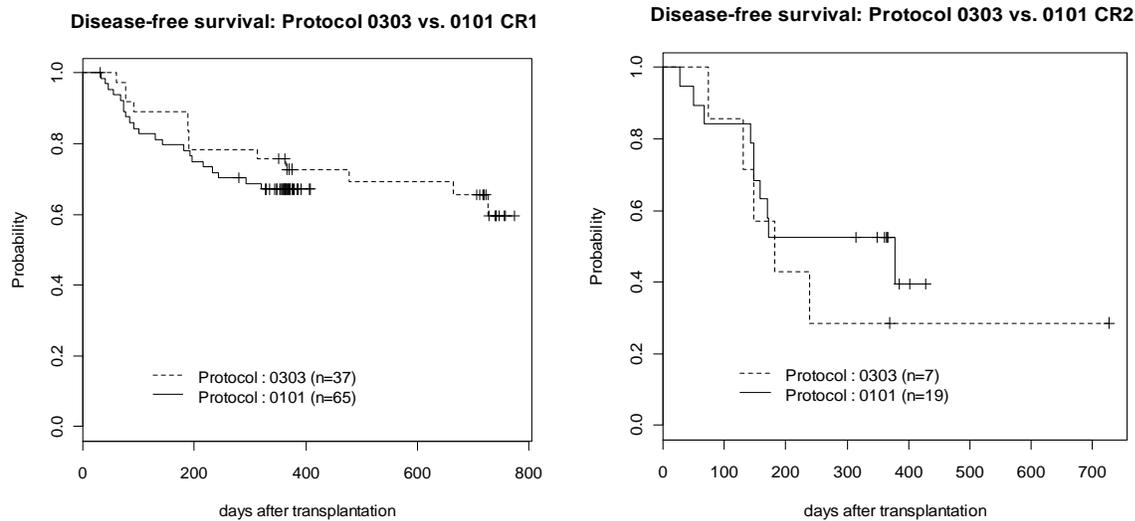


Table 13: Comparison of Disease-Free Survival

Group	Protocol	N	Hazard Ratio (95%CI) (0303 vs. 0101)	Stratified Log-rank test p-value
All	0101	84	0.836 (0.445- 1.569)*	0.71*
	0303	44		
CR1	0101	65	0.687 (0.321- 1.472)	0.38
	0303	37		
CR2	0101	19	1.415 (0.478- 4.191)	0.48
	0303	7		

* stratified by age (<=50 or >50) and remission number

5.4.6 Overall Survival (OS)

Similar to DFS, stratified analysis with stratification factors of age and remission number was performed on OS. OS was not lower in the BMT CTN 0303 population in comparison to the BMT CTN 0101 population for all subjects overall or for those in CR1 alone (Table 14 and Figures 9-10). However, for DFS, the hazard ratio for the CR2 subjects favored the BMT CTN 0101 cohort. These results are consistent with the applicant’s non-stratified analysis results.

Table 14: Comparison of Overall Survival*

Group	Protocol	N	Hazard Ratio(95%CI) (0303 vs. 0101)	Stratified Log-rank test p-value
All	0101	84	0.843 (0.403- 1.765)*	0.72*
	0303	44		
CR1	0101	65	0.715 (0.289-1.765)	0.44
	0303	37		
CR2	0101	19	1.352 (0.391-4.680)	0.61
	0303	7		

* stratified by age (<=50 or >50) and remission number

Figure 9: Comparison of Overall Survival

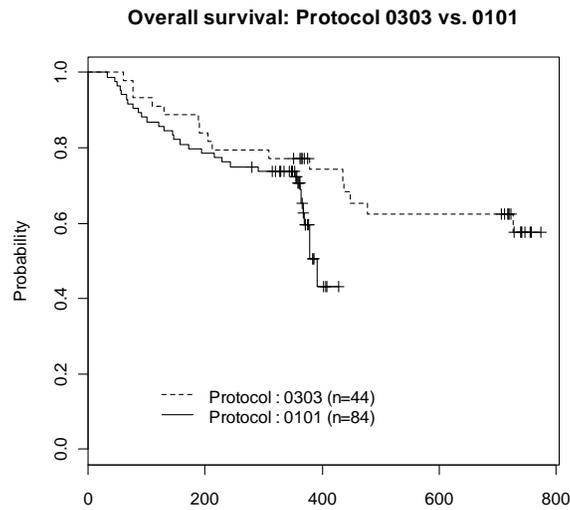
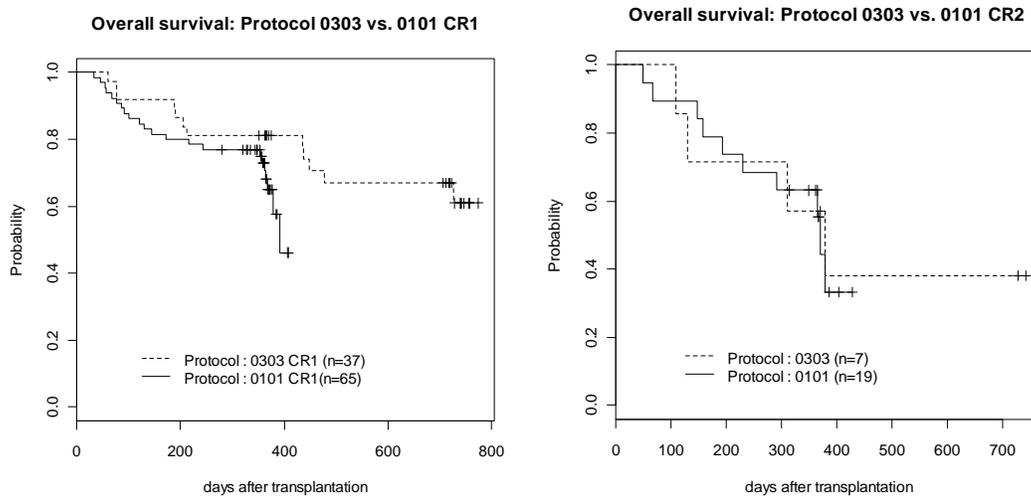


Figure 10: Comparison of Overall Survival by CR



Within one year of transplantation, 26% of subjects in BMT CTN 0101 died in comparison to 23% of subjects in BMT CTN 0303. The spectrum of causes of death was similar for the two study populations when considered overall, except that there were no deaths due to acute or chronic GVHD in the BMT CTN 0303 population (Table 15). The percentage of deaths for subjects in CR2 was higher than that for subjects in CR1, with death due to relapse being highest for those in CR2 on BMT CTN 0303.

Table 15: Causes of Death Within One Year After Transplantation

	All Subjects		CR1		CR2	
	0101 (n=84)	0303 (n=44)	0101 (n=65)	0303 (n=37)	0101 (n=19)	0303 (n=7)
Recurrence/Persistence	9 (11%)	3 (7%)	7 (11%)	1 (3%)	2 (11%)	2 (29%)
Acute GvHD	1 (1%)	0	0	0	1 (5%)	0
Chronic GvHD	1 (1%)	0	0	0	1 (5%)	0
Infection	4 (5%)	2 (5%)	2 (3%)	2 (5%)	2 (11%)	0
Bacterial Infection	2	0	0	0	2	0
Fungal Infection	1	1	1	1	0	0
Viral Infection	0	1	0	1	0	0
Organism Not Identified	1	0	1	0	0	0
Organ Failure	5 (6%)	2 (5%)	4 (6%)	2 (5%)	1 (5%)	0
Liver Failure	2	0	2	0	0	0
Pulmonary Failure	3	0	2	0	1	0
CNS Failure	0	1	0	1	0	0
Multiple Organ Failure	0	1	0	1	0	0
Idiopathic Interstitial Pneumonia	0	2 (5%)	0 (0%)	1 (3%)	0	1 (14%)
Adult Respiratory Distress Syndrome	1 (1%)	0	1 (2%)	0	0	0
Post-transplant Lymphoproliferative Disorder (PTLD)	0	1 (2%)	0	1 (3%)	0	0
Veno-occlusive Disease (VOD)	1 (1%)	0	1 (2%)	0	0	0
Total Deaths	22 (26%)	10 (23%)	15 (23%)	7 (19%)	7 (36%)	3 (43%)

In summary, for the subjects who received CD34-selected HPC-A in BMT CTN 0303, the times to neutrophil and platelet recovery and the rates of treatment-related mortality and overall survival are numerically not worse than those for the control subjects. By contrast, the rate of viral infections is higher than for the control subjects, and for subjects transplanted in CR2, the relapse rate, disease-free survival, and proportion of subjects with death due to relapse within 1 year is worse than in the control subjects. Whether these risks of viral infection and death due to relapse would affect acceptability of the clinical benefit of the device is for consideration by the advisory committee. Further, none of the subjects were less than 18 years of age, and whether similar outcomes would be expected in a pediatric population of AML patients is not clear.

6. ISSUES FOR DISCUSSION

DRAFT Questions for Miltenyi HDE Advisory Committee

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 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 (BMT CTN 0303) and from a retrospective comparison of the outcomes of this single-arm trial to a control cohort from BMT CTN 0101 receiving unmanipulated HPC-A from an HLA-matched related donor using standard immunosuppressive drugs to prevent GVHD.

SAFETY

The major safety concern regarding allogeneic transplantation using CD34-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 the table below. Please note that follow-up is incomplete for 8 subjects on BMT CTN 0303, and follow-up for the control cohort is limited to 1 year.

Table 1: Outcomes CD34-Selected Transplant Recipients (0303) and Control Cohort (0101)

Outcome	CD34-Selected 0303 (n=44)	Control Cohort 0101 (n=84)
Neutrophil Recovery by Day 30 (%, 95% CI)	100% (NA)	96.4% (88.3, 99.0)
Platelet Recovery by Day 30 (%, 95% CI)	93.2% (78.6-98.0)	83.3% (73.2-89.9)
Subjects with any infection (N,%)	32 (73%)	57 (68%)
Subjects with viral infections (N,%)	24 (55%)	30 (36%)
Subjects with EBV infection (N,%)	8 (18%)	2 (2%)
Treatment-related mortality at 1 year (%, 95% CI)	13.6% (5.46-25.54)	15.7% (8.79-24.33)
Relapse at 1 year (%, 95% CI)	20.6% (10.06-33.77)	20.5% (12.58-29.87)

Discussion Question 1: 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.

Voting Question 1: Is there reasonable assurance that the CliniMACS® CD34 Reagent System is safe for use in order 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 (GVHD) prophylaxis in patients with acute myeloid leukemia (AML) in first or second morphologic complete remission?

PROBABLE BENEFIT

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 BMT CTN 0303 received a myeloablative preparative regimen that included Rabbit Antithymocyte Globulin (ATG) at 2.5mg/kg as a single intravenous dose prior to transplant (to improve engraftment); however prophylactic immunosuppression was not given after transplantation. All patients on BMT CTN 0101 received a myeloablative preparative regimen with prophylactic immunosuppression; however ATG was administered in the preparative regimen to only 8% of patients.

The results of the outcomes for the CD34-selected transplant recipients (0303) and the control cohort (0101) are summarized in the table below.

Table 2: Outcomes for CD34-selected transplant recipients (0303) vs. controls (0101)

Outcome	CD34-selected 0303 (n=44)	Control Cohort 0101 (n=84)
Gr 2-4 acute GVHD by Day 100 (95% CI)	22.7% (11.6-36.0)	38.1% (27.7-48.4)
Gr 3-4 acute GVHD by Day 100 (95% CI)	4.5% (0.8-13.7)	9.5% (4.4-17.0)
GVHD-free survival at Day 180 (95% CI)	68.2% (52.3-79.8)	50.0% (38.9-60.1)
Chronic GVHD at 1 year (95% CI)	15.9% (6.9-28.3)	44.9% (33.4-55.8)

Discussion Question 2: 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-apheresis (HPC-A) from a related donor to obtain a CD34+ cell enriched population intended for hematopoietic reconstitu-

tion following a myeloablative preparative regimen in patients with acute myeloid leukemia (AML).

Voting Question 2: Is there reasonable assurance that the CliniMACS[®] CD34 Reagent System provides probable benefit by obtaining a CD34+ cell enriched population for patients with acute myeloid leukemia (AML) in first or second morphologic complete remission undergoing a myeloablative preparative regimen?

LABELING

If the answers to the above questions are yes, 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:

“CliniMACS[®] CD34 Reagent System is indicated for processing allogeneic HLA-matched hematopoietic progenitor cells-apheresis (HPC-A) 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 (GVHD) prophylaxis in patients with acute myeloid leukemia (AML) in first or second morphologic complete remission.”

Question 3:

An analysis of outcomes for patients by remission status is shown in the table below. Only seven of the 44 patients in BMT CTN 0303 were in CR2 at the time of transplantation. For this very small population, although the GVHD-related outcomes favor the BMT CTN 0303 patients, the relapse rate appears to be high, and the hazard rates for DFS and OS for the CR2 patients favored the control cohort.

Table 3: Outcomes by CR status

Outcome		CR1	CR2
Gr 2-4 acute GVHD by Day 100 (95% CI)	0303	24.3% (11.9-39.1)	14.3% (0.5-49.1)
	0101	35.4% (23.9-47.0)	47.4% (23.6-67.9)
Gr 3-4 acute GVHD by Day 100 (95% CI)	0303	2.7% (0.2-12.3)	14.3% (0.5-49.1)
	0101	9.2% (3.7-17.8)	10.5% (1.7-29.0)
Relapse at 1 year (% , 95% CI)	0303	13.7% (4.90-27.03)	57.1% (12.07-86.23)
	0101	17.3% (9.13-27.54)	31.6% (12.33-53.00)
GVHD-free survival HR (95% CI) for 0303 vs 0101		0.631 (0.338, 1.177)	0.634 (0.202, 1.988)
DFS HR (95% CI) for 0303 vs 0101*		0.687 (0.321-1.472)	1.415 (0.478-4.191)
OS HR (95% CI) for 0303 vs 0101*		0.715 (0.289-1.765)	1.325 (0.391-4.680)

*Analysis stratified by age (<=or > 50 years)

The applicant has proposed to include both CR1 and CR2 in the indication for their device. However, for patients in CR 2 the relapse rate is higher and the HR for survival is greater than one for patients in 0303 vs. 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.

Question 4:

All of the patients in BMT CTN 0303 were adults, and there are no data available regarding the safety of the use of this device for treatment of children with AML. Please discuss whether there would be any limitations in generalizing the results of BMT CTN 0303 to a pediatric population.

Question 5:

During clinical study BMT CTN #0303, the CliniMACS[®] CD34 Reagent System was used at eight (8) clinical sites to prepare CD34+-enriched hematopoietic progenitor cells. If approved, the number of sites where the CliniMACS[®] CD34 Reagent System will be used for the approved indication will increase. Currently, Miltenyi relies on instructions for use outlined in the CliniMACS[®] user manual, training of end users provided by certified Miltenyi employees, and the collection of data for HPC-A products processed at clinical sites participating in the BMT CTN 0303 clinical study to support its contention that consistency of performance may be expected when using the CliniMACS[®] CD34 Reagent System to process donor HPC-A. An abbreviated summary of selected attributes measured pre- and post-HPC-A processing is shown in the table below. A more complete summary of cell processing data is provided in [Appendix B](#).

Table 4: Overall Cell Processing Data Abbreviated Summary (n=84)

Attributes Measured		Mean	Std Dev	%CV
Starting TNC x 10 ¹⁰		7.46	3.26	43.67
Initial Viability (%)		97.60	2.74	2.81
CD34+ Cells x 10 ⁷	Starting Count	59.71	41.09	68.81
	Final Count	36.90	25.05	67.90
Final CD34+ Yield (%)		66.06	20.25	30.66
Final CD34+ Purity (%)		93.03	8.31	8.93
CD3+ T-Cells x 10 ⁸	Starting Count	179.50	69.80	38.87
	Final Count	0.0065	0.0103	159.39
Log ₁₀ CD3+ T-Cell Depletion		4.78	0.55	11.55
Final Viability (%)		96.57	3.84	3.97
Total CD34+ Cells Infused/Kg x 10 ⁶		8.81	5.21	59.17
Total CD3+ Cells Infused/Kg x 10 ⁶		0.015	0.020	132.9

Please discuss whether the data presented suggests end users will be able to routinely achieve consistent cellular grafts of expected quality using the CliniMACS[®] CD34 Reagent System. Please provide any additional recommendations that could serve to further ensure the safety, quality and consistency of device cellular output.

7. REFERENCES

1. Sutherland DR et al. The ISHAGE Guidelines for CD34+ Cell Determination by Flow Cytometry. *J Hematother.* 1996; 5:213-226.
2. Devine SM et al. Low Risk of Chronic Graft-versus-Host Disease and Relapse Associated with T Cell-Depleted Peripheral Blood Stem Cell Transplantation for Acute Myelogenous Leukemia in First Remission: Results of the Blood and Marrow Transplant Clinical Trials Network Protocol 0303. *Biol Blood Marrow Transplant.* 2011;17:1343-1351.
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4. Pasquini MC et al. Comparative Effectiveness Analysis of CD34+ Selected, T-Cell Depleted (TCD) HLA-Matched Sibling Grafts on Allogeneic Hematopoietic Cell Transplantation (HCT) for Patients with Acute Myeloid Leukemia (AML) in Complete Remission. *Biol Blood Marrow Transplant.* 2010;16(S2):S268.
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7. Ringhoffer M et al. CD34+ cell selection of peripheral blood progenitor cells using the CliniMACS device for allogeneic transplantation: clinical results in 102 patients. *Br J Haematol.* 2004;126:527–535.
8. Finke J et al. Standard graft-versus-host disease prophylaxis with or without anti-T-cell globulin in haematopoietic cell transplantation from matched unrelated donors: a randomised, open-label, multicentre phase 3 trial. *Lancet Oncol* 2009;10:855-64.
9. Russell JA et al. Adult recipients of matched related donor blood cell transplants given myeloablative regimens including pretransplant antithymocyte globulin have lower mortality related to graft-versus-host disease: a matched pair analysis. *Biol Blood Marrow Transplant.* 2007;13:299-306.
10. Pidala J et al. ATG prevents severe acute graft-versus-host disease in mismatched unrelated donor hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2011;17:1237-44.

8. APPENDICES

- A. Miltenyi CliniMACS[®] User Manual, US Edition
- B. Cell Processing Data Summary for BMT CTN 0303 Clinical Trial
- C. Protocol Synopsis – BMT CTN 0303 “A Single Arm, Multicenter Phase II Trial of Transplants of HLA-Matched, CD34+ Enriched, T cell Depleted Peripheral Blood Stem Cells Isolated by the CliniMACS System in the Treatment of Patients with AML in First or Second Morphologic Complete Remission. “
- D. Protocol Synopsis – BMT CTN 0101 “A Randomized Double-Blind Trial of Fluconazole versus Voriconazole for the Prevention of Invasive Fungal Infections in Allogeneic Blood and Marrow Transplant Recipients.”
- E. Protocol Synopsis – DAP 1001-34 “Comparison of BMT CTN #0303 Study Results to an AML Subset of BMT CTN #0101 as an Historical Control.”