SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. GENERAL INFORMATION

Device Generic Name:	Magnetic Cell Selection System for CD34+ cells from HPC-Apheresis used in treatment of Acute Myeloid Leukemia (AML)
Device Trade Name:	CliniMACS® CD34 Reagent System
Applicant's Name and Address:	Miltenyi Biotec Inc. (MBI) **Corporate Headquarters:** 2303 Lindbergh Street Auburn, CA 95602 **Regulatory Affairs Office:** 85 Hamilton Street Cambridge, MA 02139
Humanitarian Device Exemption (HDE) Number	BH110018
Humanitarian Use Device (HUD) Designation Number:	04-0146
Date of HUD Designation:	June 24, 2005
Date of Advisory Committee Meeting:	September 23, 2011
Date of Good Manufacturing Practice Inspection:	August 8-12, 2011
Date of Notice of Approval to Applicant:	January 23, 2014

II. INDICATIONS FOR USE

HUMANITARIAN DEVICE: Authorized by U.S. Federal law for use in the treatment of patients with acute myeloid leukemia (AML) in first complete remission. The effectiveness of the device for this use has not been demonstrated.

INDICATIONS FOR USE
The CliniMACS® CD34 Reagent System is indicated for processing hematopoietic progenitor cells collected by apheresis (HPC, Apheresis) from an allogeneic, HLA-

identical, sibling donor to obtain a $CD34^+$ cell-enriched population for hematopoietic reconstitution following a myeloablative preparative regimen without the need for additional graft versus host disease (GVHD) prophylaxis in patients with acute myeloid leukemia (AML) in first morphologic complete remission.

The indications for use statement has been modified from that granted for the Humanitarian Use Device (HUD) designation. The HUD designation was *"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."* The indications for use statement was modified to specify that there is no need for additional GVHD prophylaxis. This modification was made because the ability to achieve hematopoietic reconstitution without the need for additional GVHD prophylaxis is the primary probable benefit of the intervention, and is supported by the clinical evidence. Finally, the review team was concerned that the available evidence does not offer reasonable assurance of either safety or probable benefit in second complete remission (CR2). Therefore, the indicated patient cohort was narrowed to include only those patients in first complete remission (CR1).

III. CONTRAINDICATIONS

Do not use $CD34^+$ cells prepared with CliniMACS® CD34 Reagent System in patients with known hypersensitivity to murine (mouse) proteins or iron-dextran.

IV. WARNINGS AND PRECAUTIONS

A. Warnings

- Do not infuse the CliniMACS® CD34 Reagent or the CliniMACS® PBS/EDTA Buffer into patients directly.

- Hypersensitivity Reactions

  Hypersensitivity reactions, including anaphylaxis, have been observed during infusion of $CD34^+$ cells from the CliniMACS® CD34 Reagent System. Monitor the patient for hypersensitivity reactions, including anaphylaxis, during infusion of $CD34^+$ cells from the CliniMACS® CD34 Reagent System.

- Engraftment failure

  Failure to infuse an adequate number of functioning $CD34^+$ cells can result in engraftment failure. Collect sufficient HPC, Apheresis to yield at least 2.4×10^6 $CD34^+$ cells per kg of patient body weight after system processing (see Device Performance below). The clinical trial (see Clinical Performance below) using the CliniMACS® CD34 Reagent System to process HPC, Apheresis did not test allografts

with less than 2.4 x 10^6 $CD34^+$ cells per kg of recipient body weight. Monitor patients for laboratory evidence of hematopoietic recovery after transplantation.

- Acute and chronic graft versus host disease (GVHD)

  GVHD can occur in patients who receive HPC, Apheresis processed using the CliniMACS® CD34 Reagent System. Use pharmacologic prophylaxis if more than 1 x 10^5 $CD3^+$ cells per kilogram of recipient body weight are infused.

- Delayed immune reconstitution after transplantation

  Removal of T cells from the HPC, Apheresis can delay immune reconstitution after transplantation. Patients who receive the $CD34^+$ cell-enriched population prepared using the CliniMACS® CD34 Reagent System are at risk for serious opportunistic viral infections, including post-transplant lymphoproliferative disorder caused by Epstein-Barr virus (EBV) and cytomegalovirus (CMV). Monitor for EBV and CMV in the peripheral blood of patients after transplantation and initiate appropriate treatment promptly.

B. Precautions

- Safety and probable benefit in children under the age of 17 years have not been established.

- Drugs may be incompatible with the CliniMACS® PBS/EDTA Buffer. Do not add drugs to the buffer other than Human Serum Albumin as specified in the CliniMACS® User Manual for the CD34 Reagent System.

- Do not use cryopreserved and thawed HPC, Apheresis because cryopreservation promotes cell clumping, which may lead to device performance issues. Process HPC, Apheresis as soon as available, but not longer than 24 hours after collection.

- Use only HPC, Apheresis from an allogeneic, HLA-identical sibling donor with the CliniMACS® CD34 Reagent System.

- Collect HPC, Apheresis according to standard hospital or institutional leukapheresis procedures in standard leukapheresis collection bags. Do not include additional anticoagulants or blood additives, such as heparin, other than those normally used during leukapheresis. Keep the HPC, Apheresis at controlled room temperature (+19 °C to +25 °C (67 °F to 77 °F)) if it has to be stored, e.g., overnight, before processing. Do not allow the concentration of leukocytes to exceed 0.2 x 10^9 cells per mL.

- Only trained operators should use the CliniMACS® CD34 Reagent System to prepare $CD34^+$ cells for infusion. Operator training is provided by Miltenyi Biotec authorized personnel.

See the package inserts of the individual components of the CliniMACS® CD34 Reagent System for additional warnings and precautions specific to those components.

V. DEVICE DESCRIPTION

The CliniMACS® CD34 Reagent System is an in vitro medical device system used to select and enrich $CD34^+$ cells from HPC, Apheresis while passively depleting other cells, such as $CD3^+$ T cells, which cause graft versus host disease. The system is based on "magnetically-activated cell sorting" (MACS) employing antibodies conjugated to iron-containing particles that can be attracted to a magnetic field (referred to as "magnetic labeling"). Using the specificity of anti-CD34 antibody interaction with cell surface CD34 antigen found on hematopoietic progenitor cells, the system enriches $CD34^+$ cells from HPC, Apheresis by passing the antibody-labeled cell suspension through a separation column with a strong magnetic gradient. The separation column retains the magnetically labeled $CD34^+$ target cells while unlabeled cells flow through and are collected in the Negative Fraction Bag. Several automated washing steps are performed, disposing most of the liquid into the Buffer Waste Bag. The magnetically-selected $CD34^+$ cells are released from the separation column when the magnet is disengaged, removing the magnetic field, and the target $CD34^+$ cells are eluted into the Cell Collection Bag.

The CliniMACS® CD34 Reagent System consists of the following components:

- CliniMACS® CD34 Reagent – a dark amber, non-viscous, colloidal solution containing an antibody conjugate in buffer. The conjugate consists of a murine IgG_1 monoclonal antibody directed against the Class II epitope of the human CD34 antigen, which is chemically conjugated to dextran beads having an iron oxide/hydroxide core. (See the CliniMACS® CD34 Reagent Package Insert for more information.)
- CliniMACS® plus Instrument – a software-controlled instrument that processes the HPC, Apheresis. (See the CliniMACS® User Manual for the CD34 Reagent System for more information.)
- CliniMACS® Tubing Set (Standard (TS) or Large Scale (LS)) – a single-use, sterile, disposable tubing set with two proprietary cell separation columns. The CliniMACS® Tubing Set TS is for processing HPC, Apheresis preparations containing up to 0.6×10^9 $CD34^+$ cells out of a total cell number not exceeding 60×10^9 white blood cells. The CliniMACS® Tubing Set LS is for larger scale preparations containing up to 1.2×10^9 $CD34^+$ cells out of a total cell number not exceeding 120×10^9 white blood cells. (See the CliniMACS® Tubing Sets Package Insert and the CliniMACS® User Manual for the CD34 Reagent System for more information.)
- CliniMACS® PBS/EDTA Buffer – a sterile, isotonic phosphate-buffered, 1 mM EDTA, saline solution, used as external wash and transport fluid for the *in vitro* processing of HPC, Apheresis. (See the CliniMACS® PBS/EDTA Buffer

Package Insert and the CliniMACS® User Manual for the CD34 Reagent System for more information.)

The components of the CliniMACS® CD34 Reagent System that contact the cells during the selection process are tested for infectious disease and other safety parameters.

The CD34 monoclonal antibody is produced from a Master Cell Bank and Manufacturer's Working Cell Bank, which were developed and tested in conformance with US FDA's Points to Consider for the Manufacture and Testing of Monoclonal Antibody Products for Human Use, February 27, 1997 and with ICH Q5D Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products. Viral, bacterial, fungal, and mycoplasma contamination, as well as species-specific viruses, retroviruses and adventitious agents were tested for each cell bank as identified in the guidance documents. In addition, the authenticity of the CD34 cell line was determined after testing at reference laboratories.

The CD34 -------(b)(4)------- Final Filled Reagent are tested in conformance with US FDA's Points to Consider for the Manufacture and Testing of Monoclonal Antibody Products for Human Use, February 27, 1997 and ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. --(b)(4)----------. The Final Filled Reagent is assessed for sterility and endotoxin. Appropriate limits have been established for both. The results indicate that the CliniMACS® CD34 ------(b)(4)------- Final Filled Reagent manufacturing processes satisfy safety criteria.

The CliniMACS® Tubing Sets (Standard (TS) or Large Scale (LS)) are sterilized by ethylene oxide and tested for endotoxin, leakage, and integrity.

The CliniMACS® PBS/EDTA Buffer is heat sterilized and tested for endotoxin and ----(b)(4)-----.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

A. Conventional Treatment

The prognosis and conventional treatment options for AML depend on a number of factors, including patient age, subtype of AML, pretreatment cytogenetic and molecular findings[i], prior chemotherapy for another cancer, history of a blood disorder, metastasis to the central nervous system (CNS), and status of the disease.

The treatment plans for AML patients are typically divided into two phases: remission induction and consolidation therapy. Following successful induction therapy, the patient usually undergoes consolidation treatment, which may include several cycles of high-dose cytarabine chemotherapy, autologous stem cell transplantation (SCT), or allogeneic SCT[ii,iii,iv]. High-dose chemotherapy is generally recommended for good-risk patients in CR1[v]. Autologous SCT is recommended as consolidation treatment for good-risk AML

patients as an alternative to high-dose chemotherapy; autologous SCT is also given as a treatment option to patients with intermediate-risk AML in CR1, although there is currently no proven benefit over chemotherapy or allogeneic SCT. Another option for post-remission consolidation treatment of AML is allogeneic SCT[ii,iv,vi,vii] following high-dose chemotherapy and/or radiation therapy. Eligibility for allogeneic SCT depends on a number of prognostic factors, including age, disease state, and availability of an appropriate donor.

When comparing outcomes in allogeneic SCT for AML, considerations include the type of preparative regimen or conditioning regimen used, the immune suppression therapy to reduce the risk for graft rejection and prevent or treat GVHD (including pharmacologic and other methods used for T cell depletion), and any methods used to prevent or treat secondary infections. Donors for allogeneic SCT are mainly HLA-matched sibling donors or Matched-Unrelated Donors (MUD).

The rationale for CD34 selection of allogeneic HPC, Apheresis is to remove the T cells that cause GVHD, a potentially fatal complication of allogeneic SCT. The current standard of care for prevention of acute GVHD after HLA-identical allogeneic SCT is a combination of a calcineurin inhibitor and a short course of methotrexate. In a retrospective review of 410 patients transplanted with HLA-identical HPC, Apheresis using cyclosporine and methotrexate for GVHD prophylaxis, the cumulative incidences of grades 2–4 GVHD and grades 3–4 GVHD were 37% and 20%[viii]. The CliniMACS® CD34 Reagent System is used to remove the T cells which cause GVHD so that long-term use of immunosuppressive drugs and their attendant adverse effects can be avoided.

There are multiple investigational methods to deplete T cells from allogeneic HPC. Many negative depletion methods have not been automated; such methods are not reliably reproducible or may result in a residual T cell number that would require at least single drug immunoprophylaxis.

B. Alternative Methods for T Cell Depletion

In the United States, there are currently no approved products available for the enrichment of $CD34^+$ cells obtained for allogeneic matched SCT. The Isolex® 300i, (Baxter Healthcare Corporation) was approved in 1999 for the processing of autologous peripheral blood progenitor cell (PBPC) products to obtain a $CD34^+$ cell enriched population; however, this device was withdrawn from the market.

VII. MARKETING HISTORY

In December 1997, the CliniMACS® CD34 Reagent System received a CE mark to allow marketing in Europe. The CliniMACS® CD34 Reagent System components have been marketed in the following countries: Argentina, Australia, Belarus, Brazil, Canada, Chile, Columbia, Ecuador, Egypt, India, Iran, Israel, Korea, Kuwait, Malaysia, Mexico, Oman, Peru, Russia, Saudi Arabia, Singapore, Syria, Thailand, and Uruguay. The CliniMACS®

CD34 Reagent System has not been withdrawn from market in any country for reasons related to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events that may be associated with the use of the CliniMACS® CD34 Reagent System are listed below.

- Hypersensitivity reactions
- Acute graft versus host disease
- Chronic graft versus host disease
- Engraftment failure
- Delayed immune reconstitution after transplantation
- Viral infections (Epstein-Barr virus and cytomegalovirus)
- Death

Please see Section IV *Warnings and Precautions* for additional information regarding these adverse reactions and any steps that should be taken to prevent or mitigate such reactions. For additional information on adverse events that occurred in the clinical study BMT CTN 0303, see Section X *Summary of Clinical Information*.

IX. SUMMARY OF NONCLINICAL STUDIES

The nonclinical laboratory studies focused on safety and performance studies for each of the individual components as well as the CliniMACS® CD34 Reagent System as a whole.

A. Safety Testing of the CliniMACS® CD34 Reagent and its Intermediates

Safety and Biocompatibility Testing of the CliniMACS® CD34 Reagent

Small quantities of the CliniMACS® CD34 Reagent remain bound to $CD34^+$ cells that are infused into the patient. The safety of this mAb when delivered at levels higher than the potential maximum amount anticipated for clinical use was demonstrated in the studies summarized in Table 1.

Table 1. Summary of Toxicology and Biocompatibility Tests Conducted on the CliniMACS® CD34 Reagent	
Test	**Results**
Human Cryosection Cross Reactivity Study	The CD34 mAb reacted with cell types that express the CD34 antigen.
Interspecies Cross Reactivity Study	The CD34 mAb did not cross react with non-human primate (baboons, ---------(b)(4)--------- monkeys) hematopoietic cells expressing the CD34 antigen.
Cardiovascular Safety Study in Rhesus Monkeys	Following intravenous injection of escalating dose levels of CliniMACS® CD34 Reagent in the same animal, no effect on mean right ventricle pressure, mean arterial pressure, cardiac output, ECGs, respiratory rate, or heart rate was observed out to 150 minutes after administration.
Acute Intravenous Irritation in Rabbits	No evidence of irritation in rabbits following a single intravenous injection was observed.
14-Day Intravenous Toxicity in ----(b)(4)---- Monkeys	Intravenous administration at multiple dose levels for 14 consecutive days resulted in no significant toxicity.
Hemocompatibility	No evidence of a hemolytic response in human blood was observed.
Residual Iron, Iron-Dextran, and Anti-CD34 Antibody in $CD34^+$ Cells Isolated using the CD34 Reagent	Low levels of residual iron, iron-dextran, and anti-CD34 antibody may be infused (no toxicological concern).

Container Closure Integrity of the CliniMACS® CD34 Reagent

Miltenyi performed a Container Closure Integrity (CCI) study using bacterial challenge during three media fill runs and the results were acceptable.

B. Safety Testing of the CliniMACS® Tubing Set

Biocompatibility Testing of the CliniMACS® Tubing Set

Biocompatibility tests performed on this device component included: cytotoxicity, intracutaneous reactivity, acute systemic toxicity, hemocompatibility, and sensitization. The results showed the materials in the device component to be safe for the intended use. Leachables detected in this device component were at levels below those found to cause toxicity.

Biocompatibility Testing of the Separation Column (with the Grilamid® Column Housing)

Biocompatibility tests performed on this device component included: cytotoxicity, intradermal reactivity, acute systemic toxicity, hemocompatibility, and sensitization. The results showed the materials in the device component to be safe for the intended use. The ----------(b)(4)---------- eluted from the column are an acceptable safety risk and lacquer integrity of the column remained intact.

Container Closure Integrity of the CliniMACS® Tubing Set

The primary packaging of the CliniMACS® Tubing Sets consists of the thermoform tray which has Tyvek® sheeting sealed to it using a heat sealing machine. This tubing set tray sealing has been qualified to maintain a sterile barrier with ----------(b)(4)---------- ---------- performed on CliniMACS® Tubing Sets at release, one, two ---(b)(4)--- years after manufacture.

C. Safety Testing of the CliniMACS® PBS/EDTA Buffer

Safety and Biocompatibility Testing of the CliniMACS® PBS/EDTA Buffer

Biocompatibility tests performed on this device component included: cytotoxicity, intracutaneous reactivity, acute systemic toxicity, hemocompatibility, and sensitization. The results showed the materials in the device component to be safe for the intended use. Intravenous administration of this device component in ---(b)(4)--- monkeys for 14 consecutive days resulted in no significant toxicity.

D. Nonclinical Testing of the CliniMACS®plus Instrument

Electrical Safety of the CliniMACS® plus Instrument

The CliniMACS® plus Instrument was tested by TÜV Product Service of Munich, Germany for conformance to the requirements of EN/IEC 61010-1 *Safety Requirements for Electrical Equipment for Measurement, Control, and Laboratory Use – Part 1: General Requirements* 1995 and is designed to meet UL3101-1: *Electrical Equipment for Laboratory Use; Part 1: General Requirements* 1993. The results of the tests showed the device met the safety requirements of the above standards.

Electromagnetic Compatibility

The CliniMACS® plus Instrument was tested by TÜV Rheinland Product Service (TÜV PS) Cologne, Germany for electromagnetic compatibility requirements in accordance with EN 60601-1-2: 2001 *EMC Requirement for Medical Devices* and conforms to the above mentioned safety requirements.

CliniMACS® CD34 Reagent System: System Reliability

Reliability testing of the instrument and all of its components was performed in a simulated use study. The study projected the "stress lifetime" use of the device to be two processing runs a day for five years, with a two-fold safety factor, or the equivalent of 7300 processing runs. The equipment was operated for 300 consecutive hours during which all component subsystems were challenged at a minimum, and the results of this testing indicate that the CliniMACS® plus Instrument and each of its components functioned largely without failure throughout the study.

Software Validation

All operations of the device are controlled/monitored by software, which is responsible for the functionality, user interface, safety checks and performance accuracy. Software validation was performed according to pre-defined validation protocols, executed and documented. Risk analysis for the software was performed in accordance with EN ISO 14971:2007 to address potential risks that could be caused by changes or additions to the software.

E. Nonclinical Testing of the CliniMACS® CD34 Reagent System

CliniMACS® CD34 Reagent System Nonclinical Performance

Nonclinical performance of the CliniMACS® CD34 Reagent System was evaluated by conducting selection of $CD34^+$ cells from human leukapheresis products of 30 normal, healthy donors. Performance of the system was assessed by post–selection measurement of yield, purity, viability of the selected $CD34^+$ cells, and BFU-E (blast forming unit-erythrocyte) and GM-CFC (granulocyte-macrophage colony-forming cell) colony formation from the selected $CD34^+$ cell population *in vitro*.

The median yield of selected $CD34^+$ cells was 77.3% (range: 35.1–218.5%) and the median purity of selected $CD34^+$ cells was 95.5% (range: 71.0–98.0%). Cell viability in the selected subset was determined by trypan blue dye exclusion, and calculated as a percentage of total selected cells. Following selection, median viability of $CD34^+$ cells was 96% (range: 87–100%). Day 0 and Day 10 GM-CFC and BFU-E were quantitated. 2 to 10% of the assayed selected $CD34^+$ cells formed colonies *in vitro*.

CliniMACS® CD34 Reagent System-Alpha Test Report

An *in vitro* study was conducted to assess the performance of the CliniMACS® CD34 Reagent System when used in clinical settings to positively select $CD34^+$ cells from leukapheresis products. Leukapheresis products were obtained from twenty patients specifically for the performance testing. Performance was measured by the purity, yield, viability, and sterility of the selected $CD34^+$ cells. Median purity of selected $CD34^+$ cells was 94.2% (range: 14.4–97.5%) and median yield was 73.9% (range 27.4–283.4%). 16 total selected cell samples were tested for sterility and found to be sterile. The median

cell viability following cell selection was 94.0% (range 72.0–99.0%) compared with 94.9% (range 73.0–100.0%) prior to cell selection.

X. SUMMARY OF CLINICAL INFORMATION

Miltenyi Biotec provided the results of three studies of the CliniMACS® CD34 Reagent System to support its proposed indication for use in adults with AML in CR1 or CR2.

The first study, BMT CTN 0303, was a prospective, multicenter, single-arm clinical trial of CD34-selected HPC, Apheresis transplanted from HLA-identical donors for subjects with AML in CR1 or CR2. HPC, Apheresis were collected from filgrastim-mobilized donors; the target for collection was >5 x 10^6 $CD34^+$ cells per kg and <1 x 10^5 $CD3^+$ cells per kg after selection using the device. The study subjects were treated Days -9 to -2 with a myeloablative preparative regimen that included total body irradiation, thiotepa, cyclophosphamide, and rabbit antithymocyte globulin (ATG). The donor cells selected using the device were infused on Day 0. No additional immunosuppressive drugs were given to prevent GVHD after transplantation. No hematopoietic growth factors were used to support hematopoietic recovery. Forty-four subjects were transplanted, 37 in CR1 and 7 in CR2, and all surviving subjects have been followed for at least two years.

The CR1 subjects included 14 (38%) males and 23 (62%) females of median age 48 years (range: 21–60 years). The cytogenetics risk group was intermediate for 68%, unfavorable for 27%, and unknown for 5% of subjects. The median number of $CD34^+$ cells infused was 7.4 x 10^6 per kg recipient body weight (range: 2.4–30.4). The median number of $CD3^+$ cells infused was 0.07 x 10^5 per kg recipient body weight (range: 0.01–0.63).

The second study, DAP 1001-34, was a retrospective analysis of the outcomes for the 44 subjects in BMT CTN 0303 compared to 84 historical controls. The historical controls were selected from BMT CTN 0101, an unrelated, prospective clinical trial of fungal prophylaxis after HPC transplantation. The control cohort was selected on the basis of donor type, allograft type, age, diagnosis, and remission status. In comparison to the control cohort, the BMT CTN 0303 subjects differed significantly in gender distribution, use of total body irradiation (TBI) in the preparative regimen, use of antithymocyte globulin (ATG) in preparative regimen, and number of $CD34^+$ cells infused. The median follow-up for survivors in the control cohort was four years.

The third study, ACS 950101, was a prospective, multicenter, single-arm clinical trial of autologous CD34-selected HPC, Apheresis for patients with high-risk metastatic breast cancer. The results for the 60 subjects treated on this clinical trial were submitted to support the safety of the device, including hematopoietic recovery, immune reconstitution, and immunogenicity.

Device Performance

The safety and feasibility of use of the CliniMACS® CD34 Reagent System was evaluated in BMT CTN 0303. In this study, allogeneic donors were mobilized with daily subcutaneous granulocyte colony-stimulating factor (G-CSF) at a dose of 10 to 16 µg per kg per day. Leukapheresis was performed on a continuous flow cell separator commencing on Day 5 of G-CSF treatment, and $CD34^+$ cell enrichment of the HPC, Apheresis was performed using the CliniMACS® CD34 Reagent System. Most donors underwent at least two, but not more than three, aphereses to reach the post-selection enrichment target of $>5.0 \times 10^6$ $CD34^+$ cells per kg recipient body weight while maintaining $<1.0 \times 10^5$ $CD3^+$ cells per kg recipient body weight.

Eighty-four selection procedures were performed on HPC, Apheresis collected from a total of 44 donors. The minimum number of $CD34^+$ cells required for transplantation, $>2 \times 10^6$ per kg recipient body weight, was achieved for 100% (44) of donors. This was attained with one apheresis for 93% (41) of the donors and two aphereses for an additional 7% (3). The target number of $CD34^+$ cells, $>5 \times 10^6$ per kg recipient body weight, was achieved for 84% (37) of the 44 donors. This target number was attained with one apheresis for 36% (16), with two aphereses for 45% (20), and with three aphereses for 2% (1) of the 44 donors. Device performance is shown in the table below.

Table 2: Device Performance Summary; N=84

Attributes Measured		Mean	Std Dev	Median	Min	Max
Starting TNC x 10^{10}		7.46	3.26	6.95	2.1	18.0
Initial Viability (%)		97.60	2.74	99.0	86.9	100.0
$CD34^+$ Cells x 10^7	Starting Count	59.71	41.09	47.85	7.3	208.0
	Final Count	36.90	25.05	29.80	6.1	119.0
Final $CD34^+$ Yield (%)		66.06	20.25	65.00	29.9	125.6
Final CD34+ Purity (%)		93.03	8.31	96.65	61.5	99.8
$CD3^+$ T-Cells x 10^8	Starting Count	179.45	69.80	168.50	55.00	362.00
	Final Count	0.00652	0.01039	0.00217	0.00026	0.04971
Log_{10} $CD3^+$ T-Cell Depletion		4.78	0.55	4.90	3.2	5.9
Final Viability (%)		96.57	3.84	97.70	74.0	100.0
Total $CD34^+$ Cells Infused/kg x 10^6		8.81	5.21	7.924	2.41	30.360
Total $CD3^+$ Cells Infused/kg x 10^6		0.015	0.020	0.0066	0.0011	0.08328

Clinical Performance – Probable Benefit

GVHD: Since 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 (acute GVHD, chronic GVHD and GVHD-free survival (GFS)) were used as the primary measure of probable benefit (Table 3).

Table 3: Assessment of Graft-vs-Host Disease Endpoints

3A. BMT CTN 0303 Results			**Gr 2–4 GVHD**	**Gr 3–4 GVHD**	**Chronic GVHD**
Subgroup	**Study**	**N**	CIF[1] at Day-100 (95% CI)	CIF[1] at Day-100 (95% CI)	CIF[1] at 2 yrs (95% CI)
All	0303	44	25 (13–39)%	7 (2–17)%	15 (7–28)%
CR1	0303	37	27 (14–42)%	5 (1–16)%	19 (8–33)%
CR2	0303	7	14 (1–49)%	14 (1–49)%	0%

[1]Cumulative incidence function using death and relapse as competing risks

3B. DAP 1001-34 Results			**Gr 2–4 GVHD**		**Gr 3–4 GVHD**		**Chronic GVHD**	
BMT CTN 0101 GVHD Prophylaxis	**Study**	**N**	**SHR[2] (95%CI)**	**p**	**SHR[2] (95%CI)**	**p**	**SHR[2] (95%CI)**	**p**
All Regimens	0101	84	0.57 (0.29–1.11)	0.10	0.61 (0.17–2.19)	0.45	0.28 (0.13–0.65)	0.003
	0303	44						
Calcineurin Inhibitor Plus Methotrexate	0101	59	0.59 (0.29–1.19)	0.14	0.63 (0.16–2.45)	0.51	0.22 (0.10, 0.51)	<0.001
	0303	44						

[2]Subhazard ratio for BMT CTN 0303 vs 0101 using death and relapse as a competing risks

3C. DAP 1001-34 Results			**Gr 2–4 GFS**		**Gr 3–4 GFS**		**Total GFS[3]**	
Subgroup	**Study**	**N**	**HR[4] (95%CI)**	**p**	**HR[4] (95%CI)**	**p**	**HR[4] (95%CI)**	**p**
All	0101	84	0.72 (0.44–1.18)	0.18	0.92 (0.53–1.61)	0.826	0.44 (0.28–0.70)	0.0004
	0303	44						
CR1	0101	65	0.76 (0.44–1.32)	0.34	0.90 (0.48–1.73)	0.765	0.44 (0.27–0.74)	0.002
	0303	37						
CR2	0101	19	0.56 (0.18–1.71)	0.31	1.06 (0.34–3.33)	0.929	0.42 (0.140–1.26)	0.11
	0303	7						

[3]GVHD-Free Survival inclusive of grades 2–4 acute GVHD, chronic GVHD or death as events
[4]Hazard ratio for BMT CTN 0303 vs 0101, stratified by remission number in the analysis of all subjects

As seen in Table 3A, the Day-100 cumulative incidence function (CIF) was 25% for grades 2–4 acute GVHD and 7% for grades 3–4 acute GVHD, and the 2-year CIF was 15% for chronic GVHD for all subjects transplanted on BMT CTN 0303. Consideration was given to the possibility that the control of GVHD may have been mediated by the ATG in the preparative regimen. However, because the ATG dose was low, and there are no studies showing that single-agent ATG prevents GVHD, the salutary effects seen were attributed to use of the device rather than to the ATG. For further discussion of the role of ATG, see also Section XII *Advisory Committee Meeting*.

Since the number of subjects studied may be too small to detect a clinically meaningful difference between BMT CTN 0303 and the historical control cohort, and since the

comparisons were not from a randomized trial, the hazard ratios (HR) or subhazard ratios (SHR) were used as a means to detect potentially adverse trends rather than statistically significant differences. Table 3B shows the SHRs for the comparisons of the GVHD outcomes in BMT CTN 0303 to the historical control cohort performed for DAP 1001-34. None of the SHRs for the GVHD outcomes exceeded 1, suggesting no worsening in the control of GVHD when the device was used in comparison to immunosuppressive drugs. The combination of a calcineurin inhibitor and methotrexate is considered the current standard of care for prevention of GVHD, but that combination was used by only 70% of the historical control cohort. The SHRs for comparison of the BMT CTN 0303 subjects to the historical control subgroup using a calcineurin inhibitor and methotrexate were similar to those for the whole group overall (Table 3B).

Since the absolute value of the CIF may vary depending on the proportion of subjects who develop a competing risk, FDA performed an exploratory analysis using as the outcome GVHD-free survival (GFS), in which all subjects are included, and there are no competing risks. As shown in Table 3C, for the all-subject analyses, there was no evidence for worsening of GFS with use of the device. When considered by remission number, however, the HR for grades 3–4 GFS was greater than 1 for subjects in BMT CTN 0303 transplanted in CR2.

Transplant Outcomes: Since the objective of HPC transplantation is to reduce the risk of relapse and improve survival, the impact of device use on transplant outcomes was also determined. As shown in Table 4, for the all-subject analyses, there was no evidence for worsening of disease-free survival (DFS), overall survival (OS) or relapse with use of the device in BMT CTN 0303 in comparison to the historical controls. When considered by remission number, however, the HRs in BMT CTN 0303 were all less than 1 for subjects transplanted in CR1, and greater than 1 for subjects transplanted in CR2.

Table 4: Assessment of Transplant Outcomes

			Disease-Free Survival		**Overall Survival**		**Relapse**	
Sub-group	**Study**	**N**	**HR[1] (95%CI)**	**p**	**HR[1] (95%CI)**	**p**	**SHR[1,2] (95%CI)**	**p**
All	0101	84	0.79 (0.45-1.37)	0.44	0.88 (0.49-1.58)	0.76	0.71 (0.34-1.47)	0.36
	0303	44						
CR1	0101	65	0.71 (0.38-1.35)	0.31	0.85 (0.43-1.66)	0.65	0.53 (0.21-1.33)	0.18
	0303	37						
CR2	0101	19	1.18 (0.40-3.44)	0.80	1.11 (0.35-3.57)	0.86	2.04 (0.58-7.08)	0.26
	0303	7						

[1]Hazard or subhazard ratio for BMT CTN 0303 vs 0101, stratified by remission number in the analysis of all subjects
[2]Subhazard ratio for BMT CTN 0303 vs 0101 using death as a competing risks

All CR1 subjects in BMT CTN 0303 achieved an absolute neutrophil count that exceeded 0.5×10^9 per liter by Day 21 after transplantation. The platelet count recovered to greater than 20×10^9 per liter by Day 100 for 91.9% (95% CI, 82.4 to 100%). There was one late graft failure. At Day 100 after transplantation, the cumulative incidence of grades 2 to 4 acute GVHD was 27% (95% CI, 14 to 42%), and that for grades 3 to 4 acute GVHD was

5% (95% CI, 1 to 16%). The cumulative incidence of chronic GVHD at 2 years after transplantation was 19% (95% CI, 8 to 33%).

Clinical Performance – Risks

Among the 44 subjects in BMT CTN 0303, there were no grades 3 to 5 infusion reactions, no allergic reactions, and no graft failures. Testing for development of human anti-mouse antibodies (HAMA) was not performed. A severe or life-threatening infection was reported for 38% of the subjects. An infection by any virus was reported for 61% of the subjects, and the 1-year incidence of EBV infection in particular was 25%. One subject (2%) developed a fatal post-transplantation lymphoproliferative disorder.

The potential risks of using the CliniMACS® CD34 Reagent System were also evaluated in DAP 1001-34. Table 5 suggests that the results for the 37 CR1 subjects in BMT CTN 0303 are similar to or better than the results for the 65 CR1 subjects in the historical control dataset.

Table 5: Comparison of the Single-Arm CliniMACS® CD34 Reagent System Study to Historical Controls Using Pharmacological Immunosuppression

Endpoints	**Single-Arm CliniMACS® CD34 Reagent System (n=37) % (95% CI)**	**Historical Controls Using Pharmacological Immunosuppression (n=65) % (95% CI)**
% Neutrophil Engraftment at Day 30 (≥500/μL)[1]	100	100[2]
% Platelet Engraftment at Day 30 (≥20,000/μL)[1]	92 (82.4, 100)	84[3] (72.5, 91.4)
Acute GVHD at Day 100, Grades 2–4[1]	27 (13.9, 42.0)	35 (23.9, 47.0)
Acute GVHD at Day 100, Grades 3–4[1]	5 (1, 16.1)	9 (3.7, 17.8)
Chronic GVHD at 2 years[1]	19 (8.2, 33.0)	49 (36.5, 61.0)
Relapse Rate at 2 years[1]	16 (6.5, 29.9)	28 (17.7, 39.7)
Non-relapse Mortality at 2 years[1]	20 (8.5, 34.5)	14 (6.8, 23.4)
Overall Survival at 2 years	67 (48.8, 79.7)	67 (54.1, 77.2)
Disease-free Survival at 2 years	64 (46.0, 77.4)	58 (44.8, 68.9)
GVHD-free Survival at 2 years	46 (29.6, 60.9)	18 (9.6, 28.2)

[1] *Cumulative Incidence*
[2] *neutrophil engraftment data missing for two patients*
[3] *platelet data missing for one patient*

The results of ACS 950101 did not raise any additional safety concerns regarding use of the CliniMACS® CD34 Reagent System for selection of $CD34^+$ cells.

XI. RISK – PROBABLE BENEFIT ANALYSIS

CR1

The results of BMT CTN 0303 indicate that the use of the CliniMACS® CD34 Reagent System is sufficient for transplantation and engraftment of HPC, Apheresis from HLA-identical donors. For subjects with AML in CR1, the comparisons made in DAP 1001-34 indicate that such transplants have a rate of GVHD that is similar to or better than historical controls, but without the need for additional immunosuppressive drugs. Further, the comparisons made in DAP 1001-34 show that this benefit is achieved without a negative impact on key transplant outcomes (DFS, OS, relapse) for the subjects with AML in CR1.

Additionally, although there was a wide range in the quality characteristics of the cells selected by the device (specifically $CD3^+$ and $CD34^+$ cells), the probable benefit of the device appeared to be clinically acceptable over the entire range of numbers of cells infused within the clinical trial experience. The safety and probable benefit of use of the device outside this range are unknown.

The review of safety revealed a significant increase in the risk of viral infections, especially EBV and CMV. However, these types of infections can largely be mitigated by pre-emptive therapy guided by serial monitoring. Consequently, this risk is acceptable given the probable benefit, but is reflected in labeling, to ensure that transplant physicians are aware of the need for additional monitoring. See Section IV *Warnings and Precautions* for additional information about monitoring for these infections.

CR2

As discussed at the September 23, 2011 meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) (see Section XII), the number of CR2 subjects in the BLA trials is too small for meaningful statistical analysis. However, the results for the CR2 subjects include hazard ratios of 1.11 (95% confidence interval (CI) = 0.35 – 3.57) for overall survival (OS); 1.18 (95% CI = 0.40 – 3.44) for disease-free survival (DFS); and 2.04 (CI = 0.58 – 7.08) for relapse, when compared with the matched historical control data. In patients with leukemia, OS, DFS, and relapse are not only efficacy outcomes for the assessment of probable benefit, but also important safety measures. Thus, the DAP 1001-34 results raise concerns about both safety and probable benefit in the CR2 population.

It is not feasible to power clinical trials to assess efficacy endpoints, much less safety outcomes, in each biologically plausible subgroup. In addition, subset analyses, even if pre-specified and biologically plausible, are often misleading. Therefore, such subset analyses are best viewed as hypothesis-generating, rather than confirmatory, and usually

do not determine regulatory decisions regarding the indicated population. However, with regard to the CR2 population, the concern is based not on the lack of statistical significance to support efficacy, but rather on the fact that the point estimates for each of these important efficacy and safety parameters suggest that use of the device may be harmful in the CR2 population.

Thus, exclusion of CR2 patients from the indicated population is warranted for this HDE because of 1) the biologic plausibility of a difference between CR1 and CR2 patients, as discussed by the CTGTAC, and 2) the level of concern that this HDE does not meet either the HDE safety standard or the HDE probable benefit standard for the CR2 population.

Pediatrics

As discussed at the September 23, 2011 meeting of the CTGTAC (see Section XII), there are insufficient data on the risks of use of the device in the pediatric population. However, the level of concern regarding safety in the pediatric population is not sufficient to warrant a post-marketing requirement or commitment for a pediatric study.

XII. ADVISORY COMMITTEE MEETING

On September 23, 2011, the Cellular, Tissue, and Gene Therapies Advisory Committee discussed the HDE for the CliniMACS® CD34 Reagent System.

The Committee voted (13-2) that there is 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 GVHD prophylaxis in patients with AML in first or second morphologic complete remission. The discussion highlighted some safety concerns, particularly the increased rate of viral infections and, in the CR2 patients, the high rate of relapse. Some members of the Committee expressed the opinion that with appropriate surveillance and treatment, the infections should be manageable, such that the probable benefit may outweigh those risks of infection.

After extensive discussion, the Committee concluded that the number of subjects in CR2 was too small to make a determination regarding safety in this subgroup. There was no consensus regarding how this should be reflected in the labeling, with opinions ranging from including CR2 in the indication to excluding CR2.

The Committee voted (14-1) that there is reasonable assurance that the CliniMACS® CD34 Reagent System provides probable benefit by obtaining a CD34 positive cell-enriched population for patients with AML in first or second morphologic complete remission undergoing a myeloablative preparative regimen. The Committee discussion focused on probable benefit for chronic GVHD, particularly for those patients in CR1, since CR1 patients would not need prolonged prophylactic therapy for GVHD. Committee members stated that control of acute and chronic GVHD, as well as

preservation of GVHD-free survival without the use of immunosuppressive drugs, were major indicators of probable benefit. Some Committee members expressed the opinion that the outcomes were not likely driven by the use of ATG in the preparative regimen, since the control of GVHD extended over months, while the half-life of ATG was relatively short. Some Committee members stated that randomized trials would be necessary to confirm an actual clinical benefit of use of the device.

The Committee acknowledged that there were no data on use of the device for children with AML. However, some Committee members expressed the opinion that it was unlikely that the risks would be greater than those reported for the adults in the clinical trial, and recommended that the labeling specify the lack of data, but not preclude children from the indication.

Additional discussion addressed training, device performance, and technical labeling.

XIII. CBER DECISION

CBER has determined, based on the data submitted in the HDE, that the CliniMACS® CD34 Reagent System will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the device outweighs the risks of illness or injury, and issued an approval order on January 23, 2014.

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See Instructions for Use

Hazards to Health from Use of Device: See Indications, Contraindications, Warnings and Precautions, and Adverse Events in the labeling

Post-approval Requirements and Restrictions: See Approval Order

XV. REFERENCES

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[viii] Gallardo D, de la Camara R, et al. Is mobilized peripheral blood comparable with bone marrow as a source of hematopoietic stem cells for allogeneic transplantation from HLA-identical sibling donors? A case-control study. Haematol 2009;94:1282-1288