Clinical Review, October 2, 2012 - Ducord

Application Type
BLA, Original Application
STN
125407/0
CBER Received Date
September 9, 2011
PDUFA Goal Date
Original due date: July 9, 2012; due date after acceptance of a major amendment: October 4, 2012
Division / Office
GMB/DCEPT/OCTGT (Clinical)
TEB/DB/OBE (Statistical)
Priority Review
No
Reviewer Name
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Review Completion Date
October 2, 2012
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Applicant
Carolinas Cord Bloo
Duke University School of Medicine
Established Name
HPC (Hematopoietic Progenitor Cells), Cord Blood
(Proposed) Trade Name
DUCORD
Pharmacologic Class
Allogeneic Cord Blood
Formulation
Each Unit of DUCORD contains:

- Active ingredient: a minimum of 9.0 x 108 total nucleated cells (TNC) with a minimum of 1.25 x 106 viable CD34 cells
- Inactive ingredients: dimethyl sulfoxide (DMSO), citrate phosphate dextrose (CPD), hydroxyethylstarch, and Dextran 40

Dosage Form and Route of Administration
A cell suspension for intravenous use only

Dosing Regimen
Recommended minimum dose is 2.5 x 107 TNC/kg at cryopreservation.
Indication
DUCORD is an allogeneic cord blood hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

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GLOSSARY

Table 1. Abbreviations and Glossary

ABO
A human blood type and blood group system
AC
Advisory Committee
Age Group Definition
Neonate: <28 days; Infant: >1 month; pediatric: >1 and <18 years;
Adult: >18 years; geriatric: >65 years
AE
Adverse Event
ALL
Acute lymphoblastic leukemia
AML
Acute myelogenous leukemia
ANC
Absolute Neutrophil Count
APLB
Advertising and Promotional Labeling Branch
BLA
Biologics license application
BRMAC
The Biological Response Modifiers Advisory Committee
CBER
Center for Biologics Evaluation and Research
CBU
Cord Blood Unit
CCBB
Carolinas Cord Blood Bank
CD34
A cluster of differentiation molecule present on certain cells within
the human body
CFR

Code of Federal Regulations
(b)(4)
---------(b)(4)---------
CI
Confidence interval (95%, unless otherwise specified)
CIBMTR
Center for International Blood and Marrow Transplant research
CMC
Chemistry, manufacturing, and controls
CMV
Cytomegalovirus
COBLT
The Cord Blood Transplantation Study
CRID
CIBMTR Recipient Identification
CRO
Contract Research Organization
CPD
Citrate-Phosphate-Dextrose
eCTD
Electronic Common Technical Document
DUCORD
Duke University Cord Blood; proposed trade name
Docket Data
Raw data submitted from multiple cord blood banks and cord blood organizations, such as NMDP, NYBC, and Duke University, to Dockets FDA-1997-N-0010 (Legacy docket number 97N-0497), FDA-2006-D-0157 (Legacy Docket number 06D-0514), and FDA-
2009-D-0490.
DMSO
Dimethyl sulfoxide
EBV
Epstein-Barr virus
--(b)(4)--
----------(b)(4)----------
ES
Engraftment syndrome
FDA
Food and Drug Administration
GCP
Good Clinical Practices
GVHD
Graft versus host disease
HbsAg
Hepatitis B surface antigen
HCV

1. EXECUTIVE SUMMARY

Carolinas Cord Blood Bank (CCBB) of Duke University submitted BLA 125407 to apply for licensure of their allogeneic cord blood product DUCORD. DUCORD is comprised of hematopoietic progenitor cells (HPC) that are collected from the cord blood donor. The proposed indication is use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

To support the safety and efficacy of DUCORD, the applicant submitted their own observational dataset of 1403 patients who received allogeneic cord blood units manufactured by CCBB. In addition, the applicant made reference to a prospective study “the Cord Blood Transplantation Study” (COBLT), in which the applicant participated, and to the FDA Docket data (FDA-1997-N-0010), as well as published literature related to HPC, Cord Blood.

The efficacy of HPC, Cord Blood, including DUCORD, for hematopoietic reconstitution has been established by FDA analyses of the Docket data as well as the COBLT study and other published observational studies. These studies demonstrated a correlation of total nucleated cell (TNC) count infused with the time and proportion to engraftment. A minimum effective cell dose of >2.5 x 107 cells/kg with degree of human leukocyte antigen (HLA) match 4/6 loci and above is defined as a suitable allograft for the purposes of this BLA review.

The reviewers have evaluated the efficacy of DUCORD by analyzing the hematopoietic reconstitution, particularly neutrophil and platelet recovery, of patients who received a suitable cord blood allograft. Neutrophil recovery is defined as the time from transplantation to an absolute neutrophil cell (ANC) count greater than 500 per microliter (ANC >500/µl). Platelet recovery is the time to a platelet count greater than 20,000 per microliter (> 20,000/µl). The incidence and timing of neutrophil and platelet recovery associated with DUCORD were comparable to those outcomes in the Docket and COBLT data, supporting the efficacy of DUCORD (Table 2).

Table 2. Summary of Efficacy, Hematopoietic Reconstitution - a comparison among DUCORD, COBLT and Docket Data

Data Source Design	COBLT Study* Single-arm, prospective	Docket and Public Retrospective Data*	DUCORD Retrospective
Number of Patients	324	1299	550
Median Age (years)	4.6	7.0	11
Median TNC Dose (x107/kg)	6.7	6.4	6.6

Data Source Design	COBLT Study* Single-arm, prospective	Docket and Public Retrospective Data*	DUCORD Retrospective
Neutrophil Recovery by Day 42 (ANC>500µL)	76%	77%	95%**
Platelet Recovery by Day 100 (>20,000/µL)	57%		92%**
Median Time to Neutrophil Recovery	27 days	25 days	21 days**
Median Time to Platelet Recovery	90 days		46 days**

*HPC, Cord Blood from multiple cord blood banks
**For each variable, the analysis of hematopoietic recovery is based on a different number of treated patients, ranging from 402 – 535.
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The outcomes of hematopoietic reconstitution appear to be better for patients who received DUCORD than for subjects in the COBLT study or for the patients in the overall pooled FDA Docket data. However, the DUCORD efficacy data are incomplete due to missing data for many elements among the outcome parameters, and are based on a relatively small subset of the patients who had complete data for the analyses. In addition, there is insufficient information about the nature of the diseases and their severity, and the transplant preparative regimens in the various datasets to ensure a reasonable comparison. Therefore, the data are insufficient to support a claim of superior effectiveness of DUCORD.
The DUCORD data do not include information regarding immunologic reconstitution. However, the analyses of the docket data and the publically available data provide evidence that HPC, Cord Blood has the capacity for immunologic reconstitution for patients transplanted for primary immunodeficiency as well as for other malignant and nonmalignant disorders (see Section 12. Appendices).
The safety review of this BLA focuses on transplantation-related adverse events, including early mortality (Day 100 after transplantation), infusion reactions, graft versus host disease (GVHD), and graft failure. The assessment of these adverse events is based primarily on the analyses of the docket data and supplemented by the DUCORD data, with consideration of the publically available data. The safety analyses confirmed that the safety profile of DUCORD is comparable to the safety profile of HPC, Cord Blood in the Docket and COBLT datasets. The analyses of the DUCORD dataset do not identify any safety issues that are atypical for this class of products (Table 3).
Table 3. Summary of Safety, frequencies of Major Adverse Events – a comparison among DUCORD, DOCKET, and COBLT data

Adverse Events	*Docket or COBLT	**DUCORD

Adverse Events	*Docket or COBLT	**DUCORD
Early Mortality (Day 100)	25% (Docket)	22%
Primary Graft Failure	16% (Docket)	6%
Acute GVHD	69% (Docket)	60%
Infusion Reactions	65% (COBLT)	19%

*pooled data from multiple blood banks;
**various subgroups of datasets were used for analyzing different safety outcomes due to missing data.

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Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. The active ingredient, indication, dosage form, dosing regimen, and route of administration of DUCORD are not new, but are the same as for HEMACORD – the first FDA approved HPC, Cord Blood product, manufactured by New York Blood Center. Therefore, this application does not trigger PREA.

Although the risks of conducting HPC, Cord Blood transplantation in conjunction with a preparative regimen for hematopoietic reconstitution are high, the diseases that affect the hematopoietic system for which cord blood transplantation is indicated are usually serious or life-threatening. Therefore, the risk-benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or type of hematopoietic progenitor cells.

For post-marketing surveillance, the applicant has provided an adequate plan to review and analyze the clinical outcomes and adverse event data associated with their product; these data are collected and reported to the CCBB by the National Marrow Donor Program (NMDP) and Center for International Blood and Marrow Transplant Research (CIBMTR). The applicant will report all serious and unexpected adverse events to FDA within 15 days. The applicant will document the expected or nonrelated adverse events and submit them to FDA annually as per 21CFR 800.60.

Based on overall risk-benefit consideration of the docket data referenced in this application, supplemented by the DUCORD data, and considering the publically available data, the reviewers recommend approval of DUCORD for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. However, the risk-benefit assessment for an individual patient depends on his/her characteristics, including the disease itself, specific stage and manifestations of the disease, risk factors, characteristics of the graft, and on the availability of other types of hematopoietic progenitor cells.

Because the risks of DUCORD and its preparative regimen can be mitigated and managed through the labeling of the product and pharmacovigilance plan, the reviewers do not recommend a Risk Evaluation and Mitigation Strategy (REMS), Postmarketing Requirement (PMR), or Postmarketing Commitment (PMC) for DUCORD.
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2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied
The proposed indication for this product is for the use in unrelated donor blood hematopoietic progenitor cell transplantation procedures for hematopoietic and immunologic reconstitution for diseases affecting hematopoietic systems that are inherited, acquired, or result from myeloablative treatment. The categories of disorders for which hematopoietic and immunologic reconstitution is required include malignancies, metabolic disorders, marrow failure, hemoglobinopathy, immunodeficiency, and certain autoimmune disorders. These diseases are usually serious, life-threatening, and with unmet medical needs. Please see the FDA reviews of the docket information for malignant and non-malignant indications regarding the effect of hematopoietic and immunologic reconstitution on specific disease outcomes (See Section 12. Appendices)
2.3 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)
The FDA-approved therapies for hematological malignancies include various chemotherapy, immunotherapy, and targeted biologic agents. For some non-malignant indications, there are FDA-approved therapies including drugs, biologics, immunotherapy, and other standard supportive therapy. However, there are no FDA-approved, pharmacologically unrelated therapies for hematopoietic and immunological reconstitution as proposed in this BLA.
2.3 Safety and Efficacy of Pharmacologically Related Products
There are several sources of stem cells for allogeneic hematopoietic stem cell transplantation, including hematopoietic progenitor cells derived from bone marrow (HPC-M) and hematopoietic progenitor cells derived from peripheral blood apheresis (HPC-A). Use of unrelated cord blood has increased over the past 20 years with improved outcomes (Reference 13). Unrelated cord blood transplantation has extended the availability of allogeneic HSCT to patients who would not be eligible for this potentially curative approach because of lack of an HLA-identical bone marrow (HPC-M) or granulocyte colony-stimulating factor mobilized peripheral blood hematopoietic stem cell (PBSC, HPC-A) donor. Studies suggest that the total number of nucleated cells is the most important factor for engraftment, while favorable outcomes can occur in spite of some degree of HLA mismatch.
FDA has approved two HPC, Cord Blood products for the same indication as in this BLA. The two products are HEMACORD from New York Blood Center, Inc., approved in 2011, and HPC, Cord Blood from ClinImmune Labs, approved in 2012.
2.4 Previous Human Experience with the Product

Umbilical cord blood has been recognized as a source of hematopoietic stem cells for allo-HCT for over 20 years in the United States and worldwide. Table 4 describes the main events in the development of unrelated cord blood transplantation for the treatment of hematological malignancy and non-malignancy in children and adults.

Table 4 . Development of Unrelated Cord Blood Transplantation

Time Line	Events
1974	Identification of hematopoietic stem cell in human umbilical cord blood by Knudtzon.
1989	First successful sibling HLA-matched HPC-C transplantation in a 6 year old with Fanconi anemia reported.
1993 - 1996	First unrelated HPC-C transplant in a 4 year old boy with relapsed leukemia in 1993 and subsequently in other 24 children (Reference 3).
1997	Initiation of the Cord Blood Transplantation Study (COBLT): established 3 cord blood banks including CCBB, collection SOPs for banking, and a banking trial.
1998	First registry report of outcomes of 562 cord blood recipients from New York Blood Center (Reference 4).
2004	The CIBMTR was established by joining together the research programs of NMDP and IBMTR. CIBMTR conducts research on hematopoietic cell transplantation and provides cord blood outcome data to cord blood banks in US and worldwide.
1999-2005	A companion COBLT trial: a prospective, multi-center (n=26) clinical trial using units from CCBB and NYBC to study various disease cohorts of pediatric and adult malignancies and pediatric non-malignancies; establish the suitable HLA match >4/6 and effective dose at TNC>2.5/kg x 107 (References 2, 9, 10).

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2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the BLA Submission

9/17/2010 Pre-BLA meeting

9/9/2011 BLA original submission

9/29/2011 Teleconference with the applicant to discuss a list of minimal required variables on the BLA dataset

2/20/2012 Final dataset submitted

6/2012 CMC submission to the BLA characterized by FDA as a major amendment

10/4/2012 Revised PDUFA due date after the major amendment submission

2.6 Other relevant Background Information

On January 20, 1998 (63 FR 2985), FDA issued a notice in the Federal Register entitled “Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Blood Hematopoietic Stem/Progenitor Cell Products; Request for Comments” in which FDA proposed to determine if it would be possible to develop product standards and establishment and processing controls for minimally manipulated unrelated allogeneic hematopoietic stem/progenitor cell products intended for hematopoietic reconstitution, based on existing clinical trial data, or data developed

shortly thereafter, demonstrating the safety and effectiveness of such cells. Submitted comments were to include supporting clinical and nonclinical laboratory data and other relevant information. A period of two years was provided, until January 20, 2000, for interested persons to submit supporting clinical data. At the request of industry, the comment period was reopened for 90 days until July 17, 2000 (65 FR 20825, April 18, 2000).
On February 27, 2003, the Biological Response Modifiers Advisory Committee (BRMAC) met to discuss issues related to the use of unrelated allogeneic hematopoietic stem/progenitor cells derived from placental/umbilical cord blood for hematopoietic reconstitution, including the analysis of clinical outcome data submitted to FDA, as well as information provided by guest experts regarding the safety and effectiveness of cord blood for hematopoietic reconstitution. On the basis of the submitted information, discussion of the BRMAC, and review of published literature on this subject, FDA determined that the data were sufficient to establish the safety and effectiveness of HPC- Cs for allogeneic transplantation in the treatment of hematologic malignancies.
On January 17, 2007 (72 FR 1999), the draft guidance for licensure of minimally manipulated cord blood entitled “Guidance for Industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies” became available.
Additional discussion was held with the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) on March 30, 2007. The committee discussed access to HPC, Cord Blood units already in inventory and recommended additional clinical indications.
In the process of finalizing the guidance, the FDA considered the recommendations of the CTGTAC, the public comments to the draft guidance, and additional data submissions.
In a Federal Register notice of October 20, 2009 (74 FR 53753), FDA announced the availability of the “Guidance for Industry - Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications”. In this notice of availability, the FDA also announced that it would end the period of phased-in implementation of IND and BLA requirements for HPC, Cord Blood. This announcement established a two-year implementation period, which ended October 20, 2011, by which all distribution of HPC, Cord Blood for clinical use in the United States would need to be done under an approved BLA or active IND.
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3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness
This was a paper submission, which was accepted for filing by the review team because most elements required for review were satisfactory. The main focus of the clinical and statistical review was the clinical outcome data and adverse events that were submitted as a raw dataset in an Excel file.

FDA data analyses are based on an incomplete dataset: missing data are present in various outcome variables to different degrees. Therefore, each analysis of efficacy and safety variables is based on a different subgroup of patients as shown in Table 5. The retrospective and voluntary nature of data collection is at least partially responsible for the amount of missing data. In addition, numerous instances of miscoding and inconsistencies within the dataset have been identified and largely resolved through communication between the reviewers and the applicant (Section 2.5).

Table 5. Number of Patients Selected for FDA Analyses based on Available Data from Demographic and Outcome Parameters

FDA Efficacy and Safety Analyses of DUCORD	Demographic and outcome parameters needed for the analyses	Selected Subgroup of Patients (n)/th>	>Table # in BLA
Demographics of total population	Demographics (age, gender, ethnicity/race) and diagnosis	1403 patients with 1497 infusions	Table 11
All subjects with suitable allografts	Demographics, diagnosis, dose, and HLA match	718	Table 11
Hematopietic reconstitution in patients with suitable allograft	Dose, HLA match, time to neutrophil and platelet engraftment (if achieved) or follow-up time	550	Table 12
Dose-Response analysis	Dose, HLA match, indication of neutrophil recovery r	580	Table 13
Delayed neutrophil recovery	Dose, HLA match, time to neutrophil recovery, if achieved or follow-up time, and diagnoses of hematological malignancy	384	Table 15
Product characteristics and dose exposure	Dose, HLA match, body weight, processing methods, storage time	718	Table 16
Total and early mortality analyses	Demographics, diagnosis, dose, HLA match, time to death or follow-up time	937	Table 17
Primary causes of early death	Date of death and causes of death	646	Table 19
Primary graft failure	Dose, HLA match, time to neutrophil recovery, if achieved, or follow-up time	550	Table 20
Incidence of GVHD	Dose, HLA match, grades, date of diagnoses	646	Table 21
Incidence of infusion reactions	Dose, HLA match, infusion reaction records	388	Table 23

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3.2 Compliance With Good Clinical Practices And Submission Integrity

Good Clinical Practices (GCPs) generally apply to clinical trials. No clinical trials were conducted by the applicant. Therefore, GCPs are not applicable for this BLA.

3.3 Financial Disclosures

Although no clinical trial was conducted in this BLA, the applicant submitted Form 3454 (1.3.4) to certify that the listed physicians in the cord blood collection sites did not participate in any financial arrangement with the sponsor, had no proprietary interest in this product, and were not the recipients of significant payments of other sorts.
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4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

After the inspection of the manufacturing facility, there were many issues identified regarding validation and release criteria of the product. In response to CMC issues raised by FDA, the applicant submitted a major amendment in June 2012, which postponed the PDUFA goal date to October 4, 2012.

4.1 Chemistry, Manufacturing, and Controls

DUCORD contains a minimum of 9 x 108 nucleated cells in a (b)(4) mL mixture of Citrate Phosphate Dextrose, 10% DMSO, 1% Dextran, and (b)(4) Hespan. The cells have (b)(4) viability pre-cryopreservation and a minimum of 1.25 x 106 viable CD34+ cells.

The cord blood was collected in 13 sites in the states of North Carolina, Massachusetts, Florida, and Louisiana (Table 6). Before 2008, the cord blood units were collected using -(b)(4)- methods, but after 2008, the cord blood has been collected using an ----(b)(4)---- method – (b)(4). The sponsor intends to license the cord blood units collected by the (b)(4) method.

Table 6. CCBB Cord Blood Collection Sites

Name	Abbreviation Used in Dataset
Brigham and Women's Hospital	BWH
Durham Regional Hospital	DRH
Duke University Hospital	DU
Rex Hospital	Rex
Sarasota Hospital	SAR
Sibling Program (directed donors)	SIB
South Miami Hospital	SMH
UNC Hospital (Chapel Hill, NC)	UNC
Womack Army Medical Center	WAMC
Women's Hospital Baton Rouge	WH-BR
Women's Hospital of Greensboro	WHG
WakeMed Cary	WMC
Winnie Palmer Hospital	WP

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Please see the CMC review of this BLA for details.

Donor Information
HPC Cord Blood donations are screened to exclude potential donors with either a medical history of increased risk of infection or positive screening tests such as HIV, hepatitis, and CMV. Products are also screened for homozygous or double heterozygous hemoglobinopathy. Screens for genetic diseases that could be transmitted through transplantation are conducted through maternal and family medical history questionnaires.
Collection procedures:
The clinical reviewer reviewed the collection SOPs listed in Table 7. There are no major safety concerns regarding the SOPs listed in Table 7.

Table 7. CCBB Standard Operating Procedures for HPC, Cord Blood Collection

SOP Title	Description
Obtaining Informed Consent	Obtaining donor's permission to collect cord blood and maternal informed consent
Donor screening and evaluation	Maternal donor screening and questionnaires
Receiving and filing maternal infectious disease results	Maternal donor testing
Obtaining donor medical history procedure	Donor eligibility determination
Notifying donors of positive infectious test results	Notification of mothers/physicians regarding positive infectious disease tests
Look forward maternal contact verification	Elicitation and handling of post-donation information
Clinical outcome data	Elicitation and handling receipt of adverse events
Training non-CCBB staff in collection of CBU at CCBB fixed collection sites	Physician training procedures

4.2 Assay Validation
Please refer to the CMC review of this BLA.
4.3 Nonclinical Pharmacology/Toxicology
The device components used in manufacturing and storage are cleared by FDA for cord blood processing, and the anticoagulant and diluents are approved by FDA. No additional studies of biocompatibility were required.
Dimethyl sulfoxide (DMSO) may cause adverse reactions, such as infusion reactions. Published studies report teratogenic responses caused by intraperitoneal administration of DMSO to rodents, and hemolytic reactions caused by intravenous administration of DMSO to rodents. Please refer to the Pharmacology / Toxicology review of this BLA for details.
4.4 Clinical Pharmacology
4.4.1 Mechanism of Action
Hematopoietic stem/progenitor cells from HPC, Cord Blood migrate to the bone marrow where they divide and mature. The mature cells are released into the bloodstream,

where some circulate, and others migrate to tissue sites, partially or fully restoring blood cell counts and function, including immune function.
In patients with enzymatic abnormalities due to certain severe types of inborn disorders, mature leukocytes resulting from HPC, Cord Blood transplantation may synthesize enzymes that can improve cellular functions of some native tissues. However, the precise mechanism of action is unknown.
4.4.2 Human Pharmacodynamics (PD)
Not applicable; therefore, no information was provided.
4.4.3 Human Pharmacokinetics (PK)
Not applicable; therefore, no information was provided.
4.5 Statistical
The statistical reviewer has selected all the safety and efficacy data from the raw dataset for analyses.
4.6 Pharmacovigilance
Under Standard Operating Procedures (SOP) (3.2.R.2), the applicant submitted SOP "Clinical Outcome Data" (CCBB-Admin-014) to describe the process through which the CCBB at Duke obtains and analyzes follow-up clinical outcomes data obtained from Transplant Centers utilizing units from the CCBB for transplantation of patients in need. The data collection is supported and facilitated by the ---------(b)(4)----------, the Center for International Blood and Marrow Transplant Research (CIBMTR), and the National Marrow Donor Program (NMDP). Since 2007, transplant centers submit data to the CIBMTR, which audits and qualifies the data and performs quarterly downloads of the dataset to the banks. The dataset includes patient CIBMTR Recipient ID (CRID), date of birth, race/ethnicity, gender, diagnosis, disease state at the time of transplant, preparative regimen, GVHD prophylaxis, Cord blood ID, TNC cell dose, ----------(b)(4)----------, CD34, (b)(4) content; engraftment outcomes, day to ANC greater than 500/µL, platelet count greater than 20 and 50k/µL, chimerism, acute and chronic GVHD, relapse, non- relapse mortality, and cause of death.
Clinical outcomes analyzed include time to engraftment as a function of TNC, CD34+ cell count, and (b)(4); donor chimerism; time to engraftment as a function of time in storage (stability); incidence of acute and chronic GVHD; recovery of TNC, CD4, and (b)(4) post-thaw; and incidence of sterility post-thaw.
The Medical Director reviews the reports and identifies outliers in each category. CIBMTR, NMDP, and --(b)(4)-- also independently review data and flag outliers
Under Risk Management Plans, the applicant described procedures to collect and report adverse events. The Carolinas Cord Blood Bank (CCBB) distributes HPC, Cord Blood units to the transplant centers through the NMDP. The transplant center is required to submit and report clinical outcomes, including any adverse events (AEs) to the NMDP (National Marrow Donor Program) and CIBMTR (Center for International Blood and Marrow Transplant Research). Thus, adverse events are reported to the CCBB from two main sources, the NMDP and the CIBMTR. In general, acute, serious, unexpected, or severe AEs will be obtained from the NMDP, and other AEs or outcomes will be obtained from the CIBMTR. After receiving clinical outcomes and adverse event data from the NMDP and CIBMTR, all AE reports are reviewed by the CCBB Medical Director and the Quality Director to identify relationship, reportability to FDA, and a need for further investigation. The pending product label is used to assist

with determining expectedness and reporting category. All AEs are documented and stored in a large dataset with other clinical outcomes. Per regulations and standard procedures (CCBB-QA-010), all serious and unexpected adverse events are reported to FDA within 15 calendar days of initial receipt of the information via an Alert Report. Follow-up for each AE is performed as necessary to ensure that all additional information (needed to assess and analyze the AE) has been obtained. The reviewers considered the above risk management plan adequate.
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5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

The efficacy and the safety review of DUCORD focuses on hematopoietic reconstitution, death, graft failure, GVHD, and infusion reactions, based primarily on the docket data, supplemented by the DUCORD data, and taking into consideration the publically available data (including the COBLT Study).
Table 8 summarizes the key DUCORD data sources and key data analyses strategies.

Table 8. Summary of Key Data Sources and Data Analysis Strategies

BLA Dataset Categories	Data Summary
Total number of transplanted patients	1403
Total number of transplanted cord blood units	1497
Total number of patients overlapping with COBLT data	11%
Patients with suitable allograft*	718
Source of the outcome data	NMDP and COBMTR quarterly data report to the applicant based on transplant center reports
Cord blood collection centers	13
Dose (TNC/kg x 107)	N=831. Median=5.6 (range 1 to 90.5)
Storage time (days)	N=831. Median=973 (range 103 to 4067)
Processing method	-(b)(4)-: 82%; and (b)(4): 18% (after 2008)
Transplant period	1999 to 2011
Study design	Retrospective, no control group, non-randomized, unblinded; no prospective design or endpoints
Key demographics	N=1403. Mean age: 24 years; pediatric: 50%; malignancy: 74%
Comparator used for efficacy and safety analyses for the applicant's dataset	COBLT and Docket Data
Indicators of DUCORD efficacy	Neutrophil and platelet recovery
Indicators of DUCORD Safety	Mortality, graft failure, GVHD, and infusion reactions

* TNC dose at >2.5x107/kg and HLA match at >4/6
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5.1 Review Strategy

This BLA review is the result of a joint review by the clinical reviewer and the statistical reviewer to analyze the raw dataset regarding the safety and efficacy of the product. The statistical reviewer focused on assessment of data consistency and clarity and provided analyzed data as derived from the raw dataset. The clinical reviewer analyzed the data provided by the statistical reviewer to draw conclusions regarding efficacy and safety. Because there is no concurrent comparator group in this BLA submission, the results of the data analyses for the efficacy and the safety from the submitted data are compared with the results from COBLT and Docket data, which are the source for the efficacy and safety analyses of HPC, Cord Blood class, for the indication sought (see FDA clinical reviews in Section 12. Appendices).

Table 9 describes the demographic and outcome parameters that FDA used to analyze the efficacy and the safety of DUCORD.

Table 9. Outcome Data Parameters Required by FDA for Safety and Efficacy Analyses of DUCORD

Categories		Parameters
Patient and Product Information	**Demographics**	• Age: mean, median, range for neonates, infant, pediatric, adult, and geriatric age groups • Gender: female, male, unknown • Race/Ethnicity • Body weight at time of transplantation (kg) • Units of transfusion: one or more than one • Year of collection: <2008 (-(b)(4)-) and >2008 ((b)(4))
	Diagnosis	• By categories: Malignancies; metabolic disorders; marrow failure; hemoglobinopathy; immunodeficiency; autoimmune disorders
	HLA match	• 2-3/6; 4/6; 5/6; 6/6
	TNC dose	• Median total dose, range of total dose • Median and range of TNC dose/kg • TNC dose/kg by categories: <2.5, 2.5 -<5, 5 -<10, 10-<20, >20
	Storage time	• Median time of storage (time of cryopreservation to time of transplantation), and range of storage time
Efficacy Analysis	**Neutrophil recovery**	• Cumulative incidence of subjects with ANC > 500/μL by Day 42 or by Day 100; by all subjects and by subjects with *suitable allograft • Median time to ANC>500/μL, in all subjects and in subjects with suitable alograft • Time to engraftment beyond the expected upper 95% confidence limit: analysis of outliers

Categories		Parameters
		• Dose-Response effect of engraftment
	Platelet recovery	• Cumulative incidence of subjects with platelet>50,000/mL or >20,000 by Day 100, in all subjects and in subjects with a suitable allograft • Median time for platelet>50,000/mL or >20,000 < day 100, in all subjects and subjects with a suitable allogaft
Safety Analyses	**Death**	• Proportion of subjects with death, in all subjects • Proportion of death in subjects with TNC >2.5 x 107/kg vs. <2.5 x 107/kg • Proportion of death <100 days post-transplantation vs. >100 days • Proportion of death by age group (same as in demographics above) • Primary cause of death: proportion of subjects with different primary causes of death
	Graft failure	• Cumulative incidence of graft failure
	GVHD	• All subjects with GVHD • Acute GVHD (before 100 days post-transplant) • Chronic GVHD (after 100 days post-transplant) • Proportion of GVHD by grade 0, 1, 2, 3, 4 in all subjects and in subjects with a suitable allograft
	Infusion reactions	• Proportion of infusions with infusion reactions • Types and frequencies of adverse events: bradycardia, headache, hemoglobinuria, nausea, vomit, hypertension, tachycardia, chest pain, nausea, hypoxia, shortness of breath, hypotension, chills, hives, rigor
	Other safety information, if available	• Engraftment syndrome • Malignancies of donor origin • Transmission of rare genetic diseases, • Second transplantation (different infusion dates)

***** TNC do se at >2.5x107/kg and HLA match at >4/6

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Table 10 summarizes the data selection process for the efficacy and safety analyses based on the subset of patients who have available demographic and outcome parameters for each specific analysis (See Section 7 and 8 for detail of the analyses).

Table 10.Selection of Dataset

Step	Data file subset	Number of Subjects
1	**Submitted data file**	**1403 patients transplanted with 1497 units**
1a	And limited to records with TNC/kg dose reported	880 patients with 936 units
1b	And limited to records with HLA match reported	834 patients with 884 units
1c	And limited to records with at least age or gender Information	831 patients with 881 units
1d	If a patient received multiple units on the same day, the multiple units were combined to one infusion with the TNC doses summed up.	831 patients with 842 Infusions
1e	And limited to patients with a suitable allograft*	718 patients
2	**Subsets in this step are used for analysis of infusion reactions**	**Number of Subjects**
2a	Step 1d data file limited to records with information on whether an AE occurred	449 infusions
2b	And limited to records with TNC dose ≥ 2.5x107/kg	388 infusions
2c	And limited to records with infusion reaction data	72 patients with 72 infusions
3	**Subsets in this step are used for analysis of death and GVHD**	**Number of Subjects**
3a	Step 1d data file limited to the first transplanted unit for patients with multiple transfusion dates	831 patients with infusions
3b	And limited to patients with a date of death or last Contact	755 patients
3c	And limited to patients with a suitable allograft*	646 patients
4	**Subsets in this step are used for analysis of hematopoietic recovery**	**Number of Subjects**
4a	Step 3b data file limited to patients with hematopoietic recovery	639 patients
4b	And limited to patients with a suitable allograft	550 patients
4c	And limited to patients with complete time-to-event data for ANC>500	535 patients
4d	And limited to patients with a hematologic Malignancy	370 patients
4e	Step 4b data set limited to patients with complete time-to-event data for platelets >20K	402 patients
4f	Step 4b data set limited to patients with complete time-to-event data for platelets >50K	489 patients
4g	Step 4a data set limited to patients with neutrophil engraftment (ANC>500 by Day 42)	580 patients

*TNC dose at >2.5x107/kg and HLA match at >4/6

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5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

This review is based on the following documents from the BLA:

- Financial certification and disclosure (CTD 1.3.4)
- Correspondence regarding Pre-BLA Meeting (CTD 1.6.3)
- Labeling (CTD 1.14)
- Clinical Summary (CTD 2.7)
- Summary of clinical efficacy (CTD 2.7.3)

- Summary of clinical safety (CTD 2.7.4)
- Archive copies of maternal/family history questionnaires (CTD 3.2.A.7)
- Standard operating procedures (CTD 3.2.R.2)
- Consent forms (CTD 3.2.R.3)
- Clinical study reports and related information (CTD 5.3)
- Study reports and related information of controlled clinical studies pertinent to the claimed indications (CTD 5.3.5.1)
- Reports of analyses of data from more than one study (clinical outcome dataset in Excel) (CTD 5.3.5.3)
- Revised dataset submitted on 2/20/2012
  This review is based on the following FDA documents:
- Safety review of dockets and public information for hematopoietic progenitor cells-cord blood by Donna Przepiorka, MD, PhD, on 10/28/2011 (Appendix 12.1). This review contains the primary evidence of efficacy and safety to support this BLA.
- Efficacy review of dockets and public information for nonmalignant indications by John Hyde PhD, MD, on 11/3/2011 (Appendix 12.2).
- Efficacy review of dockets and public information on hematological malignancies by Maura O'Leary, MD, on 11/8/2011 Appendix 12.3).
- FDA guidance for industry - Minimally manipulated, unrelated allogeneic placental/umbilical cord blood intended for hematopoietic reconstruction for specified indications 2009.

  5.3 Table of Studies/Clinical Trials

  No clinical trial has been conducted by the applicant for this BLA.

  5.4 Consultations

  The reviewers have sought informal consultation from Dr. Donna Przepiorka, regarding required parameters of the dataset and the engraftment mathematical model.

  5.4.1 Advisory Committee Meeting

  On September 22, 2011, the Cellular, Tissue, and Gene Therapy Advisory Committee (CTGTAC) discussed the safety and efficacy of the BLA for HEMACORD, the first FDA-approved umbilical cord blood product manufactured by New York Blood Center.
  No Advisory Committee was held for this BLA because the DUCORD review team did not identify any novel safety concerns. Because DUCORD and HEMACORD are both umbilical cord blood products, some of the CTGTAC deliberations regarding HEMACORD (e.g., discussions of dose) are also relevant to DUCORD.

  5.4.2 External Consults/Collaborations

  No external consult was sought.

  5.5 Literature Reviewed

  1. Gluckman E, Broxmeyer HE, Auerbach AD, Friedman HS, Douglas GW, Devergie A, Esperou H, Thierry D, Socie G, Lehn P, Cooper S, English D, Kurtzberg J, Bard J, Boyse EA. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical cord blood from an HLA-identical sibling. *New Engl J Med.* 321 (17): 11741178, 1989.
  2. Cornetta K, Laughlin M, Carter S, Wall D, Weinthal J, Delaney C, Wagner J, Sweetman R, McCarthy P, Chao N. Umbilical cord blood transplantation in adults: results of the prospective cord blood transplantation (COBLT). *Biol Blood Marrow Trans.* 11 (2): 149160, 1995.

3. Kurtzberg J, Laughlin M, Graham ML, Smith C, Olson JF, Halperin EC, Ciocci G, Carrier C, Stevens CE, and Rubinstein P. Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. *New Engl J Med. 335(3):157-166,*1996.
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5. Laughlin MJ, Barker J, Bambach B, Koc ON, Rizzieri DR, Wagner J, Gerson SL, Lazarus HM, Cairo M, Stevens CE, Rubinstein P, Kurtzberg J. Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. *New Engl J Med.* 344(24):1815-1822, 2001.
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9. Wall D, Carter S, Kernan N, Kapoor N, Kamani N, Brochstein F, Frangoul H, Goyal R, Horan J, Pietryga D, Wagner J, Kurtzberg J. Busulfan/Melphalan/Antithymocyte globulin followed by unrelated donor cord blood transplantation for treatment of infant leukemia and leukemia in young children: the cord blood transplantation study (COBLT) experience. *Biol Blood Marrow Transplant.* 11(8):637-646, 2005.
10. Kurtzberg J, Prasad V, Carter S, Wagner J, Baxter Lowe L, Wall D, Kapoor N, Guinan E, Feig S, Wagner E, Kernan N. Results of the Cord Blood Transplantation Study (COBLT): Clinical outcomes of unrelated donor umbilical cord blood transplantation in pediatric patients with hematologic malignancies. *Blood.* 112(10):4318-4327, 2008.
11. Gluckman E. Ten years of cord blood transplantation: from bench to bedside. *Br J Haematol.* 147(2):192-199, 2009.
12. Styczynski et al. Outcome of treatment of Epstein-Barr virus-related post- transplant lymphoproliferative disorder in hematopoietic stem cell recipients: a comprehensive review of reported cases. *Transpl Infect Dis.* 11(5): 383-92, 2009.
13. Summary slide worldwide by Center for International Blood & Marrow transplant Research (CIBMTR): “Current uses and outcomes of hematopoietic stem cell transplantation 2011”. CIBMTR website

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

No clinical trial information was provided in this BLA.
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7. INTEGRATED OVERVIEW OF EFFICACY

The applicant did not conduct any clinical trials to assess the efficacy of DUCORD. The efficacy analysis of DUCORD is based primarily on the docket data, supplemented by the DUCORD data, and considers the publically available data.
In this section, the reviewers focus on retrospective review and analyses of the hematopoietic reconstitution, i.e., neutrophil recovery and platelet recovery, as the indicators of the efficacy for DUCORD, using an observational database of CCBB. Neutrophil recovery is defined as the time from transplantation to an absolute neutrophil count greater than 500 per microliter. Platelet recovery is the time to a platelet count greater than 20,000 per microliter. The efficacy outcomes of DUCORD are then compared to COBLT and Docket data to confirm DUCORD efficacy.
The DUCORD data do not include information to evaluate immunologic reconstitution following DUCORD transplantation. However, based on the docket data, and considering the publically available data, HPC, Cord Blood has demonstrated a benefit in immunologic reconstitution for patients transplanted for a variety of disorders associated with immunodeficiency.
7.1 Indication
DUCORD is an allogeneic cord blood hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.
7.1.1 Methods of Integration
The efficacy database is derived from a raw dataset of 1403 patients transplanted with 1497 units of DUCORD from 1999 to 2011 and collected in 13 sites. The efficacy analyses focus on the patients who received suitable allograft, which is defined as a TNC dose of >2.5 x 107/kg and HLA match >4/6. Doses of >2.5 x 107/kg are favored for a successful engraftment by the field in general (Reference 5, 7, 8). A total of 1403 patients received any number of units of DUCORD. However, only 550 patients had sufficient data to be included in the efficacy analyses (Table 10). No center-specific analyses were performed.
7.1.2 Demographics and Baseline Characteristics
Table 11 shows the demographic distribution of patients who received DUCORD units from February 5, 1999 to July 8, 2011. Because the applicant recommends using a dose at TNC>2.5x 107/kg at the time of cryopreservation and HLA match level of >4/6

(suitable allograft), the demographic data were listed for all the patients who received any dose of the DUCORD and for the patients who received suitable allograft.

Table 11. Demographic Characteristics of DUCORD Recipients

Subgroups	All Subjects N (%)	Subjects with **Suitable Allograft N (%)
Total Patients	1403	718
Age (years) Mean(SD)	24.(21) (years)	19. (20) (years)
Median	18 (years)	11 (years)
Range	0.060-80 (years)	0.071 – 79 (years)
Age Category Neonate < 28days	3 (0.21)	1 (0.14)
Infant: 1 – 12 months Pediatric: 1 – <18 years Adult: 18 – <40 years	99 (7.1)	70 (9.7)
Adult: 40 – <65 years Geriatric: ≥65 years Unknown	602 (43)	376 (52)
	295 (21)	118 (16)
	359 (26)	136 (19)
	33 (2.4)	16 (2.2)
	12 (0.86)	1 (0.14)
Gender Male	787 (56)	407 (57)
Female	601 (43)	310 (43)
Unknown	15 (1.1)	1 (0.14)
Ethnicity/Race White	767 (55)	485 (68)
African-American Hispanic Asian	176 (13)	92 (13)
*AMI/ALA Unknown	49 (3.5)	30 (4.2)
	50 (3.6)	26 (3.6)
	5 (0.36)	4 (0.56)
	356 (25)	81 (11)
Diagnosis Malignancies	1044 (74)	491 (68)
Metabolic Disorder Marrow Failure Hemoglobinopathy	177 (13)	123 (17)
Immunodeficiency Autoimmune Disorder unknown	84 (6.0)	31 (4.3)
	66 (4.7)	10 (1.4)
	16 (1.1)	59 (8.2)
	4 (0.29)	4 (0.56)
	12 (0.86)	

*American Indian/Alaska Native; **HLA Match >4/6 and TNC>2.5x107/kg

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7.1.3 Subject Disposition

Not applicable

7.1.4 Analysis of Primary endpoint - Hematopoietic Reconstitution: Neutrophil and platelet recovery

Because this BLA submission does not include prospective and controlled studies of DUCORD, no pre-specified primary or secondary endpoints were defined. In this review, the reviewers analyzed engraftment outcomes, particularly neutrophil and platelet recovery, to assess efficacy. The results of the engraftment outcomes associated with DUCORD were then compared with historic data from the Docket and from the COBLT study.

Table 12 shows FDA analyses of hematopoietic recovery data in the applicant's dataset. Because of the missing data, the analyses only represent a subpopulation from the entire dataset (see Table 10)

Table 12. Hematopoietic Reconstitution of DUCORD: Time to, or Cumulative Incidence of, Neutrophil (ANC) and Platelet (PLT) Recovery

Hematopoietic Reconstitution	Description	N	Outcomes of Subjects with Suitable Allograft
Time to ANC recovery	Median time (days) to ANC>500 k/uL	535	21 days
Cumulative Incidence of ANC recovery	ANC>500k/uL by Day 42 (95% CI*)	95 (92-96)%	
Time to Plt recovery (>20k)	Median time (days) to Plt>20k/uL	402	46 days
Cumulative incidence of Plt recovery (>20k)	Plt>20k/uL by Day 100 (95% CI)	92 (89-94)%	
Time to Plt recovery (>50K)	Median time (days) to Plt>50k	489	61 days
Cumulative incidence of Plt recovery (>50K)	Plt>50k/uL by Day 100 (95% CI)	71 (66-75)%	

*Confidence Internal

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Table 13 shows the dose-response effects of TNC doses and the categories of HLA matching on the proportion of patients achieving neutrophil engraftment after transplantation with DUCORD. A higher TNC dose with higher degree of HLA matching is associated with a higher engraftment rate.

Table 13. Proportion of patients achieving ANC >500 by Day 42, according to dose/kg and degree of HLA match (N=580)

	TNC Dose (x107 / kg)			
HLA Match	**<2.5**	**2.5 - < 5.0**	**5.0 - < 10.0**	**≥ 10.0**
3/6	1/1 (100%)	1/1 (100%)	0/0	2/2 (100%)
4/6	35/42 (83%)	108/122 (89%)	69/79 (87%)	49/53 (92%)
5/6	32/38 (84%)	64/70 (91%)	62/66 (94%)	80/84 (95%)
6/6	4/5 (80%)	19/20 (95%)	19/19 (100%)	35/37 (95%)

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Table 14 compares the engraftment data of DUCORD with COBLT and pooled docket data (See Section 12, Appendices). The outcomes of hematopoietic reconstitution appear to be better for patients who received DUCORD than for subjects in the COBLT study or for the patients in the overall pooled FDA Docket data. However, the DUCORD efficacy data are incomplete due to missing data for many outcome parameters, and are based on a relatively small subset of the patients who had complete data for the analyses. In addition, there is insufficient information about the nature of the diseases

and their severity, and the transplant preparative regimens, in the various datasets to ensure a reasonable comparison. Therefore, the data are insufficient to support a claim of superior effectiveness of DUCORD.

Table 14. Comparison of Hematopoietic Recovery for Patients Transplanted withSuitable Allograft among COBLT, Docket, and DUCORD data

Data Source **Design**	**The COBLT Study*** **Single-arm Prospective**	**Docket*** **Retrospective**	**DUCORD** **Retrospective**
Number of patients	324	1299	550
Median age (range)	4.6 (0.07 – 52.2) yrs	7.0 (<1 – 65.7) yrs	11 (0.083-79) yrs
Gender	59% male 41% female	57% male 43% female	56% male 44% female
Median TNC Dose (range) (x 107/kg)	6.7 (2.6 – 38.8)	6.4 (2.5 – 73.8)	6.6 (2.5-58.0)
Neutrophil Recovery at Day 42 (95% CI**)	76% (71% – 81%)	77% (75% – 79%)	95 %** (92% - 96%)
Platelet Recovery at Day 100 (20,000/uL) (95% CI)	57% (51% – 63%)	-	92%** (89% - 94%)
Platelet Recovery at Day 100 (50,000/uL) (95% CI)	46% (39% – 51%)	45% (42% – 48%)	71%** (66% - 75%)
Erythrocyte Recovery at Day 100 (95% CI)	65% (58% – 71%)	-	-
Median time to Neutrophil Recovery	27 days	25 days	21 days**
Median time to Platelet Recovery (20,000/uL)	90 days	-	46 days**
Median time to Platelet Recovery (50,000/uL)	113 days	122 days	61 days**
Median time to Erythrocyte Recovery	64 days	-	-

* From multiple cord blood banks; **Confidence Interval

** For each variable, the analysis of hematopoietic recovery is based on a different number of treated patients, ranging from 402 – 535.

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During her safety review of Dockets and Public Information regarding HPC, Cord Blood, Dr. Donna Przepiorka generated and validated a mathematical model from the pooled dataset to identify patients with delayed engraftment (i.e., exceed the expected upper 95% confidence limit for time to neutrophil recovery) for patients with hematological malignancies and receiving allografts with at least a 4 of 6 HLA antigen match and a TNC dose >2.5x107/kg. Applying this model to the 384 DUCORD patients with suitable allograft and diagnosis of hematological malignancy, 11 of the 384 patients (3%) had neutrophil recovery times that exceeded the expected upper 95% confidence limit (Table 15). This delayed engraftment rate is comparable to the 5% of patients in the testing set of Docket data who had neutrophil recovery times which exceeded the

expected upper 95% confidence limit (Safety Review of Dockets and Public Information, Page 25 by Donna Przepiorka, M.D., Ph.D.).

Table 15. Patients with Delayed Neutrophil Engraftment

	Age (Yr)	Sex	Race	HLA Match	Diag	TNC 107/kg (Single Unit)	Storage days	Acute GVHD	Chronic GVHD	Method	ANC >500 (Days)	Model Expect (Days)
1	8.92	M	White	4	ALL	9.5	1435	Y	N	Manual	55	44
2	3.50	F	White	5	AML	11.7	1602	Y	N	Manual	115	45
3	4.42	M	White	5	MDS	12.7	1154	N	N	Manual	66	44
4	8.67	F	White	4	MDS	6.3	1386	Y	N	Manual	80	46
5	2.67	M	White	4	AML	21.6	2063	N	N	Manual	49	41
6	20.33	F	Afr/ Am	4	Lymphoma	3.6	1892	N	N	Manual	66	48
7	18.67	M	AMI/ ALA	5	MDS	6.6	4067	N	N	Manual	62	47
8	5.75	F	UNK	4	MDS	8.1	3395	Y	Y	Manual	133	45
9	40.75	M	Asian	4	ALL	3.0	721	N	N	Manual	55	48
10	13.38	F	White	4	AML	4.7	376	Y	NE	Manual	83	47
11	1.72	M	Hisp	4	AML	4.7	869	Y	NE	Manual	55	43
ave	10			>4		8	1549				70	45

ALL=acute lymphoblastic leukemia; AML=acute myelogenous leukemia; MDS=myelodysplastic syndrome; NE: not evaluable. Hisp: Hispanic

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7.1.5 Analysis of Secondary Endpoint(s) Not applicable.

7.1.6 Other Endpoints

Not applicable.

7.1.7 Subpopulations

Pregnancy: See Section 9.1.1

Pediatric population: See Section 9.1.3

Geriatric population: See Section 9.1.5

7.1.8 Persistence of Efficacy

No information provided

7.1.9 Product-Product Interactions

No information provided.

7.1.10 Additional Efficacy Issues/Analyses

Not applicable

7.1.11 Efficacy Conclusions

Based primarily on the docket data, supplemented by the DUCORD data, and considering the publically available data, we conclude that DUCORD can function as an alternative source of hematopoietic progenitor cells for hematopoietic and immunologic reconstitution in patients with diseases affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment (see Appendices 12.1. 12.2. and 12.3).

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8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

.The applicant did not conduct any clinical trials to assess the safety of DUCORD. The safety analysis of DUCORD is based primarily on the docket data, supplemented by the DUCORD data, and considers the publically available data.

8.2 Safety Database

The DUCORD database includes a raw dataset of 1403 patients transplanted with 1497 units of DUCORD from 1999 to 2011. Of all 1403 patients, 11% participated in the COBLT study. Approximately 82% of patients received --(b)(4)-- processed cord blood units and 18% received (b)(4) processed units. The applicant is seeking licensure for all the cord blood units processed by the current (b)(4) method.

Due to missing information on many outcome parameters such as adverse event description, multiple transplant dates, date of death, and engraftment data, each category of safety outcomes is analyzed in a subset of patients, depending on available data (Table 10).

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Although Duke University participated in the COBLT study – a prospective clinical trial to define the role of unrelated cord blood for treatment of a variety of malignant and non- malignant indications, all the datasets in this BLA were retrospectively collected from the reports of NMDP and CIBMTR from voluntary reports from the transplant centers.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Please refer to Table 11 under Section 7 for the summary of the demographic characteristics of the pooled dataset for patients all received any dose of the DUCORD and for the patients who received suitable allograft.

Table 16 describes the exposure of a subset of the safety population to DUCORD. Of all 1403 recipients, 831 subjects have all the required information to generate data regarding DUCORD unit characteristics and exposure (Table 10). Eighty-seven percent of patients in this subset received the dose of TNC>2.5 x 107 /µL / kg as recommended in the label. Ninety-nine percent had a suitable HLA match of 4/6 or greater.

Table 16. DUCORD Unit Characteristics and Dose Exposure

Unit Characteristics	**Subjects with TNC>2.5/kg x 107 N (%)**
Number of Patients	**N=718**
*HLA Match Level 3/6	0
4/6	346 (48)
5/6	286 (40)
6/6	86 (12)
Total TNC Dose x 107 Median	214
Range	67-599
TNC/kg x 107 Median	6.6
Range	2.5-90

Unit Characteristics		Subjects with TNC>2.5/kg x 107 N (%)
	2.5-<5.0	276 (38)
	5.0-<10.0	216 (30)
	10.0-<20.0	155 (22)
	>20	71 (9.9)
	Storage Time (Days) Median	968
	Range	132-4067
	Processing Method -(b)(4)-	589 (82)
	(b)(4)	129 (18)

*For multiple-unit recipients, the lowest level of HLA match was chosen.

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8.2.3 Categorization of Adverse Events

The safety review focuses on the adverse events that are primarily transplantation-related, including infusion reactions, death within 100 days after transplantation (Day 100 mortality), GVHD, engraftment syndrome, malignancies of donor origin, and transmission of serious infection and rare genetic diseases. The incidences of these adverse events are compared, where possible, with those obtained from the safety review of the docket information (see Appendix 12.1).

The infusion reactions were categorized according to MedDRA preferred terms; no information regarding the severity of the infusion reaction is provided in the BLA.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

The dataset is pooled from all the voluntary reports of retrospective data. No data from clinical trials were submitted to this BLA.

8.4 Safety Results

8.4.1 Deaths

Table 17 shows the total mortality and early mortality (Day 100) in patients who received any dose of DUCORD or suitable allograft. Please refer to Table 10 for the selection of the subset of the patients.

Table 17. Mortality of DUCORD Recipients

Demographics	Total Mortality		Mortality by Day 100	
	All Patients N (%)	Patients with Suitable Allograft N (%)	All Patients N (%)	Patients with Suitable Allograft N (%)
Number of Patients	937	646	937	646
Mortality	513 (55)	343 (53)	225 (24)	144 (22)
Age Mean (SD)	26.6 (22)		28.6 (23)	
Median	20		24	
Range	0.083-80		0.083-80	
Age Groups Neonate (<28 days)	0	0	0	0
Infant (1-12 months) Pediatric (1-<18 years) Young	37 (3.9)	27 (4.2)	13 (1.4)	11 (1.7)
adult (18-<40 years)	198 (21)	151 (23)	84 (9.0)	57 (8.8)
Older adult (40-<65 years)	111 (12)	65 (10)	48 (5.1)	26 (4.0)

Demographics	Total Mortality		Mortality by Day 100	
	All Patients N (%)	Patients with Suitable Allograft N (%)	All Patients N (%)	Patients with Suitable Allograft N (%)
Geriatric (>65 years)	151 (16) 16 (1.7)	89 (14) 11 (1.7)	70 (7.5) 10 (1.1)	43 (6.7) 7 (1.1)
Gender Male Female Unknown	276 (29) 236 (25) 1 (0.11)	175 (27) 167 (26) 1 (0.15)	124 (13) 101 (11) 0	75 (12) 69 (11)
Ethnicity/Race White Black/African American Asian Hispanic *AMI/ALA Unknown	323 (34) 92 (9.8) 26 (2.8) 21 (2.2) 3 (0.32) 48 (5.1)	220 (34) 53 (8.2) 19 (2.9) 16 (2.5) 3 (0.46) 32 (5.0)	142 (15) 45 (4.8) 11 (1.2) 9 (1.0) 1 (0.11) 17 (1.8)	94 (15) 26 (4.0) 6 (0.93) 7 (1.1) 1 (0.15) 10 (1.5)
Diagnosis Malignancies Metabolic Disorder Marrow Failure Immunodeficiency Hemoglobinopathy Autoimmune Disorder	409 (44) 58 (6.2) 21 (2.2) 18 (1.9) 5 (0.53) 2 (0.21)	270 (42) 42 (6.5) 14 (2.2) 3 (0.46) 12 (1.9) 2 (0.31)	176 (19) 23 (2.5) 13 (1.4) 10 (1.1) 2 (0.21) 1 (0.11)	108 (17) 17 (2.6) 10 (1.5) 0 8 (1.2) 1 (0.15)

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As shown in Table 18, the overall death rates in DUCORD data appear comparable to that of HPC, Cord Blood products that contributed to the docket data.

Table 18. Comparison of DUCORD Mortality Data with Docket Data

Death	DUCORD N (%)	Docket N (%)
Total Mortality	343/646 (53)	635/1299 (48.9)
Early Mortality (Day 100)	144/646 (22)	328/1299 (25.3)

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As shown in Table 19, regarding early mortality (death within 100 days after transplantation), the most common primary causes of death were infection, primary disease, organ failure, graft failure, and GVHD. As seen in the Docket data (see Appendix 12.1), the most common (>5%) causes of death by Day 100 after transplantation for those who received a suitable dose (TNC>2.5 x 107/kg) were infection (7.8%) and organ failure (6.5%). Therefore, DUCORD data shows a similar incidence of the primary causes of death as the Docket data.

Table 19 . Primary Causes of Early Death (Day 100) in patients who received suitable allograft

Primary Cause of Death	DUCORD N (%)
Early mortality	144/646 (22)
Infection	**43 (6.7)**

Primary Cause of Death	DUCORD N (%)
Primary disease	32 (5.0)
Pulmonary causes	13 (2.0)
Multi-organ failure	17 (2.6)
Graft failure/rejection	11 (1.7)
GVHD	**5 (<1)**
Cardiac causes	4 (<1)
Secondary malignancy	1 (<1)
Other	18 (2.8)
Unknown	**0**

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8.4.2 Serious Adverse Events

Primary graft failure:

Primary graft failure is defined as survival for at least 14 days and 1) failure to achieve an absolute neutrophil count greater than 500/µLby Day 42 after transplantation, or 2) died after 14 days without engraftment. Immunological rejection is the primary cause of graft failure and may be fatal. As compared with the primary graft failure rate in the pooled docket dataset, patients treated with DUCORD have a lower rate of primary graft failure (Table 20). However, due to insufficient information regarding the different patient populations, disease severity, preparative regimens, HLA matching, etc., in the datasets, the data regarding graft failure are insufficient to support a better engraftment after treatment with DUCORD.

Table 20. Graft Failure

Graft Failure	DUCORD N=550 % (n)	Docket N=1299 %
ANC<500 by Day 42	6.0 (33)	16.4

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Graft versus Host Disease (GVHD):

GVHD is a common complication after unrelated cord blood transplantation, induced by immune T cells in donor cord blood that recognize the recipient as “foreign” and attack the host’s body cells. While the donor T-cells can cause undesirable systemic immune reactions, those T-cells can have a desirable graft-versus-tumor effect if the transplantation is used to treat cancer such as leukemias. Acute GVHD occurs within the first 100 days post-transplant, attacking liver, skin, mucosa, and gastrointestinal tract. Acute GVHD is classified by severity from grade 1 to 4, with grade 4 carrying a poor prognosis. Chronic GVHD occurs after 100 days post-transplant, involving different immune cell subsets, cytokines, and host targets.

A subset of the safety population has available data for the analyses of GVHD. Table 21 shows the incidences of acute and chronic GVHD as analyzed for patients who received suitable allograft.

Table 21. Incidence of GVHD

	GVHD		Subjects with Suitable Allograft N (%)
Total Patients			**N=646**
	Acute GVHD	Yes	386 (60)
		No	230 (36)
		Unknown	30 (4.6)
	Acute GVHD Grade	Grade 1	108 (17)
		Grade 2	164 (25)
		Grade 3	73 (11)
		Grade 4	32 (5.0)
		Unknown	269 (42)
	Chronic GVHD	Yes	184 (28)
		No	411 (64)
		Unknown	52 (8.1)

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As shown in Table 22, the incidence of acute GVHD in patients treated with DUCORD is comparable to the incidence of patients reported in the Docket. A subset of 646 DUCORD patients with available information on GVHD and other demographics was selected (see Table 10).

Table 22. Acute GVHD in DUCORD and Pooled Docket Data

	DUCORD *N=646 (%)	Docket **N=1182 (%)
Number of Acute GVHD (%)	386 (60)	813 (68.8)

*patients received suitable allograft;
**patients received suitable dose

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8.4.3 Study Dropouts/Discontinuations

Not applicable

8.4.4 Common Adverse Events

Infusion Reactions:

Infusion reactions are defined as adverse events occurring within 24 hours of transplantation. The causes of infusion reactions may include reactions to hemolyzed HPC, Cord Blood, allergic or anaphylactic reactions to any component of DUCORD, or bacterial contamination. Of a total 1433 infusions, 388 infusions whose recipients had suitable dose (>TNC2.5x107/kg) had documentation of whether an infusion reaction(s) occurred and the type of reaction. This subset includes 57% males and 43% females with median age of 16 years (range 0.083-79 years). Table 23 displays the different types of infusion reactions with their frequencies from 72 infusions (see patient selection in Table 10) of DUCORD and corresponding data from the COBLT study. For the DUCORD recipients, the most common infusion reactions in >1% infusions were hypertension (15%), nausea or vomiting (3.4%), sinus bradycardia (1.8%), chest pain (1.3%). The infusion reactions that occurred in <1% infusions were heachache, hypoxia,

chills, rigors, fever, hemoglobinuria, hypotension, tachycardia, shortness of breath, and hives. There were no unexpected adverse events reported. The types of infusion reactions are similar to those described in the COBLT study. The incidences of infusion reactions are much higher in the COBLT study than in the DUCORD data. This discrepancy is likely to be due to the prospective design and prespecified plan for documentation of infusion reactions in the COBLT study.

Table 23. Infusion Reactions

Infusion Reactions	**DUCORD % (n)**	**COBLT %**
Patients with **AE records	**N=388**	**N=442**
Patients with any infusion reaction	19 (72)	65.4
Hypertension	15 (60)	48
Nausea	3.4 (13)	12.7
Vomiting	3.4 (13)	14.5
Sinus Brachycardia	1.8 (7)	10.4
Chest pain	1.3 (5)	0
Headache	<1 (3)	0
Hypoxia	<1 (1)	2
Hemoglobinuria	<1 (2)	2.1
Hypotension	<1 (2)	2.5
Hives	<1 (2)	0
Shortness of breath	<1 (1)	0.9
Chills	<1 (1)	0.9
Fever	<1 (1)	5.2
Sinus Tachycardia	0	4.5
Other	1.6 (6)	0

* TNC dose at >2.5x107/kg and HLA match at >4/6;
** Adverse Events

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8.4.5 Clinical Test Results

Refer to Hematopoietic Reconstitution (Section 7.1.4) for neutrophil and platelet recovery data.

8.4.6 Systemic Adverse Events

Refer to Infusion Reactions (Section 8.4.4), graft failure, and GVHD (Section 8.4.2).

8.4.7 Local Reactogenicity

No information submitted.

8.4.8 Adverse Events of Special Interest

Engraftment syndrome:

Engraftment syndrome manifests as unexplained fever and rash in the peri-engraftment period. Patients with engraftment syndrome also may have unexplained weight gain, hypoxemia, and pulmonary infiltrates, in the absence of fluid overload or cardiac disease. If untreated, engraftment syndrome may progress to multiorgan failure and death. The treatment of choice to ameliorate the symptoms is systemic corticosteroids. No information regarding engraftment syndrome was submitted in this BLA.

Malignancies of donor origin:
Patients who have undergone HPC, Cord Blood transplantation may develop post-transplant lymphoproliferative disorder (PTLD), manifest as a lymphoma-like disease favoring non-nodal sites. PTLD is usually fatal if not treated. The incidence of PTLD appears to be higher in patients who have received antithymocyte globulin. The etiology is thought to be donor lymphoid cells transformed by Epstein-Barr virus (EBV). Serial monitoring of blood for EBV DNA may be warranted in high-risk groups. Leukemia of donor origin also has been reported in HPC-C recipients. The natural history is presumed to be the same as that for *de novo* leukemia (Reference 12).
No reports of malignancies of donor origin were submitted to this BLA.
Transmission of serious infections:
Transmission of infectious disease may occur because HPC, Cord Blood is derived from human blood. Disease may be caused by known or unknown infectious agents. Donors are screened for increased risk of infection with human immunodeficiency virus (HIV), human T-cell lymphotropic virus (HTLV), hepatitis B virus (HBV), hepatitis C virus (HCV), *T. pallidum*, *T. cruzi*, West Nile Virus (WNV), transmissible spongiform encephalopathy (TSE) agents, and vaccinia. Donors are also screened for clinical evidence of sepsis, and communicable disease risks associated with xenotransplantation. Maternal blood samples are tested for HIV types 1 and 2, HTLV types I and II, HBV, HCV, *T. pallidum*, WNV, and *T. cruzi*. These measures do not totally eliminate the risk of transmitting these or other transmissible infectious diseases and disease agents.
No information regarding transmission of serious infection was submitted to this BLA.
Transmission of rare genetic disorders:
HPC, Cord Blood may transmit rare genetic diseases involving the hematopoietic system for which donor screening and/or testing has not been performed. Cord blood donors have been screened by family history to exclude inherited disorders of the blood and marrow. HPC-C are tested to exclude donors with sickle cell anemia, and anemias due to abnormalities in hemoglobins C, D, and E.
No information regarding transmission of rare genetic disorders was submitted to this BLA.
8.5 Additional Safety Evaluations
8.5.1 Dose Dependency for Adverse Events
No analyses of dose dependency for adverse events were conducted for this BLA.
8.5.2 Time Dependency for Adverse Events
See 8.4 for analyses of total death and death at day 100 post transplantation.
8.5.3 Product-Demographic Interactions
See Dr. Przepiorka's safety review of docket and public information (Appendix 12.1, Tables 10 and 13) for analyses of product-demographic interactions regarding safety (graft failure) and efficacy (neutrophil recovery) by age, gender, and race/ethnicity.
8.5.4 Product-Disease Interactions
The BLA submission does not include data regarding product-disease interactions.
8.5.5 Product-Product Interactions
The applicant did not submit any information to support analysis of product-product interactions.
8.5.6 Human Carcinogenicity

No information submitted.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Single doses of DUCORD up to 9.5 x 108 TNC/kg have been administered. There has been no experience with overdosage of HPC-C in human clinical trials. Since HPC-C prepared for infusion may contain dimethyl sulfoxide (DMSO), accumulation of DMSO due to higher units of transfusion may cause toxicity. The maximum tolerated dose of DMSO has not been established, but it is customary not to exceed a DMSO dose of 1 gm/kg/day when given intravenously. Several cases of altered mental status and coma have been reported with higher doses of DMSO.

No data regarding overdose, drug abuse potential, withdrawal, and rebound associated with cord blood were submitted to this BLA.

8.5.8 Immunogenicity (Safety)

DUCORD is an allogeneic cord blood product containing hematopoietic progenitor cells as well as inactive gradients such as DMSO, Dextran 40, and human albumin for use in the unrelated recipients. GVHD is a common and serious adverse reaction after DUCORD transplantation (See GVHD in Section 8.4.3). However, graft versus tumor effect may benefit the cord blood recipients with hematological malignancies. Allergic reactions and anaphylaxis may occur after DUCORD transfusion due to hemolyzed cellular cord blood components or any components of the final product, such as DMSO, Dextran 40, Hespan, and albumin (see Infusion Reactions in Section 8.4.4).

8.5.9 Person-to-Person Transmission, Shedding

Transplantation of DUCORD may result in the development of malignancies of donor origin, transmission of serious infection, and rare genetic diseases from the donor to the recipients. No such cases were reported in this BLA. See Dr. Przepiorka's review on the safety of HPC, Cord Blood (Appendix 12.1).

8.6 Safety Conclusions

The reviewers summarize the integrated safety review as follows:

- The safety review of DUCORD is based on the established safety analyses of HPC, Cord Blood class from the Docket and published data (see Dr. Przepiorka's review in Appendix 12.1) and the analyses of the safety outcomes of the DUCORD dataset in this BLA.
- The DUCORD dataset is incomplete with missing data in different outcome parameters due to voluntary and retrospective data collection. Therefore, the safety analyses of different categories of adverse events were conducted in various subsets of the patient population.
- The total mortality and mortality by 100 days after transplantation are 53% and 22% in subjects who received suitable allograft of DUCORD, comparable to the Docket data (total: 49% and Day 100: 25%). The main causes for the early mortality are infection, primary disease, organ failure, pulmonary etiologies, graft failure, transplantation, and GVHD.
- Graft failure occurred in 6% (33/550) of patients who received a suitable DUCORD allograft, compared to 16% in the Docket data.
- Acute GVHD occurred in 60% of patients who received a suitable DUCORD allograft, compared to 69% in the Docket data.
- Infusion reactions were documented in 19% (72/388) of DUCORD infusions.
  The most common infusion reactions in >1% of the population were hypertension,

nausea, vomiting, sinus bradycarda, and chest pain. In comparison, 65% (n=523) of subjects in the prospective COBLT study reported infusion reactions. The types of DUCORD infusion reactions are similar to the COBLT data.

- No reports of unexpected adverse reactions were submitted to the BLA. Conclusion: The main adverse reactions associated with DUCORD are death, graft failure, GVHD, and infusion reactions. These adverse reactions are often serious and fatal. The safety analyses of DUCORD data showed a similar safety profile in terms of types and frequencies of the adverse events as compared to the overall rates in the pooled Docket data for HPC, Cord Blood. The safety analyses based on the DUCORD dataset are limited by the retrospective nature of the data collection, historic comparison, large amount of missing data, and different patient populations.

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9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There are no animal or human studies of DUCORD or HPC, Cord Blood in pregnant women; therefore, potential risks of fetal harm or effects on reproduction capacity are unknown. A decision to treat a potentially fatal malignant or non-malignant condition not only with the cord blood infusion, but also the rigorous chemotherapy regimen which accompanies hematopoietic transplantation, must be made by the patient and the physician directing her care, considering overall risks and benefits.

9.1.2 Use During Lactation

There are no studies in nursing women. Potential risks are unknown. In general, nursing mothers do not go through an HPC, Cord Blood transplant. However, a decision to treat a potentially fatal malignant or non-malignant condition with the cord blood infusion as well as the accompanying chemotherapy regimen must be made by the patient and the physician, considering the overall risks and benefits.

9.1.3 Pediatric Use and PREA Considerations

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. The active ingredient, indication, dosage form, dosing regimen, and route of administration of DUCORD are not new because they are the same as for HEMACORD manufactured by New York Blood Center. Therefore, this application does not trigger PREA.

9.1.4 Immunocompromised Patients

DUCORD has been used in patients who are immunocompromised due to either the preparative regimen prior to transplantation or due to the underlying disease(s). Adverse events associated with DUCORD are discussed in Section 8 of this review.

9.1.5 Geriatric Use

Of 1403 DUCORD recipients, only 2% (n=33) were geriatric patients (>65 yrs), which did not constitute a sufficient number of patients to determine whether they respond differently to DUCORD compared to younger patients. A decision to treat potentially fatal malignant or non-malignant conditions with cord blood infusion as well as rigorous accompanying chemotherapy should be made by the patient and the treating physician, considering overall risks and benefits. In general, administration of DUCORD to patients aged 65 and over should be cautious, reflecting their greater frequency of decreased hepatic, renal, or cardiac function, and presence of concomitant disease or other drug therapy.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

None.

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10. CONCLUSIONS

Based primarily on the docket data, supplemented by the DUCORD data, and considering the publically available data, we conclude that DUCORD is capable of hematopoietic and immunologic reconstitution in conjunction with an appropriate preparative regimen. DUCORD can function as an alternative source of hematopoietic progenitor cells for transplantation to treat diseases affecting hematopoietic system. DUCORD transplantation for hematopoietic and immunologic reconstitution is a potentially life-saving treatment for certain diseases affecting the hematopoietic system; however, the risks are serious and potentially fatal. The risks associated with DUCORD include early death, infusion reactions, GVHD, and graft failure.

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11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 24 provides a detailed assessment of risk-benefit considerations for DUCORD.

Table 24. Risk benefit considerations for DUCORD

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment Etiology categories include Hematological malignancies, metabolic disorders, marrow failure, hemoglobinopathy, immunodeficiency, and autoimmune disorders	Hematological malignancies and marrow failure are life-threatening diseases Metabolic disorder, Hemoglobinopathy, immunodeficiency, and autoimmune disease are group of serious

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Unmet Medical Need	Unrelated donor hematopoietic progenitor cell transplantation procedures Preparative regimen for hematopoietic and immunologic reconstitution Chemotherapy, immunotherapy targeted biologic agents Other therapies include hematopoietic stem cells (HSC) from the sources of HLA-matched related or unrelated bone marrow transplant, HLA-matched related cord blood transplant, or granulocyte colony-stimulating factor mobilized peripheral blood donor The above HSC sources are limited and HPC. Cord Blood provides wider source of HSC for allogeneic HSC transplant.	disorders, and can be life- threatening if severe and at late-stage In patients who do not have, or cannot use, available HSC sources from autologous or allogeneic bone marrow or peripheral blood, cord blood is a reasonable option.
Clinical Benefit	A single-arm prospective study (COBLT) and retrospective reviews of an observational database in the dockets and public data have demonstrated the effectiveness of class of HPC-C as defined by hematopoietic reconstitution. The total nucleated cell dose and the degree of HLA match were associated with the time to neutrophil recovery. Retrospective analyses of the DUCORD database demonstrated comparable results of hematopoietic reconstitution as compared with the COBLT and Docket data. Uncertainties in non-oncological indications such as hemoglobinopathy (n=16), and autoimmune disease (n=4), subgroups of neonates (<28 days, n=3) and geriatric population (>65 years, n=33) because of limited sample size in DOCORD retrospective dataset.	HPC, Cord Blood can be effectively used in patients who have disorders affecting the hematopoietic system and who have life- threatening or serious diseases but have failed standard therapy and no available other HSC sources for transplant. The effect of the HPC,Cord Blood is related to the numbers of TNC in the cord blood. HPC, Cord Blood can provide a broader and prompt source of HSC. Effectiveness may vary depending on age of the patients, type and stage of disease, and comorbidity.
Risk	Based on Docket and COBLT data, All cause mortality rate of 30% at 100 days post-transplant as result of infection, primary disease, pulmonary causes, multi-organ failure, and GVHD. Acute GVHD in 69% of population, which may benefit for malignant patients as Graft versus tumor effect. Infusion reactions in 65% of population (COBLT), including hypertension, nausea, vomiting, sinus bradycardia,fever, sinus tachycardia, allergy, hypotension, hemoglobinuria, and hypoxia. Primary Graft failure in 16% of population)	The overall risks of the HPC, Cord Blood transplantation along with a myeloablative preparative regimen can be serous and fatal Standard approved chemotherapy or biologics should be considered first. If failed standard therapy, other HSC source such s autologous or matched bone marrow or cord blood or peripheral cells should be considered Type of the disease such as hematological malignancies vs. non-oncological disease, stages of the disease, patient health conditions (age, comorbilities, functional status) should be considered when

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
		considering using DUCORD
Risk Management	The risk of fatal infusion reactions, GVHD, engraftment syndrome and graft failure are addressed in the black box warning of the Prescribing Information for HPC, Cord Blood class Risks of infusion reactions, malignancies of donor origin, transmission of serious infections or rare genetic disease are addressed under Warning and Precaution of the PI. Risk/benefit assessment should include analyzing disease type and stage, risk factors, number of the TNC and level of HLA match, other available treatment or types of HSCs. Post-market: clinical outcome data collection; adverse events reporting: serious and unexpected	Labeling information and post-marketing pharmocovigilance monitoring should suffice for risk management; no REMS or PMR is necessary

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11.2 Risk-Benefit Summary and Assessment

Transplantation of DUCORD resulted in hematopoietic reconstitution, indicated by neutrophil, platelet and erythrocyte recovery.

Based on the docket data and supported by the publically available data, HPC, Cord Blood has demonstrated the ability to reconstitute the immunologic system in patients transplanted for primary immunodeficiency, as well as for other malignant and nonmalignant disorders (Section 12, Appendices).

DUCORD transplantation for hematopoietic and immunologic reconstitution is a potentially life-saving treatment for certain diseases affecting the hematopoietic system; however, the risks are serious and potentially fatal. The risks associated with DUCORD include early death, infusion reactions, GVHD, and graft failure. The risk-benefit assessment for an individual patient depends on the patient characteristics, including disease stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

11.3 Discussion of Regulatory Options

No major safety and efficacy concerns were identified from the clinical and statistical review to warrant a complete response action for the DUCORD BLA. The overall risks of DUCORD can be mitigated in labeling. There are no unexpected or special risks identified from the BLA review to trigger a REMS, PMC or PMR. A post-marketing pharmacovigillance plan, as proposed by the applicant, should be sufficient to monitor the safety of DUCORD.

11.4 Recommendations on Regulatory Actions

The reviewers recommend approval of DUCORD for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in

patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

11.5 Labeling Review and Recommendations

The package insert (PI) originally submitted to the BLA and all subsequent amendments related to the label were reviewed. Labeling for HPC, Cord Blood is primarily class labeling. Therefore, the labeling of DUCORD follows the format of labeling of previously approved HPC, Cord Blood products. Sections 5.1 and 5.7 of the package insert were revised to reflect that some cord blood donors receive intrapartum antibiotics, which could increase the potential for allergic reactions in antibiotic-sensitive DUCORD recipients, and may have an effect on the reliability of sterility test results.

11.6 Recommendations on Postmarketing Actions

The risks of DUCORD and its related preparative regimen can be mitigated and managed through the labeling of DUCORD and pharmacovigilance plan. No unexpected safety issues are identified in this BLA review that warrant post-marketing requirements or commitments. The reviewers do not recommend Risk Evaluation and Mitigation Strategies (REMS) nor Postmarket Requirement or Commitments (PMR or PMC) for DUCORD.

The review team recommended, and the applicant agreed, to do the following:

1. Implement a safety outcomes monitoring and analysis plan. This plan will include a) maintenance of an observational database to include, for all DUCORD units released, information including but not limited to, time to neutrophil recovery, graft failure, survival, cause of death, infusion reactions, and other adverse experiences, b) aggregate analyses of interval and cumulative adverse experience reports, and c) safety outcomes analyses of interval and cumulative data that address early mortality, graft failure-related mortality, graft failure, time to neutrophil recovery, infusion-related events, and other adverse experiences. Reports will include a description of the population analyzed, results of the analyses, whether outcomes indicators were triggered and, if so, what actions were implemented as a result.
2. Submit a 15-day “alert report” for each serious infusion reaction associated with administration of DUCORD.

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12. APPENDICES: FDA CLINICAL REVIEWS ON HEMATOPOIETIC PROGENITOR CELLS, CORD BLOOD

12.1 Donna Przepiorka. Safety Review Dockets and Public Information. 2011

12.2 John Hyde. Clinical Efficacy Review Nonmalignant Indications. 2011

12.3 Maura O’Leary. Clinical Efficacy Review for Hematological Malignancies. 2011

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