Application Type	BLA, original application
STN	125657/0
CBER Received Date	June 26, 2017
PDUFA Goal Date	June 26, 2018
Division/Office	DCEPT/OTAT (Clinical) DB/OBE (Statistical)
Priority Review	No
Reviewers	Meghna Alimchandani, M.D. (Clinical) Yuqun Abigail Luo, Ph.D. (Statistical)
Review Completion/Stamped Date	May 18, 2018
Supervisory Concurrence	Lei Xu, M.D., Ph.D. (Branch Chief, OTAT) Tejashri Purohit-Sheth, M.D. (Division Director, OTAT) Shiowjen Lee, Ph.D. (Team Leader, OBE)
Applicant	MD Anderson Cord Blood Bank
Established Name	HPC, Cord Blood
(Proposed) Trade Name	None
Pharmacologic Class	Allogeneic Cord Blood
Formulation(s), including adjuvants, etc.	Each unit contains: • Active ingredient: a minimum of (b)(4).0 x 10^8 total nucleated cells (TNC) with at least 1.25 x 10^6 viable CD34 cells • Inactive ingredients: dimethyl sulfoxide (DMSO), citrate phosphate dextrose (CPD), hydroxyethyl starch, and Dextran 40
Route of Administration	Intravenous
Dosing Regimen	2.5 x 10^7 total nucleated cells (TNC)/kg at cryopreservation
Indication(s) and Intended Population(s)	Hematopoietic Progenitor Cell (HPC), Cord Blood, is an allogeneic 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.
Orphan Designated (Yes/No)	No

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LIST OF ABBREVIATIONS

AE	Adverse event
ANC	Absolute neutrophil count
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	Confidence interval (95%, unless otherwise specified)
CIBMTR	Center for International Blood and Marrow Transplant Research
CMC	Chemistry, manufacturing, and controls
COBLT	The Cord Blood Transplantation Study
DMSO	Dimethyl sulfoxide
GCP	Good Clinical Practices
GVHD	Graft versus host disease
HLA	Human leukocyte antigen
HPC-A	Hematopoietic progenitor cells, Apheresis
HPC-M	Hematopoietic progenitor cells, Marrow
HSCT	Hematopoietic stem cell transplantation
NMDP	National Marrow Donor Program
PeRC	Pediatric Review Committee (CDER & CBER)
PI	Package Insert
PLT	Platelet
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PREA	Pediatric Research Equity Act
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious adverse event
SCTOD	Stem Cell Therapeutic Outcomes Database
SOP	Standard Operating Procedure
TNC	Total nucleated cells

1. EXECUTIVE SUMMARY

On June 26, 2017, MD Anderson Cord Blood Bank (MDACBB) submitted an original BLA 125657/0 seeking licensure for hematopoietic progenitor cell (HPC), Cord Blood (no trade name) for the following indication:

> Hematopoietic Progenitor Cell (HPC), Cord Blood, 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. 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.

MDACBB did not conduct prospective clinical trial(s) to study the efficacy or the safety of its HPC, Cord Blood. To support this BLA, the applicant submitted its own retrospectively collected observational dataset and referenced the FDA dockets (FDA-1997-N-0010 and FDA-2006-D-0157) and published literature. The applicant's dataset includes data obtained from the MDACBB internal database and from the Stem Cell Therapeutic Outcomes Database (SCTOD) provided by the Center for International Blood & Marrow Transplant Research (CIBMTR). The efficacy of HPC, Cord Blood for hematopoietic reconstitution has been established by previous FDA analyses of the pooled data from multiple cord blood banks in the FDA dockets[1] as well as the Cord Blood Transplantation (COBLT)[2,3] Study (Appendix).

Efficacy is assessed in terms of hematopoietic reconstitution demonstrated by neutrophil and platelet recovery. For this BLA review, a *suitable allograft* contains total nucleated cells (TNC) $\geq 2.5 \times 10^7$/kg of recipient weight, and has $\geq 4/6$ degree of human leukocyte antigen (HLA) match. The applicant's dataset included 846 patients who received a suitable allograft from at least a single cord blood unit manufactured at MDACBB, alone or in combination with another unit of HPC, Cord Blood. Among the 846 patients, the cumulative incidence of neutrophil recovery defined as absolute neutrophil count (ANC) greater than 500 cells/μL by Day 42 was 88.2%, similar to that demonstrated in the pooled docket dataset (77%) and in the COBLT study (76%). The median time from transplantation to an ANC greater than 500 cells/μL was 19 days, also comparable to the docket dataset (25 days) and COBLT study (27 days). The cumulative incidence of platelet recovery defined as a platelet count greater than 20,000 cells/μL by Day 100 was 73.6%, and the median time from transplantation to a platelet count greater than 20,000 cells/μL was 47 days (Table 1). The cumulative incidence of neutrophil and platelet recovery with the MDACBB product appears comparable to the docket data. While the data suggest favorable trends toward the applicant's HPC, Cord Blood, the data are insufficient to support its superior efficacy due to limitations of the retrospective dataset. Comparisons of the applicant's dataset to the COBLT and docket datasets are limited by the following factors: incomplete and missing data from retrospective observational data (including insufficient information about the nature and severity of the diseases that were the primary indications for transplantation and the conditioning regimens) and demographic differences between the applicant's dataset and the docket and COBLT study. The applicant's dataset serves

as supportive data to supplement the primary evidence of effectiveness for HPC, Cord Blood that was demonstrated by the docket data and the COBLT study.

Table 1: Summary of Efficacy Demonstrated by Hematopoietic Reconstitution
[Source: Table 2.6-1 *Summary of Clinical Studies*, response to statistics information request dated March 27, 2018]

Data Source	**The COBLT Study**	**Docket and Public Data**	**MDACBB***
Design	Single-arm prospective	Retrospective	Retrospective
Number of patients	324	1299	846
Median age (range) in years	4.6 (0.07 – 52.2)	7.0 (<1 – 65.7)	24.8 (0.1 – 73.3)
Sex	59% Male 41% Female	57% Male 43% Female	58% Male 42% Female
Median weight at transplant (kg) (range)	NA	NA	59.0 (2.6 – 146)
Median TNC Dose (x 10^7/kg) (range)	6.7 (2.6 – 38.8)	6.4 (2.5 – 73.8)	5.4 (2.5 – 76.9)
Neutrophil Recovery at Day 42 (ANC > 500/µL) (95% CI)	76% (71%, 81%)	77% (75%, 79%)	88.2% (85.9%, 90.2%)
Platelet Recovery at Day 100 (20,000/µL) (95% CI)	57% (51%, 63%)	NA	73.6% (70%, 77%)
Platelet Recovery at Day 100 (50,000/µL) (95% CI)	46% (39%, 51%)	45% (42%, 48%)	43% (39%, 46%)
Erythrocyte Recovery at Day 100 (95% CI)	65% (58%, 71%)	NA	NA
Median time to Neutrophil Recovery	27 days	25 days	19 days
Median time to Platelet Recovery (20,000/µL)	90 days	NA	47 days
Median time to Platelet Recovery (50,000/µL)	113 days	122 days	65 days
Median time to Erythrocyte Recovery	64 days	NA	NA

*Data from patients who received a suitable allograft (TNC ≥ 2.5 x 10^7/kg and ≥ 4/6 HLA match). Note that evaluable data for outcomes were not available for all patients and there are various amounts of missing data.
NA: Data not available

MDACBB data do not include information regarding immunologic reconstitution. However, based on the analyses of the docket data and the publicly available data, HPC, Cord Blood has demonstrated the ability of immunologic reconstitution for patients transplanted for primary immunodeficiency as well as for other malignant and nonmalignant disorders (Appendix).

HPC, Cord Blood 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 safety review of this BLA focuses on transplantation-related adverse events (AEs), including early mortality (prior to Day 100), infusion reactions, graft versus host disease (GVHD), and graft failure summarized in Table 2. The incidence of AEs associated with the applicant's HPC, Cord Blood appears comparable to the incidence of these AEs in the pooled data from multiple cord blood banks that contributed to the docket and public data.

Table 2: Summary of Major Adverse Events

[Source: Table 1 from applicant response to information request dated January 24, 2018]

Major Adverse Events	**Docket or COBLT**	**MDACBB*** (N = 846)
Early mortality (Day 100)	25% (Docket)	17%
Primary Graft Failure	16% (Docket)	12%
Acute graft versus host disease (acute GVHD)	69% (Docket)	58.6%
Infusion Reactions	65% (COBLT)	22.1%

* Data from patients who received a suitable allograft (TNC ≥ 2.5 x 107/kg and ≥ 4/6 HLA match). Note that evaluable data for outcomes were not available for all patients and there are various amounts of missing data.

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 the applicant's HPC, Cord Blood, are not new because they are the same as for the first FDA-approved HPC, Cord Blood, HEMACORD, manufactured by New York Blood Center. Therefore, this application does not trigger PREA.

There are no safety issues related to the applicant's HPC, Cord Blood that warrant either a postmarketing requirement (PMR) or postmarketing commitment (PMC) study or a Risk Evaluation and Mitigation Strategy (REMS). The applicant will conduct routine pharmacovigilance in accordance with 21 CFR 600.80. Postmarketing surveillance for the HPC, Cord Blood product class also includes the implementation of a safety outcomes monitoring and analysis plan[4]. The applicant has agreed to conduct the following:

a. Implement a safety outcomes monitoring and analysis plan. This plan will include: 1) maintenance of an observational database to include, for all MD Anderson HPC, Cord Blood units released, information including but not limited to, time to neutrophil recovery, graft failure, survival, cause of death, infusion reactions, and other adverse experiences; 2) Aggregate analyses of interval and cumulative adverse experience reports; and 3) 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.

b. Submit a 15-day alert report for each serious infusion reaction associated with administration of the applicant's HPC, Cord Blood

Based on overall benefit-risk consideration of the docket and published data referenced in this application, supplemented by the MDACBB dataset, the FDA clinical and statistical reviewers recommend approval of the applicant's HPC, Cord Blood 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. The benefit-risk 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.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The median age of patients who received suitable allografts was 24.8 years, ranging from 0.1 to 73.3 years. There were 348 pediatric patients, including 69 patients < 2 years of age. There were 491 (58%) males and 355 (42%) females. There were 336 (39.7%) White, 268 (31.7%) Hispanic, and 115 (13.6%) African American patients. Most patients in the MDACBB dataset had hematologic malignancies (708 patients, 83.7%). The detailed demographics of the patient population in the MDACBB dataset, including a comparison to the docket data, are provided in Table 3, section 7.1.2.

1.2 Patient Experience Data

This submission did not include patient experience data and FDA is unaware of any patient perspective/experience studies relevant to review of this submission.

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.			

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

HPC, Cord Blood has been used as a source of HPCs for transplantation to treat a variety of diseases affecting the hematopoietic system, such as hematological malignancies, hematological non-malignant disorders, primary immunodeficiency, and inborn errors of metabolism. These diseases are usually serious, life-threatening, and with unmet medical needs. Please see the FDA reviews of the docket data for malignant and non-malignant indications regarding the effect of hematopoietic and immunologic reconstitution on the specific disease outcomes (Appendix).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

The FDA-approved therapies for hematological malignancies include 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.

2.3 Safety and Efficacy of Pharmacologically Related Products

There are several sources of stem cells for allogeneic hematopoietic stem cell transplantation (HSCT), including HPCs derived from bone marrow (HPC-M) and HPCs derived from peripheral blood apheresis (HPC-A). The choice of HPC source for allogeneic transplantation is individualized for each patient and depends on several factors, including donor availability, HLA-matching, and overall benefit-risk assessment. Use of unrelated cord blood has increased over the past 22 years with improved outcomes. 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 with some degree of HLA mismatch.

Currently there are 7 licensed HPC, Cord Blood products:

i. HEMACORD [STN 125397], manufactured by New York Blood Center.
   FDA approval: 2011
ii. HPC, Cord Blood [STN 125391], manufactured by ClinImmune Labs (University of Colorado Cord Blood Bank)
   FDA approval: 2012
iii. DUCORD [STN 125407], manufactured by Carolinas Cord Blood Bank (Duke University School of Medicine).
   FDA approval: 2012
iv. ALLOCORD [STN 125413], manufactured by SSM Cardinal Glennon Children's Medical Center.
   FDA approval: 2013
v. LifeSouth HPC, Cord Blood [STN 125432], manufactured by LifeSouth Community Blood Centers.
   FDA approval: 2013

vi. HPC, Cord Blood [STN 125585], manufactured by Bloodworks.
FDA approval: 2016
vii. CLEVECORD [STN 125594], manufactured by Cleveland Cord Blood Center.
FDA approval: 2016

The applicant's product is another preparation of HPC, Cord Blood produced under the same regulations and Guidance documents and for the same indication as the licensed products.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

In 1996, two groups (Kurtzberg, Laughlin, et al. and Wagner, Rosenthal, et al.) first reported use of umbilical cord blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. Since then, the clinical use of umbilical cord blood as an alternative source of stem cells has been growing steadily. By 2013, more than 30,000 HSCTs have been performed by using cord blood as the source of stem cells worldwide. The disease distributions were 57% for malignancies, 32.5% for hemoglobinopathies, 6% for severe combined immunodeficiency disease (SCID) or related T-lymphocyte disorders, and 1.5% for other disorders (American Academy of Pediatrics, 2017).

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

June 26, 2017	Original BLA 125657/0 submission
August 22, 2017	BLA filed
January 8, 2018	Mid-cycle meeting
June 26, 2018	Action Due Date

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*," which explained that it may 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. To provide a scientific basis for the proposed standards, FDA requested the submission of comments proposing establishment controls, process controls, and product standards designed to ensure the safety and effectiveness of minimally manipulated unrelated allogeneic hematopoietic stem/progenitor cell products derived from peripheral and cord blood for hematopoietic reconstitution. 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 experts

regarding the safety and effectiveness of cord blood for hematopoietic reconstitution. Based on the submitted information, BRMAC discussion, 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 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 the Federal Register notice on 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 (US) would need to be done under an approved BLA or active IND.

The new, updated final *Guidance for Industry: Biologics License Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System,* was issued in March 2014 and included updates resulting from FDA's re-examination of the legacy docket data and FDA's consideration of the proceedings of the September 2011 CTGTAC meeting.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

BLA 125657/0 submission was accepted for filing by the review team on August 22, 2017. The applicant submitted data in Excel format that included outcome information from their internal database and information submitted to the SCTOD by individual transplantation centers. The dataset included data from 846 patients, who received a suitable allograft (TNC $\geq 2.5 \times 10^7$/kg and $\geq$ 4/6 HLA match) with the applicant's HPC, Cord Blood. Due to the retrospective and voluntary nature of data collection, the following limitations were present:

- Incomplete and missing data
    - Information is not available on diagnostic criteria for diseases that comprised the primary indication for transplantation
    - Information is not available on the conditioning regimen(s)
    - Case report forms (CRFs) for patients are not available, as data is collected incidentally in the course of clinical practice

  - Evaluable data for outcomes was not available for all patients and there are various amounts of missing data.
- Uncertainties
  - Lack of standardization of data collection and reporting for the voluntarily-collected retrospective dataset

3.2 Compliance with Good Clinical Practices (GCP) and Submission Integrity

Not Applicable

3.3 Financial Disclosures

Not Applicable

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls (CMC)

Please see CMC review of this BLA for details.

4.2 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. Please see the pharmacology/toxicology review of this BLA.

4.3 Clinical Pharmacology

4.3.1 Mechanism of Action

This product consists of HPCs collected from the cord blood donor for intravenous infusion. Hematopoietic stem progenitor cells 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 counts and function, including immune function, of blood-borne cells of marrow origin. However, the precise mechanism of action is unknown.

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 Statistical

The data analyses are based on 846 patients who received a suitable allograft (TNC $\geq$ 2.5 x 10^7/kg and $\geq$ 4/6 HLA match) with at least one unit of HPC, Cord Blood manufactured by MDACBB. Due to the voluntary nature of data collection, missing data occurred for different outcome variables.

4.5 Pharmacovigilance

The applicant submitted a routine pharmacovigilance plan, which is adequate to monitor the risks associated with HPC, Cord Blood manufactured by MDACBB. The available data do not suggest a safety signal that would trigger a Risk Evaluation and Mitigation Strategy (REMS), a postmarketing commitment (PMC) or a postmarketing requirement (PMR) study. Therefore, the BLA review does not include a Pharmacovigilance Plan Review from the Office of Biostatistics and Epidemiology. However, a postmarketing safety outcomes monitoring and analysis plan, and expedited reporting of serious infusion reactions, will be useful to monitor the postmarketing safety of the product (please see section 11.5 of this review for details).

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

5.1.1 Scope of Efficacy Review

The efficacy review focuses on the ability to achieve hematopoietic reconstitution, based primarily on the docket data, publicly available data (including the COBLT Study), and supplemented by the applicant's data. Hematopoietic reconstitution is demonstrated by neutrophil and platelet recovery after transplantation. The ability of the applicant's HPC, Cord Blood to reconstitute the immune system and erythrocytes can be reliably extrapolated from FDA reviews of the docket and public data (Appendix).

5.1.2 Scope of Safety Review

The safety review focuses on transplantation-related AEs, including infusion reactions, death within the first 100 days after transplantation (Day 100 mortality), and GVHD. The safety review is based primarily on the docket data, publicly available data (including the COBLT Study), and supplemented by the applicant's data. The applicant did not report any cases of engraftment syndrome, malignancies of donor origin, or transmission of serious infection or rare genetic diseases.

5.1.3 Controls

The applicant's data are collected from uncontrolled clinical experience. The FDA reviews of the docket and public data, which are the primary data to support the safety and efficacy of HPC, Cord Blood product class, serve as references for both efficacy (hematopoietic reconstitution) and safety (transplantation-related adverse events) (Appendix).

5.1.4 Statistical Considerations

Descriptive statistical analyses are used in this review. This memorandum is a collaborative review by the clinical and statistical review teams.

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

The following documents serve as the basis for this review:

- Original BLA 125657/0 submission

- FDA reviews of the docket information (FDA- 1997- N- 0010, Legacy Docket number 97N- 0497 and FDA- 2006- D- 0157, Legacy Docket number 06D- 0514)
- FDA review of the COBLT Study (data available from the National Heart, Lung, and Blood Institute via its data-sharing portal at https:/biolincc.nhlbi.nih.gov/home/)

The following FDA reviews are included in the Appendix:

- Safety Review of Docket and Public Information (Appendix 12.1)
- Efficacy Review (Non-Oncology) – Docket and Public Information (Appendix 12.2)
- Efficacy Review (Oncology) – Docket and Public Information (Appendix 12.3)

5.3 Table of Studies/Clinical Trials

Not Applicable

5.4 Consultations

None

5.4.1 Advisory Committee Meeting

On September 22, 2011, the Cellular, Tissue, and Gene Therapies Advisory Committee discussed HEMACORD, which was the first-in-class HPC, Cord Blood BLA. No Advisory Committee Meeting was held for this BLA because there were no new concerns.

5.4.2 External Consults/Collaborations

None.

5.5 Literature Review

a. American Academy of Pediatrics, 2017, Cord blood banking for potential future transplantation. Pediatrics. 2017 Nov;140(5).
b. American Academy of Pediatrics, 2007, Cord blood banking for potential future transplantation. Pediatrics 119(1): 165-170.
c. Kurtzberg, J, M Laughlin, ML Graham, et al., 1996, Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. N Engl J Med 335:157-166B
d. Wagner, JE, J Rosenthal, R Sweetman, et al., 1996, Successful transplantation of HLA-matched and HLA-mismatched umbilical cord blood from unrelated donors: analysis of engraftment and acute graft-versus-host disease. Blood 8:795-802.
e. Yellowlees, P, C Greenfield, N McIntyre, 1980, Dimethyl sulfoxide-induced toxicity. Lancet 2:1004-1006.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

Not Applicable

7. INTEGRATED OVERVIEW OF EFFICACY

The efficacy of the HPC, Cord Blood product is assessed in terms of hematopoietic reconstitution in patients who received a suitable cord blood allograft (TNC $\geq 2.5 \times 10^7$/kg of recipient weight, and $\geq 4/6$ degree of HLA match with patient). The MDACBB dataset included 846 patients who received a suitable allograft with 100-day follow-up data. The applicant's data were obtained from the MDACBB internal database and from the Stem Cell Therapeutic Outcomes Database (SCTOD), provided by the Center for International Blood & Marrow Transplant Research (CIBMTR). The timeframe for the data reported is August 11, 2006 to October 23, 2015. Of the 846 patients, 324 patients were transplanted with single units manufactured by the applicant and 522 patients were recipients of double units where at least one unit was manufactured by the applicant. Transplantation of the applicant's product resulted in hematopoietic reconstitution, indicated by neutrophil and platelet recovery.

The applicant's data do not include information to evaluate immunologic reconstitution following transplantation with HPC, Cord Blood manufactured by the applicant. However, based on the Docket and publicly available data, HPC, Cord Blood has demonstrated a benefit in immunologic reconstitution for patients transplanted for primary immunodeficiency as well as for other malignant and nonmalignant disorders (Appendix).

7.1 Indication

MDACBB HPC, Cord Blood, is an allogeneic 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.

The benefit-risk 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.

7.1.1 Methods of Integration

Published data and the docket data were reviewed independently and compared to data from MDACBB for this review.

7.1.2 Demographics and Baseline Characteristics

The demographics of the patient population in the MDACBB dataset are shown in Table 3 and compared to the docket data. The MDACBB dataset included more adults (58.9% vs. 9%), and a higher percentage of patients who were reported to be male (58% vs. 40%), and undergoing transplantation for a primary indication of malignant disease (83.7% vs. 66%). Due to deficiencies with the applicant's retrospective observational dataset, and associated missing data, no conclusions can be made about the correlation between demographics and clinical outcomes.

Table 3: Demographic Characteristics

[Source: Table 2 from applicant response to information request dated January 24, 2018]

Patient Characteristics	**Docket** (N = 1299)	**MDACBB*** (N = 846)
Median Age in Years (Range)	7 (< 1 – 66)	24.8 (0.1 – 73.3)
Age groups (years)		
< 2 y	393 (30%)	69 (8.2%)
2 – 16/17 y	786 (61%)	279 (33%)
> 16/17y	120 (9%)	498 (58.9%)
Unknown		
Sex		
Male	524 (40%)	491 (58%)
Female	389 (30%)	355 (42%)
Unknown	386 (30%)	
Ethnicity/Race		
White	573 (44%)	336 (39.7%)
African-American	90 (7%)	115 (13.6%)
Hispanic	129 (10%)	268 (31.7%)
Asian	28 (2%)	48 (5.7%)
Other	14 (1%)	17 (2%)
Unknown/Missing data	465 (36%)	62 (7.3%)
Diagnosis		
Hematologic Malignancies	862 (66%)	708 (83.7%)
Non-malignant disease	437 (34%)	138 (16.3%)
Inborn Errors of Metabolism	0 (0%)	0 (0%)
Immunodeficiency	93 (7%)	31 (3.7%)
Metabolic Disorders	134 (10%)	36 (4.3%)
Bone Marrow Failure	95 (7%)	16 (1.9%)
Hemoglobinopathy	8 (0.6%)	32 (3.6%)
Other	107 (8%)	23 (2.7%)

*Data from patients who received a suitable allograft (TNC dose $\geq 2.5 \times 10^7$ cells/kg and HLA match $\geq 4/6$)

Product Characteristics

Major characteristics of the MDACBB units are summarized in Table 4. Analysis of the docket data indicates that the TNC dose and degree of HLA match are inversely associated with the time to neutrophil recovery. The median TNC dosage and HLA matching status of the applicant's HPC, Cord Blood appears comparable to those of the HPC, Cord Blood products that contributed to the Docket.

Table 4: MDACBB HPC, Cord Blood Unit Characteristics

[Source: Adapted from Table 2.3-4, p.24 and Table 2.6-1, p. 28; module 5.3.5.3 Clinical Review, BLA 125657/0.1. Verified by applicant response to information request dated January 24, 2018]

	MDACBB* N = 846	**Docket ** **
TNC Dose/kg		
Median (x 10^7/kg)	5.4	6.4
Range (x 10^7/kg)	(2.5 – 76.9)	2.5 – 73.8
HLA Matching		
6/6	109 (13%)	143 (11%)
5/6	423 (50%)	524 (40%)
4/6	314 (37%)	583 (45%)
2 – 3/6	–	40 (3%)

*Data from patients who received a suitable allograft (TNC dose ≥ 2.5 x 10^7 cells/kg and HLA match ≥ 4/6)
**Patients who received a TNC dose ≥ 2.5 x 10^7/kg

7.1.3 Subject Disposition

Not Applicable

7.1.4 Analysis of Primary Endpoint(s)

There is no pre-specified primary endpoint because no clinical trial was conducted. However, this review uses neutrophil and platelet recovery as the indicators of hematopoietic reconstitution.

Neutrophil and Platelet Recovery

Neutrophil and platelet recovery was assessed for patients who received suitable allografts. The comparison of hematopoietic recovery in the COBLT, Docket, and MDACBB datasets is shown in Table 5. The cumulative incidence of neutrophil recovery and the median time to neutrophil recovery, associated with MDACBB's HPC, Cord Blood are comparable to these outcomes for HPC, Cord Blood products that contributed to the docket data and the COBLT study. The incidence of primary graft failure of the applicant's product also appears comparable to that of the HPC, Cord Blood products that contributed to the docket data. Note that while the data suggest favorable trends in favor of the applicant's product, the data are insufficient to support its superior effectiveness due to limitations of the retrospective MDACBB dataset. Comparisons are limited by incomplete and missing data from retrospective observational data (including insufficient information about the nature and severity of the diseases that were the primary indications for transplantation and the conditioning regimens) and demographic differences between the applicant's dataset and the docket and COBLT study.

Table 5: Neutrophil and Platelet Recovery
[Source: Adapted from Table 2.6-1, p. 28; module 5.3.5.3 Clinical Review, BLA 125657/0.1 and Table 1 from applicant response to information request dated January 24, 2018]

Data Source	MDACBB* (N = 846)	COBLT Study (N = 324)	Docket (N = 1299)
Neutrophil recovery at Day 42 (95% CI)	88.2% (85.9%, 90.2%)	76% (71%, 81%)	77% (75%, 79%)
Platelet recovery at Day 100 (20,000/μl) (95% CI)	73.6% (70%, 77%)	57% (51%, 63%)	NA
Platelet recovery at Day 100 (50,000/μl) (95% CI)	52.2% (48.7% – 55.6%)	46% (39%, 51%)	45% (42%, 48%)
Median time to Neutrophil Recovery	19 days	27 days	25 days
Median time to Platelet Recovery (20,000/μl)	47 days	90 days	–
Median time to Platelet Recovery (50,000/μl)	57 days	113 days	122 days
Primary Graft Failure	12%	–	16.4%

*Data from patients who received a suitable allograft (TNC dose ≥ 2.5 x 10^7 cells/kg and HLA match ≥ 4/6)
Note that evaluable data for outcomes was not available for all patients.
NA: Not Available

Neutrophil Recovery, HLA matching and TNC Dose

Analysis of docket data has indicated that the TNC dose and degree of HLA match are inversely associated with the time to neutrophil recovery (see Section 12. Appendices).

During her review of Dockets of 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., exceeding the expected upper 95% confidence limit for time to neutrophil recovery) for patients with hematological malignancies and receiving allografts with at least 4 of 6 HLA antigen match and a TNC dose of >2.5 x 10^7 cells/kg. This model could help to identify whether the efficacy of the MDACBB product is different from the efficacy of HPC, Cord Blood in the docket experience. A total of 708 records with suitable allografts (HLA match ≥4/6, dose ≥2.5 x 10^7/kg), transplanted for hematologic malignancies, was found in the joint clinical/statistical review of this BLA application. Of these, 4 (0.6%) had a missing value ("NA") for the variable, "DaystoNeutrophilRecovery". In this review, these 4 records are excluded from the calculation. The calculated 95% limit in the applicant's dataset ranges from 39 to 50 days. Based on application of this model to the applicant's dataset, 41 out of the remaining 704 (5.8%) records exceeded the 95% limit. Thus, the efficacy of the MDACBB HPC, Cord Blood, appears comparable to that of the HPC, Cord Blood products that contributed to the docket information. However, due to the observational nature and incompleteness among the COBLT, docket, and applicant's datasets, this calculation, by itself, does not definitively demonstrate comparability of the HPC, Cord Blood products.

7.1.5 Other Endpoint(s)

None

7.1.6 Persistence of Efficacy

The BLA submission does not include data on the duration of the therapeutic effect.

7.1.7 Product-Product Interactions

The BLA submission does not include data regarding the effect of concomitant medications, devices, or therapies on the efficacy of the applicant's HPC, Cord Blood product.

7.1.8 Additional Efficacy Issues/Analyses

None

7.1.9 Efficacy Conclusions

Based primarily on the docket data, supplemented by the MDACBB data, and taking into consideration the publicly available data, the applicant's HPC, Cord Blood can function as an alternative source of HPCs for hematopoietic and immunologic reconstitution in patients with diseases affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment (Appendix).

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The applicant did not conduct any clinical trials to assess the safety of their HPC, Cord Blood product. The safety analysis of this product is based primarily on the Docket data, supplemented by the MDACBB data, and taking into consideration the publicly available data.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The applicant did not conduct any clinical trials.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Please see Table 3 for the demographic characteristics, and Table 4 for the dose exposure and cord blood unit characteristics for the population of patients in the MDACBB dataset who received a suitable allograft (section 7.1.2 of this review).

8.2.3 Categorization of Adverse Events

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

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

Not Applicable

8.4 Safety Results

8.4.1 Deaths

The overall death rate of the applicant's HPC, Cord Blood appears comparable to that of HPC, Cord Blood products that contributed to the docket data (Table 6). Early mortality is defined as death within 100 days post-transplantation (Day 100 mortality). In the MDACBB dataset, 17% of patients who received a suitable allograft experienced early mortality.

Table 6: Comparison of MDACBB HPC, Cord Blood Mortality Data with Docket Data
[Source: Table 4 from applicant response to information request dated January 24, 2018]

Deaths	**Docket N (%)**	**MDACBB N (%)**
Total Mortality	635/1299 (48.9%)	405/846 (47.8%)
Early Mortality (Day 100)	328/1299 (25.3%)	143/846 (16.9%)

Table 7 compares the demographic characteristics for patients who experienced early mortality in the MDACBB dataset to the Docket data. The MDACBB dataset is insufficient to draw conclusions about the interaction between demographics and early mortality; however, the limited data categorizing early mortality outcomes by demographic characteristics appear to be comparable to the experience in the Docket data.

Table 7: Early Mortality with Demographic Characteristics
[Source: Table 5 from applicant response to information request dated January 24, 2018]

Demographics	**Docket Dataset Patients with TNC ≥ 2.5 x 10^7/kg**	**MDACBB Patients with a Suitable Allograft**	
	Deaths ≤ Day-100 (%)	**Number of Patients (N = 846)**	**Deaths ≤ Day 100 (N =143)**
Median Age (range) years		24.8 (10 – 73.3)	36.4 (37 – 73.34)
Age Groups (years)			
< 2 y	22.3%	8.2%	13%
2 – 16/17 y	27.4%	33%	11.8%
≥ 17 y	48.6%	58.9%	20.3%
Sex			
Male	18.1%	58.2%	15.4%
Female	27.0%	41.8%	18.9%
Race/Ethnicity			
White	22.3%	41.4%	17.3%
African American	28.9%	13.7%	23.5%
Hispanics	18.9%	34.4%	15.2%
Asian	19.4%	5.6%	10.4%
Other	31.3%	1.8%	5.9%
Unknown		3.2%	22.2%
Diagnosis			
Hematologic malignancies	46.5%	83.7%	18.4%
Inborn error of metabolism	32.0%	8.1%	9.6%
Primary Immunodeficiency	17.7%	3.7%	9.7%
Metabolic disorder			
Bone marrow failure	23.4%	1.9%	12.5%
Hemoglobinopathy		3.8%	6.3%
Other		0.8%	14.3%

Table 8 shows the causes of death after transplantation. For MDACBB patients who received a suitable allograft, death prior to Day 100 post-transplantation was most commonly caused by infection (33, 23.1%), organ failure (26, 18.2%) and primary disease (23, 16.1%). Available data from the docket dataset also showed that the most common causes of early mortality for those who received a TNC ≥ 2.5 x 10^7/kg were infection (8%), organ failure (7%), and primary disease (3%). The primary cause of early death from graft failure in the MDACBB data (3.5%) is similar to the docket (3%). Therefore, the most common causes of early mortality are comparable between the MDACBB and docket data.

Table 8: Causes of Death after Transplantation in the MDACBB and Docket Datasets
[Source: Adapted from Table 6, applicant response to information request dated January 24, 2018]

	MDACBB Dataset		**Docket Dataset**	
	Patients with a Suitable Allograft (N=846)		**Patient with a Suitable Allograft** (N=1289)	
Causes of Death	**Total Deaths** N = 405	**Deaths ≤ Day 100** N = 143	**Total Deaths N=631 (49%)**	**Deaths ≤ Day 100** N=328 (25.3%)
Graft failure (n%)	5 (1.2%)	5 (3.5%)	48 (4%)	33 (3%)
Organ failure (n%)	45 (11.1%)	26 (18.2%)	115 (8.9%)	84 (7%)
Infection (n%)	77 (19%)	33 (23.1%)	170 (13%)	101 (8%)
GVHD (n %)	30 (7.4%)	9 (6.3%)	72 (6%)	39 (3%)
Primary disease (n%)	141 (34.8%)	23 (16.1%)	168 (13%)	39 (3%)
2nd Malignancy (n%)	5 (1.2%)	0 (0%)	4(<1%)	0
Prior malignancy (n%)	5 (1.2%)	1 (0.7%)		
Hemorrhage (n%)	5 (1.2%)	3 (2.1%)		
Pulmonary toxicity (n%)	35 (8.6%)	13 (9.1%)		
Unknown (n%)	9 (2.2%)	4 (2.8%)		
Other* (n%)	48 (11.9%)	26 (18.2%)		

* Note that further interpretation of this category was not possible due to the limitations of the data provided by CIBMTR.

8.4.2 Nonfatal Serious Adverse Events

Primary Graft Failure

Primary graft failure is defined as failure to achieve ANC > 500/μL by Day 42. Patients who do not have evaluable data for neutrophil recovery by Day 42, due to death prior to Day 42, are not included in the analysis of primary graft failure. Immunological rejection is the primary cause of graft failure and may be fatal. Primary graft failure was reported in 12% of recipients, within the population of patients in the MDACBB dataset who received suitable allografts and had evaluable hematopoietic reconstitution data. This is comparable to the 16% incidence of primary graft failure in the docket data.

Infusion Reactions

Infusion reactions are defined as AEs occurring within 24 hours after transplantation. The causes of infusion reactions may include reactions to hemolyzed HPC, Cord Blood, allergic or anaphylactic reactions to any component of HPC, Cord Blood, or bacterial contamination.

The data from the COBLT study, shown in Table 9, included exposure to 442 infusions of HPC, Cord Blood (from multiple cord blood banks) in patients treated with TNC >2.5 x 10^7/kg in a single-arm trial. The population, which was 60% male and had a median age of 5 years (range 0.05 - 68 years), included patients treated for hematologic malignancies, inherited metabolic disorders, primary immunodeficiencies, and bone marrow failure. Preparative regimens and graft-versus-host disease prophylaxis were not standardized. The most common infusion reactions were hypertension, vomiting, nausea, and bradycardia. Hypertension and Grade 3-4 infusion-related reactions occurred more frequently in patients receiving volumes greater than 150 milliliters and in pediatric patients. The rate of serious adverse cardiopulmonary reactions was 0.8%.

Table 9: Incidence of Infusion-Related Adverse Reactions Occurring in ≥ 1% of Infusions in the COBLT Study

Adverse Reaction	Any Grade	Grade 3-4
Any reaction	65.4%	27.6%
Hypertension	48.0%	21.3%
Vomiting	14.5%	0.2%
Nausea	12.7%	5.7%
Sinus bradycardia	10.4%	0
Fever	5.2%	0.2%
Sinus tachycardia	4.5%	0.2%
Allergy	3.4%	0.2%
Hypotension	2.5%	0
Hemoglobinuria	2.1%	0
Hypoxia	2.0%	2.0%

Information on infusion reactions was available from voluntary reports for 846 patients who received suitable allografts with the applicant's HPC, Cord Blood. Table 10 shows that the incidence of infusion reactions with the applicant's product is comparable to the COBLT data. Preparative regimens and GVHD prophylaxis were not standardized. The reactions were not graded for severity. The most common infusion reactions with the applicant's product, were hypertension (17.1%), nausea (4.3%), vomiting (3.9%), and headache (1.2%).

Table 10: Incidence of Infusion Reactions
[Source: Table 7 from applicant response to information request dated January 24, 2018]

Infusion Reactions	**Patients who Received ≥ 1 MDACBB Unit with a TNC Dose ≥ 2.5 x 10^7/kg and HLA ≥ 4/6** N = 846	**COBLT Infusions with a TNC Dose ≥2.5 x 10^7/kg** Number of Infusions Assessed: N = 442
Total	**187 (22%)**	**65.4%**
Hypertension	145 (17.1%)	48.0%
Nausea	37 (4.3%)	12.7%
Vomiting	33 (3.9%)	14.5%
Hypotension	4 (0.5%)	2.5%
Hypoxia	6 (0.7%)	2%
Headache	10 (1.2%)	0
Tachycardia	8 (0.9%)	4.5%
Shortness of breath	7 (0.8%)	0.9%
Chest Pain	7 (0.8%)	0
Fever	6 (0.7%)	5.2%
Chills	2 (0.2%)	0.9%
Hives	3 (0.3%)	0
Bradycardia	0	10.4%
Other	26 (3.1%)	

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 leukemia. Acute GVHD is defined as occurring within the first 100 days post-transplant, attacking predominantly liver, skin, mucosa, and gastrointestinal tract. Acute GVHD is classified by severity from grade 1 to 4. Data for acute GVHD in the MDACBB dataset was available for 838 patients who received a suitable allograft. Of these patients, 491 (58%) experienced acute GVHD, which appears to be comparable to the incidence of acute GVHD in the Docket data, in which 69% of patients who received a TNC dose ≥2.5 x 10^7/kg experienced acute GVHD (See Table 11).

Table 11: Incidence of Acute GVHD
[Source: Table 8 from applicant response to information request dated January 24, 2018]

Occurrence of Acute GVHD	MDACBB*	Docket**
No	347 (41%)	369 (31%)
Yes	491 (58%)	813 (69%)
Unknown	8 (0.94%)	
Grade		
1	101 (11.9%)	315 (27%)
2	232 (27.4%)	276 (23%)
3	108 (12.8%)	149 (13%)
4	50 (5.9%)	73 (6%)
Unknown	8 (0.9%)	

* Data from 846 patients who received a suitable allograft (TNC $\geq 2.5 \times 10^7$/kg and $\geq$ 4/6 HLA match).
** Data from patients who received TNC $>2.5 \times 10^7$/kg

Chronic GVHD occurs after 100 days post-transplant, involving different immune cell subsets, cytokines, and host targets. Data for chronic GVHD in the MDACBB dataset was available for 468 patients who received a suitable allograft (see Table 12). Extensive chronic GVHD was reported in 136 (16.1%) patients.

Table 12: Incidence of Chronic GVHD after Infusion with MDACBB
[Source: Adapted from Table 9 from applicant response to information request dated January 24, 2018]

Occurrence of Chronic GVHD	MDACBB*
Yes	234 (27.65%)
Limited	90 (10.6%)
Extensive	136 (16.1%)
Not Indicated	8 (0.9%)

* Dataset includes 846 patients who received a suitable allograft (TNC $\geq 2.5 \times 10^7$/kg and $\geq$ 4/6 HLA match). Note that evaluable data for this outcome was available from 468 patients. Due to the retrospective and voluntary nature of data collection, there are various amounts of missing data for different outcomes.

Engraftment Syndrome

Engraftment syndrome (ES) 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 the BLA. To support the safety of MDACBB, the reviewers took into consideration information on engraftment syndrome based on the docket data, and on the publicly available data (Appendix). ES occurred in 15% (95% CI: 11.7 %, 18.0%) of the 364 patients in the COBLT study. Median time to onset of the event was 10 days after transplantation (range, 5 - 35 days). In literature reports, the incidence of ES varies from 30% to 78%. The data in the docket dataset do not address the risk of ES.

Malignancies of Donor Origin, Transmission of Serious Infection and Rare Genetic Diseases

There are no reports of possible transmission of malignancy, serious infection, or genetic disease from the donor material in the MDACBB dataset. To support the safety of the applicant's HPC, Cord Blood, the reviewers took into consideration information from the docket data, and the publicly available data (Appendix). Data from published literature and from observational registries, institutional databases, and cord blood bank reviews reported to the docket for HPC, Cord Blood (from multiple cord blood banks) revealed nine cases of donor cell leukemia, one case of transmission of infection, and one report of transplantation from a donor with an inheritable genetic disorder. The data are not sufficient to support reliable estimates of the incidences of these events.

8.4.3 Study Dropouts/Discontinuations

Not Applicable

8.4.4 Common Adverse Events

Please see section 8.4.2 for details.

8.4.5 Systemic Adverse Events

Please see section 8.4.2 for details.

8.5 Additional Safety Evaluations

None.

8.5.1 Dose Dependency for Adverse Events

Dose dependency for adverse events has been discussed in the safety review of the docket and public information (Appendix). Therefore, this review does not include analysis of dose dependency for adverse events.

8.5.2 Time Dependency for Adverse Events

Please see section 8.4 for analyses of total death and early mortality at Day 100 post-transplantation.

8.5.3 Product-Demographic Interactions

Please see FDA review of docket and public information (Appendix) for analyses of product-demographic interactions regarding safety (graft failure) and efficacy (neutrophil recovery) by age, sex, and race/ethnicity.

8.5.4 Product-Disease Interactions

The BLA submission does not include data to assess the product-disease interactions.

8.5.5 Product-Product Interactions

The BLA submission does not include data to assess any product-product interactions.

8.5.6 Human Carcinogenicity

The BLA submission does not include data regarding human carcinogenicity.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

See FDA review of Docket and public information (Appendix) for information on overdose of HPC, Cord Blood products. MDACBB did not provide information on overdose of their product. The product contains dimethyl sulfoxide (DMSO). 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. Toxic overdose of DMSO has been reported in a subject undergoing autologous HPC – bone marrow transplantation (Yellowlees, Greenfield, et al. 1980). There is no report in the literature of a DMSO overdose related to HPC, Cord Blood transplantation.

The BLA submission does not include data regarding the abuse potential, withdrawal, and rebound of the applicant's product.

8.5.8 Immunogenicity (Safety)

HPC, Cord Blood manufactured by MDACBB is an allogeneic cord blood hematopoietic progenitor cell therapy for use in an unrelated recipient. An appropriate preparative regimen using chemotherapy and/or total body irradiation is required for engraftment. As a result, clinical complications related to both immunogenicity and the preparative regimens are major safety concerns. Please see Sections 8.4.1 and 8.4.2 of this review for details.

8.5.9 Person-to-Person Transmission, Shedding

Transplantation of the applicant's HPC, Cord Blood may result in the development of malignancies of donor origin in the recipient, transmission of serious infection and rare genetic diseases from the donor to the recipient (Appendix). No such cases were reported in this BLA.

8.6 Safety Conclusions

Based primarily on the Docket data, supplemented by the MDACBB data, and taking into consideration the publicly available data, the risks associated with MDACBB HPC, Cord Blood transplantation are serious and potentially fatal. The adverse events include early death, infusion reactions, graft versus host disease (GVHD), and graft failure. Due to differences in the size and quality of the datasets, the review team assessed the safety data from the pooled docket dataset and other publicly available data as the best indicator of the likely postmarketing performance of HPC, Cord Blood. Therefore, the package insert gives precedence to this pooled, publicly available safety data over the MDACBB safety data.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There are no data with the applicant's HPC, Cord Blood use in pregnant women to inform a product-associated risk. Animal reproduction studies have not been conducted with this product. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

9.1.2 Use During Lactation

There is no information regarding the presence of the applicant's HPC, Cord Blood in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for this product and any potential adverse effects on the breastfed infant from HPC, Cord Blood or from the underlying maternal condition.

9.1.3 Pediatric Use and PREA Considerations

MDACBB's HPC, Cord Blood has been used in pediatric patients with disorders affecting the hematopoietic system that are inherited, acquired, or resulted from myeloablative treatment.

Under 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 the applicant's HPC, Cord Blood are not new because they are the same as for the first FDA-approved HPC, Cord Blood product, HEMACORD, manufactured by New York Blood Center. Therefore, this application does not trigger PREA.

9.1.4 Immunocompromised Patients

The applicant's HPC, Cord Blood has been used in immunocompromised patients due to either the preparative regimen prior to transplantation or the underlying disease(s). Adverse events associated with its use are discussed in Section 8 of this review.

9.1.5 Geriatric Use

Clinical studies of HPC, Cord Blood from multiple cord blood banks did not include sufficient numbers of subjects ≥ 65 years of age to determine whether geriatric subjects respond differently from younger subjects. In general, administration of the applicant's product to patients ≥ 65 years should be cautious, considering the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or use of other drug therapy in this demographic subset.

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

None

10. CONCLUSIONS

Based primarily on the Docket data, supplemented by the applicant's data, and considering the publicly available data, we conclude that the applicant's HPC, Cord Blood is capable of hematopoietic and immunologic reconstitution in conjunction with a preparative regimen. The applicant's HPC, Cord Blood can function as an alternative source of hematopoietic progenitor cells for transplantation to treat diseases affecting the hematopoietic system.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 13 documents the risk-benefit considerations for this BLA.

11.2 Risk-Benefit Summary and Assessment

Based on the Docket data and the publicly available data, HPC, Cord Blood has demonstrated the ability to reconstitute the immunologic system in patients transplanted for primary immunodeficiency, malignant and nonmalignant disorders (Section 12, Appendices).

Transplantation of the applicant's HPC, Cord Blood resulted in hematopoietic reconstitution, indicated by neutrophil and platelet recovery.

Transplantation for hematopoietic and immunologic reconstitution is a potentially life-saving treatment for certain diseases affecting the hematopoietic system. 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. Risks include early death, infusion reactions, GVHD, engraftment syndrome, and graft failure.

11.3 Discussion of Regulatory Options

No major safety or efficacy concerns were identified from the clinical and statistical review to warrant a complete response action for the MD Anderson BLA 125657/0. The overall risks of the applicant's HPC, Cord Blood can be mitigated in labeling.

11.4 Recommendations on Regulatory Actions

The FDA clinical and statistical reviewers recommend approval of the applicant's HPC, Cord Blood 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

Labeling for HPC, Cord Blood is primarily product class labeling. The labeling of the applicant's HPC, Cord Blood will follow the labeling of previously approved HPC, Cord Blood products.

11.6 Recommendations on Postmarketing Actions

There are no safety issues related to the MDACBB HPC, Cord Blood that trigger a Risk Evaluation and Mitigation Strategy (REMS) or warrant postmarketing requirement (PMR) or postmarketing commitment (PMC) studies. The applicant will perform routine pharmacovigilance, which includes AE reporting in accordance with 21 CFR 600.80: 15-day expedited reporting for serious and unexpected adverse events and submission of periodic safety reports (quarterly for 3 years after licensure, annual thereafter). In response to an information request dated January 10, 2018, the applicant also confirmed that they will perform the following activities that are conducted for this product class:

a. Implement a safety outcomes monitoring and analysis plan. This plan will include: 1) maintenance of an observational database to include, for all HPC, cord blood units released, information including but not limited to, time to neutrophil recovery, graft failure, survival, cause of death, infusion reactions, and other adverse experiences; 2) aggregate analyses of interval and cumulative adverse experience reports; and 3) 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.
b. Submit a 15-day alert report for each serious infusion reaction associated with administration of HPC, cord blood.

These measures will be adequate to monitor postmarketing safety for the applicant's HPC, cord blood.

Table 13: Benefit-Risk Considerations
[Source: FDA review]

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, autoimmune disorders • Unrelated donor hematopoietic progenitor cell transplantation procedures require potentially toxic preparative regimens	• Hematological malignancies and marrow failure are serious and life-threatening diseases. • Metabolic disorder, hemoglobinopathy, immunodeficiency, and autoimmune disease are a group of serious disorders, and can be life-threatening if severe and at late-stage.
Unmet Medical Need	• Chemotherapy, immunotherapy, and targeted biologic agents have significant adverse event potential • 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.	• Not all patients have, or can use, available HSC sources from autologous or allogeneic bone marrow or peripheral blood. In such situations, cord blood fills an unmet medical need by providing a reasonable option for hematopoietic transplantation.
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, Cord Blood 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 MDACBB database demonstrated comparable results of hematopoietic reconstitution as compared with the COBLT and Docket data	• 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 MDACBB dataset does not include information regarding immunologic reconstitution. However, based on the analyses of the docket data and supported by the publicly available data, HPC, Cord Blood has demonstrated the ability of immunologic reconstitution for patients transplanted for primary immunodeficiency as well as for other malignant and nonmalignant disorders. • 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 serious and fatal. Standard approved chemotherapy or biologics should be considered first. • If failed standard therapy, other HSC source such as 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, comorbidities, functional status) should be considered. • The profile of adverse reactions associated with MDACBB HPC, Cord Blood is comparable to that observed in other HPC, Cord Blood products contributing to docket dataset.
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 product 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. • Postmarket: clinical outcome data collection; adverse event reporting under 21 CFR 600.80, and expedited reporting of serious infusion reactions.	Labeling information and postmarketing pharmacovigilance and safety monitoring should suffice for risk management; no REMS or PMR/PMC is necessary.

12. APPENDICES

Appendix 12.1 Safety Review: Hematopoietic Progenitor Cells-Cord Blood; Primary Reviewer: Donna Przepiorka, MD, PhD

Appendix 12.2 Clinical Efficacy Review, Nonmalignant Indications: Hematopoietic Progenitor Cells-Cord Blood; Primary Reviewer: John E. Hyde, Ph.D., M.D.

Appendix 12.3 Clinical Efficacy Review, Malignant Indications: Hematopoietic Progenitor Cells-Cord Blood; Primary Reviewer: Maura O'Leary, M.D.

[1] 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.
[2] Cornetta K, Laughlin M, Carter S, et al. Umbilical cord blood transplantation in adults: results of the prospective Cord Blood Transplantation (COBLT). Biol Blood Marrow Transplant 2005;11:149-60.
[3] Kurtzberg J, Prasad VK et al. Results of the Cord Blood Transplantation Study (COBLT): clinical outcomes of unrelated donor umbilical cord blood transplantation in pediatric patients with hematologic malignancies. Blood. 2008 Nov 15;112(10):4318-27.
[4] FDA Guidance for Industry: Biologics License Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System (2014)

SAFETY REVIEW
DOCKETS AND PUBLIC INFORMATION

Hematopoietic Progenitor Cells-Cord Blood

Review Completion Date	10/28/2011
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Table of Abbreviations

AE	Adverse event
ALD	(X-linked) Adrenoleukodystrophy
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
ATG	Antithymocyte globulin
BLA	Biologics license application
BMF	Bone marrow failure
CFU	Colony forming unit
CI	Confidence interval (95%, unless otherwise specified)
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
COBLT	The Cord Blood Transplantation Study
DMSO	Dimethyl sulfoxide
EAP	Expanded Access Protocol
EBV	Epstein Barr virus
ES	Engraftment syndrome
Gr	Grade
GVHD	Graft versus host disease
HHV	Human herpes virus
HLA	Human leukocyte antigen
HPC-A	HPC-apheresis
HPC-C	Hematopoietic progenitor cells – cord blood
HPC-M	HPC-marrow
HUS/TTP	Hemolytic uremic syndrome/thrombotic thrombocytopenic purpura
LGL	Large granular lymphocytic leukemia
MDS	Myelodysplastic syndrome
MPD	Myeloproliferative disorder
MPS	Mucopolysaccharidosis
NHLBI	National Heart, Lung and Blood Institute
NMDP	National Marrow Donor Program
NYBC	New York Blood Center
OS	Overall survival
PCR	Polymerase chain reaction
PID	Primary immunodeficiency disorders
PIR	Pre-engraftment immune reaction
PLT	Platelet
PTLD	Posttransplant lymphoproliferative disorder
RAEB	Refractory anemia with excess blasts
SHR	Subhazard ratio
THAL	Thalassemia
TNC	Total nucleated cells
TRM	Treatment related mortality
VCA IgG	Viral capsid antigen immunoglobulin G

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

See the BLA clinical review for recommendations on regulatory actions.

1.2 Risk Benefit Assessment

See the BLA clinical review for the risk benefit assessment.

2 Introduction and Regulatory Background

The purpose of this review is to provide an assessment of the safety of minimally manipulated, unrelated donor, hematopoietic progenitor cells-cord blood (HPC-C). This document represents a collaboration between the clinical and statistical reviewers. This review is limited in scope to information in the published literature, the FDA dockets FDA-1997-N-0010 and FDA-2006-D-0157, and data in the public domain. This review will serve to complement the clinical reviews of BLAs for HPC-C submitted in accordance with the FDA publication "Guidance for Industry: Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Specified Indications," and which cross reference the dockets for supporting safety information. See the BLA clinical review for the regulatory background.

3 Ethics and Good Clinical Practices

See Efficacy Review (Non-Oncology) – Dockets and Public Information for a description of the data quality and integrity.

4 Significant Issues Related to Other Review Disciplines

See the BLA clinical review for issues related to other disciplines.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The key materials used in this review include:

- Dataset for The COBLT Study (Available from the National Heart, Lung and Blood Institute (NHLBI) via its data-sharing portal at https://biolincc.nhlbi.nih.gov/home/)
- Docket FDA-1997-N-0010 (Legacy Docket number 97N-0497)
- Docket FDA-2006-D-0157 (Legacy Docket number 06D-0514)
- Relevant literature

5.2 Study Information

5.2.1 The COBLT Study

The COBLT Study (NCT00000603) is comprised of a main protocol and an expanded access protocol. Version 07/00 of the main protocol and version 07/00 of the expanded access protocol were obtained from The COBLT Study web site at https://web.emmes.com/study/cord/. The main protocol is a prospective, single-arm trial of unrelated donor HPC-C transplantation for patients with hematological malignancies, marrow failure, inborn errors of metabolism, and primary immunodeficiency disorders. The preparative regimens and GVHD prophylaxis were predefined. The minimal HLA matching was at least 4/6 with serological typing for Class I or at least 3/6 with high resolution typing at all loci. The minimum required cell dose was 1×10^7 TNC/kg. The expanded access protocol was open to subjects with a disease that warranted HPC-C transplantation but who were not eligible for the main protocol. Treatment on the expanded access protocol was not standardized. Safety and outcomes data were to be submitted by the investigator at specified time points using standardized data collection forms. This dataset represents the only available raw data from a prospectively conducted clinical trial of unrelated donor HPC-C transplantation. Study synopses are provided in Appendices 9.3.1 and 9.3.2.

5.2.2 Dockets

See Efficacy Review (Non-Oncology) – Dockets and Public Information for a description of the information in dockets FDA-1997-N-0010 and FDA-2006-D-0157.

5.2.3 Literature Review

The literature was searched for publications in peer-reviewed journals associated with HPC-C transplantation. The literature search strategy and cited references are provided in Section 9.

5.3 Review Strategy

The safety review emphasized early deaths, infusion reactions, delayed hematopoietic recovery and graft failure, acute GVHD, engraftment syndrome, and transmission of malignancy, infection or genetic disorder from the donor to the recipient.

Information submitted to the docket was reviewed for reports for each of the safety outcomes. The results were supplemented with analyses of the COBLT dataset. Where sufficient detail is available, the safety outcomes were also assessed for each proposed indication. The published literature was searched for additional information addressing the description, diagnosis, risk factors for and methods of mitigation of the critical safety events.

Datasets where available were pooled to allow for a better assessment of correlations between product characteristics (e.g., cell dose) and safety outcomes. The pooled dataset was also used to develop mathematical models for safety outcomes that could be used to assist with safety reviews of BLAs. p-Values <0.05 were considered to be significant. However, p-values

presented in the following sections should be interpreted with caution due to the exploratory nature of the analyses.

6 Review of Efficacy

See Efficacy Review (Non-Oncology) – Dockets and Public Information and Efficacy Review (Oncology) – Dockets and Public Information for the review of data supporting the efficacy of unrelated donor HPC-C transplantation for the treatment of patients with hematologic malignancies, Hurler Syndrome (MPS I), Krabbe Disease (Globoid Leukodystrophy), X-linked adrenoleukodystrophy, primary immunodeficiency diseases, bone marrow failure and beta thalassemia.

7 Review of Safety

7.1 Safety Summary

The safety of HPC-C was based on a review of submission to Docket FDA-1997-N-0010 (Legacy Docket number 97N-0497) and to Docket FDA-2006-D-0157 (Legacy Docket number 06D-0514), the dataset for The COBLT Study, and published literature. The COBLT study is the only prospective clinical trial included in this review. The information reviewed pertained to HPC-C from various manufacturers, but due to the lack of clear identification of manufacturer for individual subject data, no comparisons between manufacturers were made.

Raw datasets in the docket were submitted from the National Marrow Donor Program (NMDP), New York Blood Center (NYBC) and Duke University, and the COBLT dataset was obtained from the NHLBI. Cases that were not overlapping between these sources were pooled for statistical analyses. The pooled docket dataset included 1572 subjects of median age 6 years (range <1-66 yrs) transplanted from 1993 - 2006. The male:female ratio was 1.4:1. Over 70% of the subjects were being treated for a hematological malignancy. The donor was HLA matched with the subject at 6/6 loci for 11% of the pairs, 5/6 for 39%, 4/6 for 46% and <4/6 for 4%. The median cryopreserved TNC dose was 5.3 (range, 0.7-73.8) x 10^7/kg. A TNC dose $\geq$2.5 x 10^7/kg was administered to 1299 (81.6%) of the subjects.

The safety review emphasized early deaths, delayed hematopoietic recovery and graft failure, acute graft-vs-host disease (GVHD), engraftment syndrome, infusion reactions, and transmission of malignancy, infection or genetic disorder from the donor to the recipient.

Deaths: There were 838 deaths reported (53.3% of the cohort); 469 deaths (29.8% of the cohort) occurred by 100 days after transplantation. The most common (>5%) causes of death by day 100 after transplantation for those who received a TNC $\geq$2.5 x 10^7/kg were infection (7.8%) and organ failure (6.5%). Graft failure was the primary cause of death in 3.7% of the patients, and 69% of the deaths due to graft failure occurred by day 100.

When comparing subjects who received a TNC $\geq 2.5 \times 10^7$/kg vs $<2.5 \times 10^7$/kg, patients with the higher TNC dose had fewer deaths overall (49% vs 74%, $p<0.001$) and fewer deaths by day 100 (25% vs 52%, $p<0.001$). There was a continuous downward trend in early mortality with increasing increments of TNC dose by 1×10^7/kg with an apparent inflection point in the curve between 2 and 3×10^7 TNC/kg. Other factors that correlated with day-100 death were age, gender, diagnosis and degree of HLA mismatch.

The proportions of subjects who died by day 100 varied significantly ($p<0.001$) by indication, ranging from 5% to 41.1% for those who received a TNC dose $\geq 2.5 \times 10^7$/kg. There was a significant inverse correlation between TNC dose and early mortality for patients with hematological malignancies and marrow failure, but not for the other indications, although the numbers of subjects in each group may have been too small to detect a significant correlation.

Graft Failure: The primary graft failure rate was 16.4% (95% CI 14.4-18.6%) for subjects receiving a TNC dose $\geq 2.5 \times 10^7$/kg. The graft failure rates fell below 20% only for incremental TNC doses $\geq 4 \times 10^7$/kg and remained at approximately 7-20% until falling further at TNC doses $\geq 17 \times 10^7$/kg. On multivariate analysis, there was a significant association between graft failure and diagnosis ($p=0.006$), degree of HLA mismatch ($p<0.001$), and TNC dose group ($P<0.001$). The literature review also suggested that alloimmunization may increase the risk of graft failure.

The graft failure rate varied with diagnosis and ranged from 9.5% to 31.1%. When assessed by individual diagnosis, there was a significant inverse correlation between TNC dose group and graft failure for the subjects transplanted for hematological malignancies, bone marrow failure and immunodeficiency disorders. The literature review suggested that a higher TNC dose may be required for patients transplanted for thalassemia to prevent graft failure, but there were too few patients with thalassemia in the pooled dataset to allow for a meaningful analysis within this subgroup of patients.

Time to Neutrophil Recovery: The cumulative incidence of neutrophil recovery by day 42 was 77% (75%-79%) and the median time to neutrophil recovery was 25 days for subjects receiving a TNC dose $\geq 2.5 \times 10^7$/kg. The median time to neutrophil recovery varied by diagnosis and ranged from 19 days to 30 days. This variation was due in part to differences in TNC dose. For all subjects, the median time to neutrophil recovery was delayed substantially with TNC doses $<2 \times 10^7$/kg, but even with TNC doses as high as 20×10^7/kg, the time to neutrophil recovery still exceeded 30 days for 10% of the subjects, a much higher rate of delayed recovery than with HPC-M or HPC-A. On multivariate analysis, degree of HLA mismatch and TNC dose were significantly associated with the time to neutrophil recovery.

Acute GVHD: For patients who received a TNC dose $\geq 2.5 \times 10^7$/kg, the incidence of grades 2-4 GVHD was 42.1%, and for grades 3-4 GVHD it was 18.8%. There was no significant difference in the rates of acute GVHD when comparing TNC doses above vs below 2.5×10^7/kg.

Engraftment Syndrome (ES): ES was reported in 14.7% (11.7-18.0%) of the patients in the COBLT study. Median time to onset of the event was 10 days after transplantation (range, 5-35 days). In literature reports, the reported incidence of ES varied from 30% to 78%.

Infusion Reactions: The COBLT dataset was used for the assessment of infusion reactions. This included 523 infusions of HPC-C in 511 patients. The population included 310 males and 201 females of median age 6 years (range 0.05-67 years). Preparative regimens and graft-vs-host disease prophylaxis were not standardized amongst the patients. Infusion reactions were defined as prespecified events usually associated with HPC-C infusions and occurring within 24 hours of transplantation. These were graded by the National Cancer Institute Common Toxicity Criteria (NCI CTC). The most common infusion reactions noted were hypertension, vomiting, nausea and bradycardia. The rate of serious adverse cardiopulmonary events was 0.8%.

Table 1: Incidence of Infusion-Related Adverse Events Occurring in ≥1% of Subjects in The COBLT Study

	All Infusions (N=523)		Infusions with a TNC Dose ≥2.5 x 10^7/kg (N=442)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any reaction	65.4%	26.6%	65.4%	27.6%
Hypertension	46.5%	19.9%	48.0%	21.3%
Vomiting	15.7%	0.2%	14.5%	0.2%
Nausea	14.8%	6.1%	12.7%	5.7%
Sinus bradycardia	10.3%	0.0%	10.4%	0.0%
Fever	5.5%	0.2%	5.2%	0.2%
Sinus tachycardia	5.2%	0.8%	4.5%	0.2%
Allergy	3.1%	0.2%	3.4%	0.2%
Hypoxia	2.9%	2.7%	2.0%	2.0%
Hypotension	2.9%	0.6%	2.5%	0.0%
Hemoglobinuria	1.9%	0.0%	2.1%	0.0%
Dyspnea	1.7%	1.1%	0.9%	0.7%
Infection	1.5%	1.5%	0.9%	0.9%
Chills	1.3%	0.0%	0.9%	0.0%

On multivariate analysis, younger age and higher volumes of infusate were significantly associated with development of a grades 3-4 adverse event and with development of any grade of hypertension.

Review of the literature suggested the adverse infusion reactions may in part be due to Dextran 40. DMSO can also cause significant toxicity. Overdosage with DMSO may cause elevated liver enzymes and severe encephalopathy. The toxic effects can be ameliorated in part by plasma exchange. Severe DMSO toxicity can also be prevented by limiting DMSO administration to less than 1 gm/kg/day.

Donor Cell Leukemia: The risk of donor cell leukemia, myelodysplastic syndrome or a myeloproliferative disorder after HPC-C transplantation is estimated as 9/10,000.

Transmission of Serious Infection: The risk of transmission of serious infection is 1/10,000 based on a case report. However, in vitro testing suggests that 0.6% of units may be positive for HHV-6, and 0.15% of units from CMV-seronegative donors may be positive for CMV by PCR.

Transmission of Rare Genetic Disorders: There are no reported cases of transmission of a rare genetic disorder by HPC-C transplantation. The risk is estimated to be less than 1/10,000.

7.2 Methods

7.2.1 Studies/Clinical Trials Used to Evaluate Safety

The key materials used in the review include:

- Dataset for The COBLT Study
- Docket FDA-1997-N-0010 (Legacy Docket number 97N-0497)
- Docket FDA-2006-D-0157 (Legacy Docket number 06D-0514)
- Relevant literature

7.2.2 Categorization of Adverse Events

There were no standard definitions of endpoints or consistent use of grading for the data in the docket. Endpoint definitions and grading systems for The COBLT Study are provided in Section 5.2 above.

7.2.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Raw datasets in the docket were submitted from the NMDP, NYBC and Duke University, and the COBLT dataset was obtained from the NHLBI.

- The NMDP dataset included 581 US subjects who received a single, nonexpanded HPC-C unit from February 2000 to December 2006 for their first allogeneic transplantation.

- The NYBC dataset included the first 562 subjects transplanted from August 1993 to January 1998 with HPC-C units from the NYBC.

- The Duke dataset included 160 subjects transplanted with unrelated donor HPC-C for an inherited metabolic disorder at Duke University August 1995 to March 2007.

- The COBLT dataset include 364 subjects from the main protocol with outcomes information and 163 subjects from the expanded access protocol with partial information. These subjects were transplanted December 1998 to February 2004.

The dataset from Duke had substantial overlap with those from COBLT, NMDP and NYBC, but it also indicated the bank from which each unit was obtained, so overlapping cases could be excluded by matching the source bank and time period. The final pooled dataset included the data from COBLT, NMDP, NYBC and the non-overlapping entries from the Duke dataset. The subjects had to have at least a total nucleated cell dose, diagnosis and some outcome information to be included in the pooled dataset.

7.3 Adequacy of Safety Assessments

7.3.1 Overall Exposure at Appropriate Doses

The pooled docket dataset includes 1572 subjects; 577 subjects are from NMDP, 550 from NYBC, 356 from COBLT and 89 from Duke. A TNC dose $\geq$2.5 x 10^7/kg was administered to 1299 (81.6%) of the subjects. The demographics for the pooled dataset are shown in Table 2.

Table 2: Demographics of Pooled Dataset

Subject Characteristics		All Subjects Transplanted (N=1572)		Subjects with a TNC Dose $\geq$2.5 x 10^7/kg (N=1299)	
Median Age (Range)		6 (<1-66) yrs		7 (<1-66) yrs	
Age Category	<2 yr	394	(25.1%)	393	(30.3%)
	2 – <17 yr	902	(57.4%)	786	(60.5%)
	$\geq$17 yrs	276	(17.6%)	120	(9.2%)
Gender	Male	592	(37.7%)	524	(40.3%)
	Female	430	(27.4%)	389	(30.0%)
	Unknown	550	(35.0%)	386	(29.7%)
Ethnicity	White	646	(41.1%)	573	(44.1%)
	African-American	104	(6.6%)	90	(6.9%)
	Hispanic	143	(9.1%)	129	(9.9%)
	Asian	31	(2.0%)	28	(2.2%)
	Other	16	(1.0%)	14	(1.1%)
	Unknown	632	(40.2%)	465	(35.8%)
Diagnosis	Hematologic malignancies	1103	(70.2%)	862	(66.4%)
	Hurler Syndrome	74	(4.7%)	74	(5.7%)
	Krabbe Disease	41	(2.6%)	40	(3.1%)
	X-linked Adrenoleukodystrophy	25	(1.6%)	20	(1.5%)
	Primary immunodeficiency diseases	96	(6.1%)	93	(7.2%)
	Bone marrow failure	114	(7.3%)	95	(7.3%)
	Beta thalassemia	8	(0.5%)	8	(0.6%)
	Other	111	(7.0%)	107	(8.2%)
Year of Transplantation	1993-2000	633	(40.3%)	459	(35.3%)
	2001-2006	939	(59.7%)	840	(64.7%)
Lowest HLA Match Level	2-3	55	(3.5%)	40	(3.1%)
	4	723	(46.0%)	583	(44.9%)
	5	613	(39.0%)	524	(40.3%)
	6	170	(10.8%)	143	(11.0%)
	Unknown	11	(0.7%)	9	(0.7%)
Median Dose (TNC x 10^7/kg) (Range)	All	5.3 (0.7-73.8)		6.4 (2.5-73.8)	
	Adults	2.3 (0.7-6.5)		3.2 (2.5-6.5)	
	Children	6.4 (0.8-73.8)		6.9 (2.5-73.8)	

The majority of the population was comprised of children with a diagnosis of a hematological malignancy. There were 13 patients with hemoglobinopathy, including 8 identified as beta thalassemia, and there were a total of 236 patients with inherited metabolic disorders. Over 80% of the patients received a TNC dose $\geq 2.5 \times 10^7$/kg.

It was noted that there was a high degree of correlation in the pooled dataset between the established prognostic factors (including age group, gender, race, diagnosis, degree of HLA match and TNC dose group). The p-values for the correlations by Chi square are shown in Table 3.

Table 3: Significance Values For Correlations Between Prognostic Factors

	Age	Gender	Race	Diagnosis	HLA
Gender	0.26	-	-	-	-
Race	***<0.001***	0.21	-	-	-
Diagnosis	***<0.001***	***<0.001***	***<0.001***	-	-
HLA	***<0.001***	0.56	***<0.001***	***0.009***	**-**
TNC Dose	***<0.001***	0.60	0.52	***<0.001***	***<0.001***

7.3.2 Explorations for Dose Response

The dose of cells to be administered was chosen by the treating physician and not stipulated by the manufacturer with the exception of the COBLT Study where the minimum TNC dose indicated in the protocol was 1×10^7/kg. A summary of the doses by indication and dose group is shown in Table 4. The dose range is sufficiently wide to allow as assessment of safety outcomes by dose.

Table 4: TNC Doses by Diagnosis – Pooled Dataset

Diagnosis	N	Median TNC x 10^7/kg (range)	% of Patients in Each TNC Dose Group (x 10^7/kg)				
			<2.5	2.5-<5	5-<10	10-<20	≥20
Heme Malignancies	1103	4.3 (0.7-35.0)	21.9	35.5	27.5	13.5	1.6
Hurler Syndrome	74	10.1 (3.4-30.0)	0.0	4.1	46.0	41.9	8.1
Krabbe Disease	41	15.2 (2.4-50.4)	2.4	2.4	24.4	46.3	24.4
Adrenoleukodystrophy	25	4.3 (1.7-14.2)	20.0	36.0	24.0	20.0	0.0
Immunodeficiency	96	10.2 (1.7-73.8)	3.1	9.4	34.4	36.5	16.7
Marrow Failure	114	4.4 (0.8-36.8)	16.7	36.8	24.6	19.3	2.6
Thalassemia	8	6.4 (2.5-18.2)	0.0	25.0	50.0	25.0	0.0
Other	111	7.3 (2.1-33.6)	3.6	13.5	47.8	30.6	4.5
All	1572	5.3 (0.7-73.8)	17.4	30.1	30.0	18.9	3.7

7.3.3 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The assessment of safety for HPC-C units provided in this review of information covers information for HPC-C from different manufacturers as available in the docket and in the public domain. However, since most of the information concerned patient outcomes and did not always link outcome to the source of the HPC-C, comparisons between manufacturers were not made in this review.

7.4 Deaths

7.4.1 Review of Docket Submissions

1997-N-0010-DRAFT-0042: NYBC submitted a tabulation of detailed causes of death without further analysis. No conclusions could be drawn.

7.4.2 Analysis of the Pooled Dataset

There were 838 deaths reported (53.3% of the cohort); 469 deaths (29.8% of the cohort) occurred by 100 days after transplantation. When comparing those who received a TNC $\geq 2.5 \times 10^7$/kg vs $<2.5 \times 10^7$/kg, patients with the higher TNC dose had fewer deaths overall (49% vs 74%, $p<0.001$) and fewer deaths by day 100 (25% vs 52%, $p<0.001$).

The most common causes of death were infection, recurrence of the primary disease and organ failure (Table 5). The most common causes of death by day 100 were infection and organ failure. Graft failure was the primary cause of death in almost 4% of the patients, and 74% of the deaths due to graft failure occurred by day 100.

Table 5: Causes of Death After Transplantation – Pooled Dataset

	All Subjects Transplanted (N=1572)		**Subjects with a TNC Dose >2.5 x 10^7/kg (N=1299)**	
	Total	**Day 100**	**Total**	**Day 100**
Number of Deaths	838 (53.3%)	469 (29.8%)	635 (49.2%)	328 (25.3%)
Causes of Death				
Graft Failure	57 (3.6%)	42 (2.7%)	48 (3.7%)	33 (2.5%)
Organ failure	153 (9.7%)	112 (7.1%)	115 (8.9%)	84 (6.5%)
Infection	249 (15.8%)	168 (10.7%)	170 (13.2%)	101 (7.8%)
GVHD	98 (6.2%)	55 (3.5%)	72 (5.6%)	39 (3.0%)
Primary disease	202 (12.9%)	50 (3.2%)	168 (13.0%)	42 (3.2%)
Second malignancy	5 (0.3%)	0 (0.0%)	4 (0.3%)	0 (0.0%)
Other*	31 (2.0%)	23 (1.5%)	19 (1.5%)	13 (1.0%)
Unknown	43 (2.7%)	19 (1.2%)	39 (3.0%)	16 (1.2%)

*Other includes hemorrhage, pulmonary embolism, HUS/TTP, cardiac events and drug reactions.

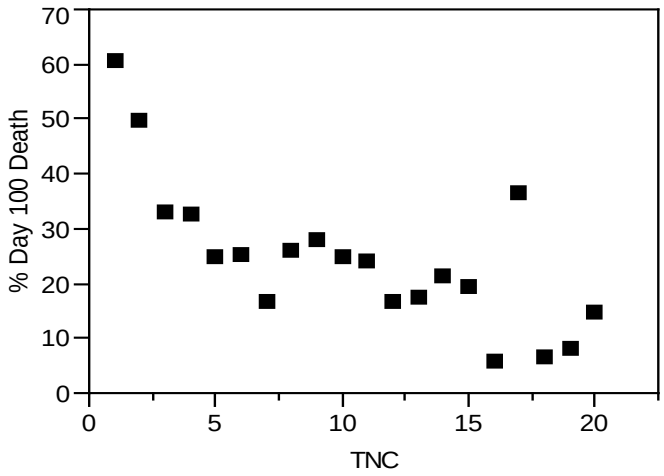
Table 6 below lists the day 100 death rates by indication. The proportions of subjects who died by day 100 varied significantly by indication, ranging from 4.0% to 46.5% for all subjects and from 5% to 41.1% for those who received a TNC dose $\geq$2.5 x 10^7/kg.

Table 6: Day 100 Deaths by Indication

Diagnosis	Total N	All Subjects Transplanted		Subjects with a TNC Dose ≥2.5 x 10^7/kg	
		Deaths (%)		Deaths (%)	
Heme Malignancies	1103	353	(32.0%)	229	(26.6%)
Hurler Syndrome	74	13	(17.6%)	13	(17.6%)
Krabbe Disease	41	4	(9.8%)	4	(10.0%)
Adrenoleukodystrophy	25	1	(4.0%)	1	(5.0%)
Immunodeficiency	96	17	(17.7%)	16	(17.2%)
Marrow Failure	114	53	(46.5%)	39	(41.1%)
Thalassemia	8	2	(25.0%)	2	(25.0%)
Other	111	26	(23.4%)	24	(22.4%)
p (Chi Square)		***<0.001***		***<0.001***	

To determine if there was a clear cut point in TNC dose for death by day 100, the day 100 death rates were graphed by TNC dose rounded to the nearest whole number. Only data through TNC doses of 20 x 10^7/kg were used, since the numbers of patients at higher doses was too low to provide a meaningful analysis. The plot in Figure 1 shows a continuous downward trend in mortality with no clear plateau with increasing TNC dose, with the especially highest rates of early mortality (>40%) at TNC doses of $\leq$2 x 10^7/kg.

Figure 1: Day 100 Deaths By TNC Dose (x 10^7/kg)



Whether day 100 mortality varied by dose for specific indications was also assessed. Figure 2 below shows the percentage of subjects who died by day 100 by incremental increases in TNC dose for each indication and for the remaining diagnoses grouped as "Other." By Cuzick's test for trend, there was a significant correlation between TNC dose group and day 100 mortality for the subjects transplanted for hematological malignancies and marrow failure.

Figure 2: Day 100 Deaths By TNC Dose Group And Indication
(TNC Dose Group 1=<2.5, 2=2.5 - <5, 3=5 - <10, 4=10 - <20, 5=≥20)
Abbreviations: Heme Mal, hematological malignancies; Hurler, Hurler Syndrome; Krabbe, Krabbe Disease; ALD, Adrenoleukodystrophy; PID, primary immunodeficiency disorders; BMF, bone marrow failure disorders; THAL, beta thalassemia major; OTHER, other diagnoses.

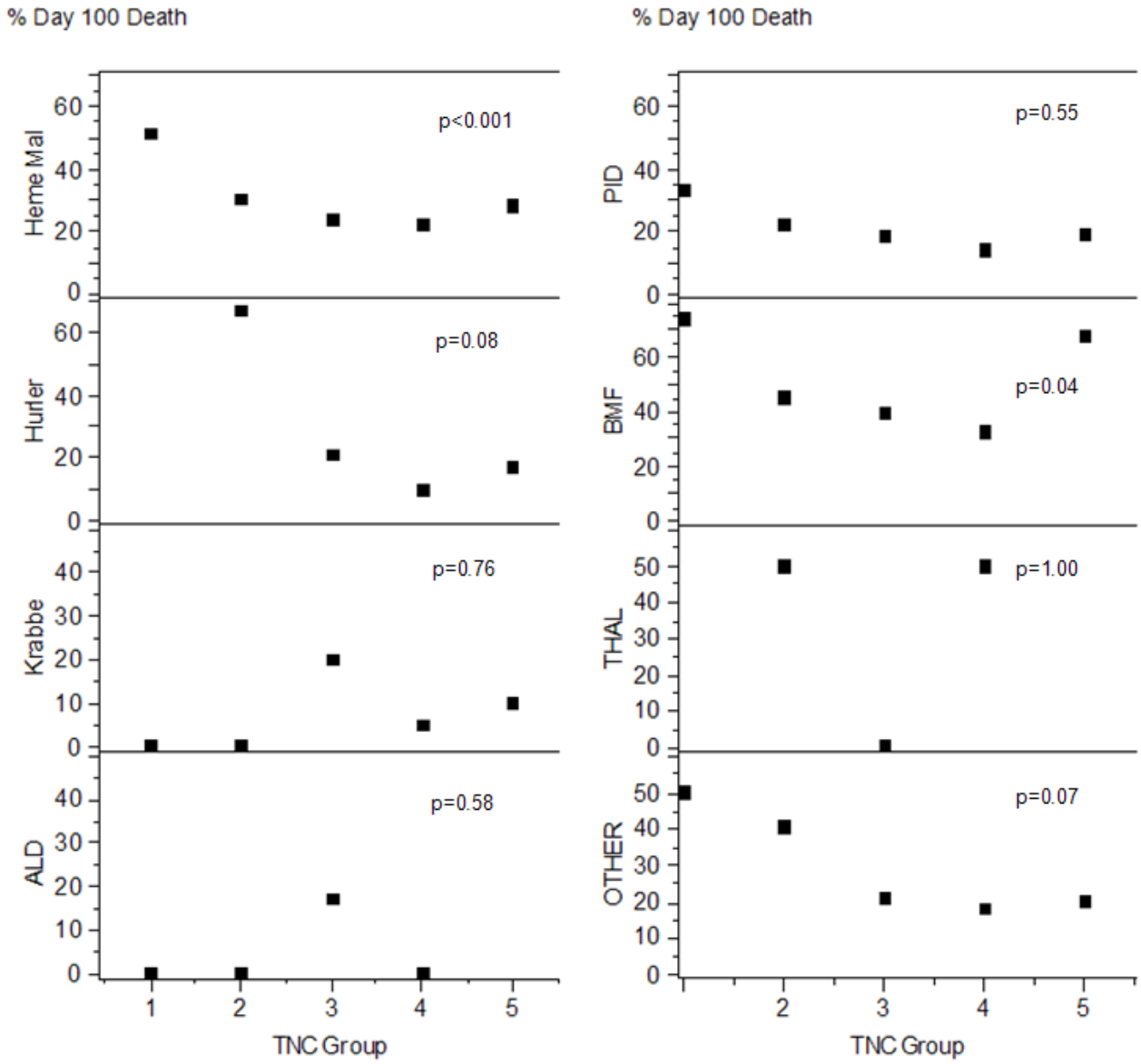


Table 7: Univariate Analysis of Factors Correlated with Day 100 Death

		Day-100 Mortality	p
Age Category	<2 yrs	88 / 394 (22.3%)	***<0.001***
	2 – <17 yrs	247 / 902 (27.4%)	
	≥17 yrs	134 / 276 (48.6%)	
Gender	Male	107 / 592 (18.1%)	***<0.001***
	Female	116 / 430 (27.0%)	
Ethnicity	White	144 / 646 (22.3%)	0.38
	African-American	30 / 104 (28.9%)	
	Hispanic	27 / 143 (18.9%)	
	Asian	6 / 31 (19.4%)	
	Other	5 / 16 (31.3%)	
Diagnosis	Hematologic malignancies	353 / 1103 (32.0%)	***<0.001***
	Hurler Syndrome	13 / 74 (17.6%)	
	Krabbe Disease	4 / 41 (9.8%)	
	X-linked Adrenoleukodystrophy	1 / 25 (4.0%)	
	Primary immunodeficiency diseases	17 / 96 (17.7%)	
	Bone marrow failure	53 / 114 (46.5%)	
	Beta thalassemia	2 / 8 (25.0%)	
	Other	26 / 111 (23.4%)	
Lowest HLA Match Level	2-3	24 / 55 (43.6%)	***<0.001***
	4	243 / 723 (33.6%)	
	5	165 / 613 (26.9%)	
	6	35 / 170 (20.6%)	
	Unknown		
TNC Dose (x 10^7/kg)	<2.5	141 / 273 (51.7%)	***<0.001***
	2.5 - <5	148 / 473 (31.3%)	
	5 - <10	110 / 471 (23.4%)	
	10 - <20	57 / 297 (19.2%)	
	≥20	13 / 58 (22.4%)	

Other factors that correlated with day 100 mortality were also sought. By univariate analysis, age, gender, diagnosis and degree of HLA mismatch, in addition to TNC dose, were found to correlate with the rate of death at day 100 (Table 7).

7.4.3 Summary

In summary, the early mortality was 25%, and 3.7% of subjects died from graft failure. The major causes of early death were infection (7.8%) and organ failure (6.5%). There was a strong correlation between day-100 mortality and TNC dose, with significant differences when comparing above and below 2.5 x 10^7TNC/kg. No more specific TNC cut point was identified by an assessment of mortality with incremental increases in TNC dose. Day-100 mortality also varied by diagnosis, and this variation was not clearly related to TNC dose alone.

7.5 Hematopoietic Recovery

7.5.1 Review of Docket Submissions

1997-N-0010-DRAFT-0016, -0019, 0032: NMDP submitted summary statistics for 353 patients transplanted 2000-2005 for various diseases on their IND. The median TNC dose transplanted was 5.7 x 10^7/kg cryopreserved and 4.1 x 10^7/kg post thaw. Neutrophil recovery was reported for 86% of patients, and platelets recovered to >50,000 for 59% of patients. The median time to neutrophil recovery was 21 (1-88) days, and the median time to platelet recovery was 61 (1-473) days.

An analysis of a raw dataset for 548 patients transplanted 2000-2006 was also submitted. The median TNC dose for adults was 2.3 x 10^7/kg and 6.6 x 10^7/kg for children. For adults, significant factors in a logistic regression model for engraftment at day 42 included a combination of HLA match and cell dose (p=0.022) and male gender (p=0.039). For the model for platelet recovery to >50,000 by day 100, only CMV serostatus was significant (p=0.019). For children, there were no significant factors for neutrophil recovery, and age was the only significant factor for platelet recovery (p=0.045).

1997-N-0010-DRAFT-0034: St. Louis Cord Blood Bank submitted summary statistics for 161 patients. Data was not complete for all patients. The median time to neutrophil recovery was 22 days (2-81), and the median time to platelets >50,000 was 62 days (25-136). Hematopoietic recovery correlated with TNC doses. The summary indicates no significant differences in time to neutrophil or platelet recovery by duration of storage of the unit prior to transplantation when categorized as <12 months, 12-24 months, and >24 months. They recommend a minimum cell dose of 3 x 10^7 TNC/kg.

1997-N-0010-DRAFT-0039: University of Minnesota submitted summary statistics for hematopoietic recovery for 257 patients undergoing HPC-C transplantation 1993-2000 for various malignant and nonmalignant conditions. The median TNC dose in the unit was 3.7 x 10^7/kg (range, 0.7-57.9).

Forty-five (18%) patients failed to engraft by day 45. The probability of neutrophil recovery by day 45 was 87% (83-92%), and the median time to neutrophil recovery was 25 days (range,10-59 days). On univariate analysis, factors significantly associated with neutrophil recovery included patient age (p<0.01), patient weight (p<0.01), disease category (malignant vs benign) (p=0.04), preparative regiment (p<0.01), TNC dose (p<0.01), CD34 dose (p<0.01), and prior transplantation (p=0.04).

The probability of platelet recovery to >50,000 by 6 months was 51% (45-58%). On univariate analysis, factors significantly associated with platelet recovery included patient age (p<0.01), patient weight (>19 kg) (p<0.01), disease category (malignant vs benign) (p<0.01), preparative regimen (p=0.01), CMV serostatus (p=0.01), and TNC dose >6 x 10^7/kg (p<0.01).

Degree of HLA mismatch was not a factor for either endpoint. The report concluded that for a successful outcome, the product should include a TNC dose >1.5 x 10^7/kg at cryopreservation, and HLA mismatches up to 3 of 6 antigens was permissible.

1997-N-0010-DRAFT-0042, -0043: The NYBC submitted summary statistics and a raw dataset for 562 patients undergoing HPC-C transplantation 1993-1998 for various conditions. They report that 70% of patients had neutrophil recovery, and 42% had recovery of platelet to >50,000.

1997-N-0010-DRAFT-0035: The NYBC submitted summary statistics for 1019 patients with various diagnoses transplanted 1993-2000. They report that by multivariate analysis, the factors associated with time to neutrophil recovery are the TNC dose ($p<0.001$), HLA Mismatch ($p=0.005$), diagnosis ($p=0.003$) and geographic location ($p<0.001$). In subsequent analyses, progenitor cell content was a better predictor of time to neutrophil and platelet recovery than TNC dose.

2006-D-0157-0007: CIBMTR submitted summary statistics for neutrophil recovery for 677 patients undergoing HPC-C transplantation 1996-2006 for selected nonmalignant conditions. The cumulative incidence of neutrophil recovery varied by diagnosis and ranged from 54-100%.

2006-D-0157-0044, -0045: Duke submitted summary statistics for 158 children transplanted 1995-2007 for various inherited metabolic disorders.

The probability of neutrophil recovery by day 42 was 83% (77-89%). Factors significantly associated with neutrophil recovery in the multivariate model include age <2 years ($p=0.002$) and CD34 cell dose post thaw ($p=0.01$).

The probability of neutrophil recovery by day 180 was 69% (61-76%). Factors significantly associated with platelet recovery in the multivariate model include age <2 years ($p=0.003$), female gender ($p=0.004$), and colony forming units (CFU) dose post thaw ($p<0.0001$).

2006-D-0157-DRAFT-0064: The NYBC submitted summary statistics for an analysis of 1618 patients transplanted for various diseases 1993-2005. They report that neutrophil recovery varied significantly with disease category, being most rapid with inherited metabolic disorders and least successful with severe aplastic anemia. Neutrophil recovery also varied with CD34 dose.

2006-D-0157-DRAFT-0070, -0077: StemCyte submitted summary statistics for 118 patients with various disease transplanted 2001-2005. The median TNC dose cryopreserved was 5.6 x 10^7/kg. Neutrophil recovery was achieved by 90% of patients, and the median time to recovery was 22 days. Platelet recovery to 20,000 was achieved by 77% of patients. On univariate analysis, time to neutrophil recovery was significantly longer for patients with a diagnosis of malignancy ($p=0.01$), and platelet recovery was significantly less frequent with a diagnosis of malignancy ($p=0.008$).

StemCyte also later submitted summary statistics for 283 patients with various diseases undergoing HPC-C transplantation 2001-2006. Neutrophil recovery was achieved by 93% of the patients, and platelet recovery by 77%.

7.5.2 Analysis of the Pooled Dataset

The analysis of hematopoietic recovery for the pooled dataset is summarized in Table 8. The primary graft failure rate was 18.8%. Subjects with graft failure had a median survival of 59 days, day-100 survival of 33% (95% CI, 27-39%), and 1-year survival of 13% (95% CI 9-17%). The graft failure rate was significantly lower in those who received a TNC dose ≥2.5 x 107/kg (16.4% vs. 30.4%, p<0.001).

Table 8: Hematopoietic Recovery – Pooled Dataset

	All Subjects Transplanted	**Subjects with a TNC Dose ≥2.5 x 10^7/kg**
Primary graft failure* (%, 95% CI)	18.8% (16.8-20.8%)	16.4% (14.4-18.6%)
Cumulative Incidence$^+$ of ANC>500 by day 42 (%, 95%CI)	74% (72-76%)	77% (75%-79%)
Proportion with PLT >50,000 by Day 100 (%, 95% CI)	41% (38-43%)	45% (42-48%)
Median time to ANC>500	27 days	25 days
Median time to PLT>50,000	153 days	122 days

* Includes death, 2nd infusion or autologous recovery for patients surviving at least 14 days without ANC recovery
$^+$Using death, 2nd infusion, autologous recovery and relapse as competing risks.
Abbreviations: CI, confidence interval; ANC, absolute neutrophil count; PLT, platelet count.

The cumulative incidence of neutrophil recovery by Day 42 was 74%, and an additional 6% had delayed recovery. The time to neutrophil recovery was significantly faster with a TNC dose ≥2.5 x 10^7/kg than with a lower dose (median 25 vs. 36 days, p<0.001).

Table 9: Hematopoietic Recovery by Indication

	N	**Median time to ANC>500$^+$**	**Primary graft failure (%, 95%CI)$^{+,*}$**
Hematologic malignancies	843	26 days	16.3 (13.8-18.9)%
Hurler Syndrome	74	21 days	9.5 (3.9-18.5)%
Krabbe Disease	39	22 days	10.3 (2.9-24.2)%
X-linked Adrenoleukodystrophy	19	22 days	10.5 (1.3-33.1)%
Primary immunodeficiency diseases	86	19 days	12.8 (6.6-21.7)%
Bone marrow failure	90	30 days	31.1 (21.8-41.7)%
Beta thalassemia	7	31 days	28.6 (3.7-71.0)%
Other	102	25 days	15.7 (9.2-24.2)%

+ Subjects with a TNC Dose >2.5 x 10^7/kg
* Includes death, 2nd transplantation or autologous recovery for patients surviving at least 14 days without neutrophil recovery
Abbreviations: CI, confidence interval; ANC, absolute neutrophil count

Neutrophil recovery was also assessed by the individual indications for those receiving a TNC dose ≥2.5 x 10^7/kg (Table 9 above). The primary graft failure rates ranged from 9.5% to 31.1%, and the median times to ANC>500 ranged from 19 days to 31 days. However, as shown in Table 4 above, there was also a difference in TNC dose median and range for each indication, which confounds direct comparisons of hematopoietic recovery between indications.

To determine if there was a cut point in the TNC dose for neutrophil recovery or primary graft failure, the median time to neutrophil recovery and graft failure rates were graphed by TNC dose rounded to the nearest whole number. Only data through TNC doses of 20 x 10^7/kg were used, since the numbers of patients at the higher doses was too low to perform the analysis. There is a continuous improvement in the hematopoietic outcomes over the range of TNC doses assessed, and no plateau is identified (Figures 3 and 4).

Figure 3: Time to ANC>500 By TNC Dose (x 10^7/kg)

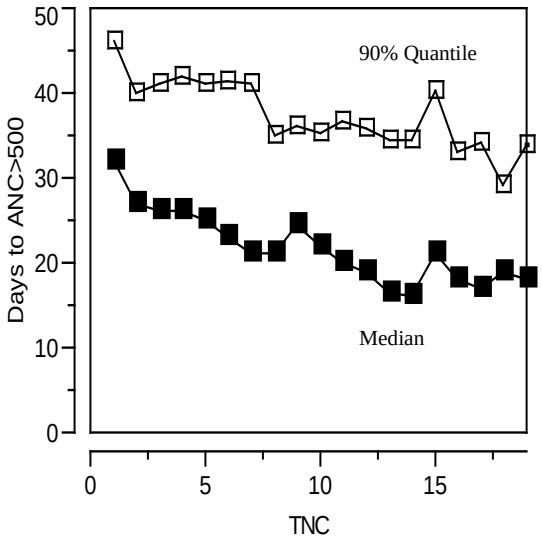
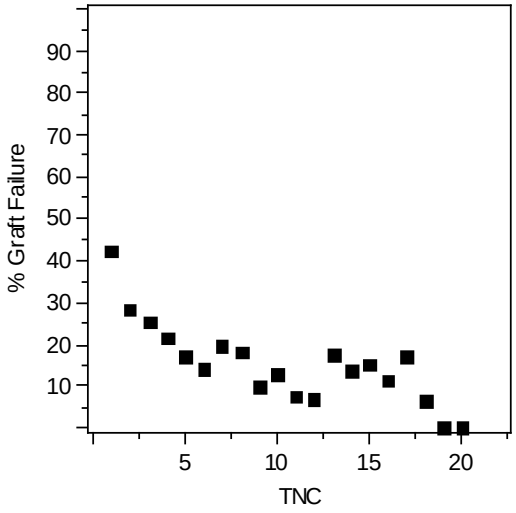


Figure 4: Primary Graft Failure By TNC Dose (x 10^7/kg)

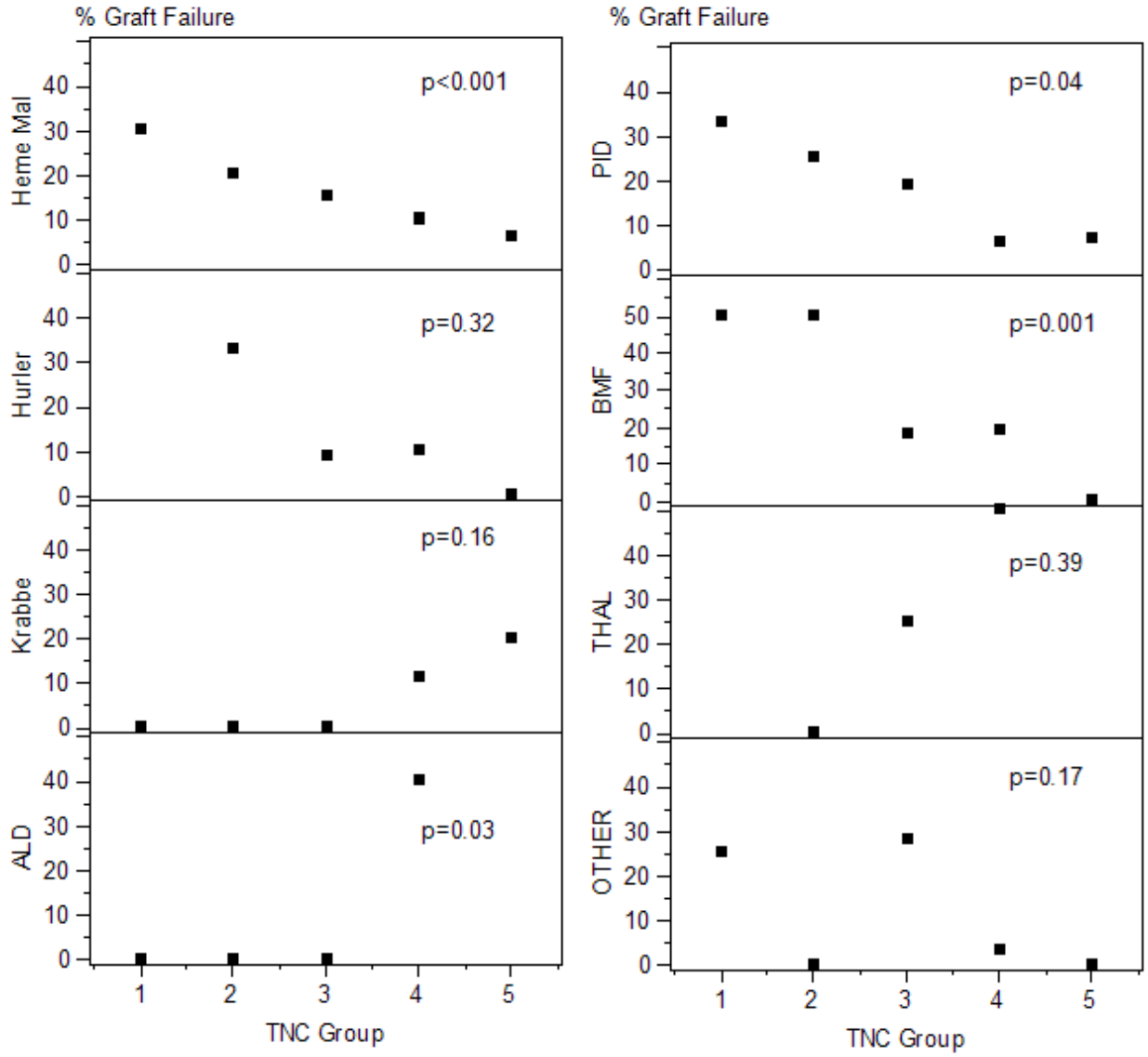


Most patients undergoing HPC-M transplantation achieve neutrophil recovery by 30 days after transplantation. For subjects in the pooled dataset, the median time to neutrophil recovery was less than 30 days for TNC doses >2 x 10^7/kg; however, even with TNC doses as high as 20 x 10^7/kg, the time to neutrophil recovery still exceeded 30 days for 10% of the subjects (Figure 3).

By contrast, graft failure rates fell below 20% only for TNC doses ≥4 x 10^7/kg and remained at approximately 5-20% until falling further at TNC doses ≥17 x 10^7/kg (Figure 4).

***Analyses of Graft Failure*:** Whether hematopoietic outcomes varied by dose for specific indications was also assessed. Figure 5 shows the percentage of subjects with primary graft failure through incremental increases in TNC dose for each indication and for the remaining diagnoses grouped as "Other." By Cuzick's test, there was a significant inverse correlation between TNC dose group and graft failure for the subjects transplanted with hematological malignancies, adrenoleukodystrophy, immunodeficiency disorders, and marrow failure. It should be noted that 96% of the patients with Hurler Syndrome received a TNC dose $\geq$5 x 10^7/kg, and with so few subjects at the lower dose levels, a trend might not be detectable.

Figure 5: Primary Graft Failure By TNC Dose Group And Indication
(TNC Dose Group 1=<2.5, 2=2.5 - <5, 3=5 - <10, 4=10 - <20, 5=>20)
See Figure 4 for abbreviations.



Other factors that correlated with graft failure were also sought. By univariate analysis, graft failure correlated with age group, diagnosis, degree of HLA mismatch and TNC dose group (Table 10).

Table 10: Univariate Analysis of Factors Correlated with Primary Graft Failure

		Primary Graft Failures	p
Age Category	<2 yr	41 / 376 (10.9%)	***<0.001***
	2 – <17 yr	179 / 884 (20.2%)	
	≥17 yrs	65 / 257 (25.3%)	
Gender	Male	96 / 581 (16.5%)	0.23
	Female	58 / 421 (13.8%)	
Ethnicity	White	91 / 632 (14.4%)	0.51
	African-American	21 / 103 (20.4%)	
	Hispanic	19 / 141 (13.5%)	
	Asian	6 / 29 (20.7%)	
	Other	2 / 15 (13.3%)	
Diagnosis	Hematologic malignancies	205 / 1071 (19.1%)	***<0.001***
	Hurler Syndromes	7 / 74 (9.5%)	
	Krabbe Disease	4 / 40 (10.0%)	
	X-linked Adrenoleukodystrophy	2 / 24 (8.3%)	
	Primary immunodeficiency diseases,	12 / 89 (13.5%)	
	Bone marrow failure	36 / 106 (34.0%)	
	Beta thalassemia	2 / 7 (28.6%)	
	Other	17 / 106 (16.0%)	
Lowest HLA Match Level	2-3	18 / 51 (35.3%)	***<0.001***
	4	149 / 701 (21.3%)	
	5	105 / 590 (17.8%)	
	6	13 / 165 (7.9%)	
TNC Dose (x 10^7/kg)	<2.5	78 / 257 (30.4%)	***<0.001***
	2.5 - <5	99 / 451 (22.0%)	
	5 - <10	75 / 464 (16.2%)	
	10 - <20	29 / 291 (10.0%)	
	≥20	4 /54 (7.4%)	

A multivariate logistic regression model was developed by backward stepping starting with the factors significant on univariate analysis. The final model identified diagnosis, degree of HLA mismatch, and TNC dose group as significantly associated with primary graft failure (Table 11).

Table 11: Primary Graft Failure – Multivariate Analysis

Factor	Odds Ratio	p
HLA Match[1]		***<0.001***
2	14.67	
3	4.89	
4	3.15	
5	2.76	
Diagnosis[2]		***0.006***
Hurler Syndrome	0.74	
Krabbe Disease	0.86	
Adrenoleukodystrophy	0.42	
Immunodeficiency	1.14	
Marrow Failure	2.54	
Thalassemia	2.77	
Other	1.20	
TNC x 10^7/kg[3]		***<0.001***
<2.5	1.64	
5-<10	0.72	
10-<20	0.42	
≥20	0.30	

[1]vs 6/6 match
[2]vs Hematological malignancies
[3]vs TNC dose 2.5 to <5 x 10^7/kg

The subjects with hematopoietic malignancies represent the largest subgroup with sufficient homogeneity to serve as an example of how TNC dose and degree of HLA match affect graft failure. Table 12 shows the incidence of primary graft failure for patients with hematologic malignancies by TNC dose and number of HLA antigens matched.

Table 12: Incidence of Graft Failure by HLA Mismatch for Hematologic Malignancies

	TNC Dose (x 10^7/kg)			
HLA Match	**<2.5**	**2.5 - <5**	**5 - <10**	**≥10**
4	31.1% (37/123)	21.4% (43/201)	15.2% (21/138)	9.0% (6/67)
5	35.1% (26/74)	16.1% (19/118)	18.7% (23/123)	9.0% (7/78)
6	4.8% (1/21)	18.4% (7/38)	2.9% (1/34)	11.1% (2/18)

***Analyses of Neutrophil Recovery*:** Other factors that correlated with time to neutrophil recovery were assessed by competing risk regression. On univariate analysis, graft failure correlated with age group, diagnosis, degree of HLA mismatch and TNC dose group (Table 13). A competing-risk regression model was developed by backward-stepping starting with the factors significant on univariate analysis. Death, 2nd transplantation, autologous recovery and relapse were use as competing risks. The final model identified degree of HLA mismatch ($p<0.001$) and TNC dose group ($p<0.001$) as significant. The subhazard ratios for the model are also displayed in Table 13.

Table 13: Analysis of Factors Correlated with Time to Neutrophil Recovery

	Univariate		Multivariate	
Covariate*	**SHR (95% CI)**	**p**	**SHR (95% CI)**	**p**
Age Category	0.72 (0.66-0.80)	***<0.001***	-	-
Gender	1.03 (0.91-1.18)	0.62	-	-
Race	0.99 (0.94-1.04)	0.75	-	-
Diagnosis	1.08 (1.04-1.13)	***<0.001***	-	-
HLA Mismatch	1.22 (1.13-1.31)	***<0.001***	1.16 (1.08-1.26)	***<0.001***
TNC Dose Group	1.35 (1.28-1.43)	***<0.001***	1.33 (1.25-1.41)	***<0.001***

*See Table 10 above for subgroup definitions.

A model was developed from the pooled dataset to determine the expected upper 95% confidence limit for time to neutrophil recovery using the degree of HLA mismatch and TNC dose as covariates. The analysis cohort was limited to patients with hematological malignancies receiving allografts with at least a 4 of 6 HLA antigen match and a TNC dose $\geq 2.5 \times 10^7$/kg. The parameters of the model are shown in Table 14. Using the model, 4.4% of subjects in the training set and 4.6% of subjects in the testing set had neutrophil recovery times that exceeded the expected upper 95% confidence limit.

Table 14: Parameters for Calculation of Expected Upper 95% Confidence Interval of Time to Neutrophil Recovery*

Term	**Estimate**	**Std Error**	**p**
Intercept	110.79	0.06	***<0.001***
HLA match 6/6	-0.96	0.004	***<0.001***
HLA match 5/6	1.32	0.003	***<0.001***
Log TNC dose	-8.36	0.008	***<0.001***

*For engrafting patients with hematological malignancies receiving allografts with at least a 4 of 6 HLA antigen match and a TNC dose $\geq 2.5 \times 10^7$/kg

7.5.3 Relevant Literature

In a comprehensive review, Petropoulou and Rocha[1] reported that the cumulative incidence of graft failure after unrelated donor HPC-C transplantation varied from 10% to 20%, and the median time to neutrophil recovery was 22 to 27 days. Factors affecting neutrophil recovery were diagnosis, cell dose (TNC, CFU or CD34), HLA matching, presence of noninherited maternal HLA antigens on the cord blood cells, use of fludarabine in the preparative regimen, and use of methotrexate for prevention of GVHD.[1,2]

The correlation between diagnosis and risk of graft failure was especially high in patients with nonmalignant disorders, such as hemoglobinopathies. Such patients are more likely to be alloimmunized from transfusion of nonlymphodepleted blood products, and they have not been exposed to immunosuppressive and myelosuppressive chemotherapy prior to transplantation. Ruggeri et al have found that this risk can in part be overcome by increasing the TNC dose to $>5 \times 10^7$/kg.[3]

How alloimmunization impacts neutrophil recovery is not clear. The risk of graft rejection is higher in haploidentical and unrelated donor transplant recipients who have antibodies directed against the mismatched donor HLA antigens, raising the concern that the same may be true for mismatched HPC-C transplant recipients. Cutler et al[4] and Takanashi et al[5] have, in fact, reported that the presence of anti-donor HLA antibodies in HPC-C transplant recipients correlated with a higher rate of graft failure, prolonged time to engraftment in those who did engraft, and an inferior overall survival. The risk of graft failure was especially high in double cord transplant recipients when antibodies were directed against both units being transplanted (odds ratio 16.3, p=0034). By contrast, Brunstein et al[6] found that time to neutrophil recovery was longer in those with anti-donor antibodies than in those without (24 days vs 19 days), albeit the difference was not significant, and the rates of graft failure were similar (78% vs 86%, respectively). The reason for the disparities between publications is not clear.

7.5.4 The COBLT Study

The COBLT study represents the only prospective clinical trial of minimally-manipulated, unrelated-donor HPC-C transplantation for which data are available for review. The main protocol of The COBLT Study (described in Appendix 9.3.1) is a single-arm trial that enrolled 364 subjects. Hematopoietic recovery data are available for 324 subjects from the main protocol who received TNC doses $\geq 2.5 \times 10^7$/kg. Demographics are shown in Table 15.

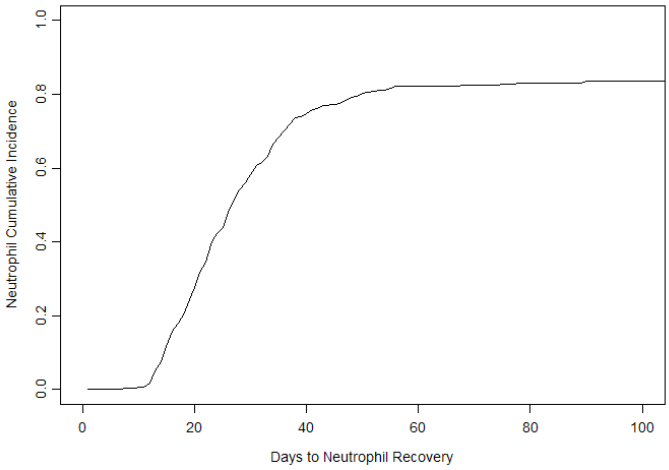
Table 15: Demographics of Subjects with a TNC Dose ≥2.5 x 10^7/kg in The COBLT Study Main Protocol (N=324)

Median Age (Range)		4.6 years (0.07–52.2 years)
Gender	Male	192 (59.3%)
	Female	132 (40.7%)
Ethnicity	White	168 (51.9%)
	African-American	36 (11.1%)
	Hispanic	35 (10.8%)
	Asian	10 (3.1%)
	Other	1 (0.3%)
	Unknown	74 (22.8%)
Diagnoses	Hematologic malignancies	231 (71.3%)
	Inherited Metabolic Disorders	69 (21.3%)
	Primary immunodeficiency diseases	19 (5.9%)
	Bone marrow failure	5 (1.5%)
HLA Match Level	Unknown	1 (0.3%)
	2-3	6 (1.8%)
	4	171 (52.8%)
	5	120 (37.0%)
	6	26 (8.0%)
Median TNC Dose (Range)		6.7 x 10^7/kg ($2.6 – 38.8 \times 10^7$/kg)

The primary endpoint of the study was day-180 survival. The target day-180 survival is 60%. A sample size of 300 with a true survival proportion of 60% provides at least 94% power to exclude a survival probability of 50% or less. The Kaplan-Meier estimate (95% CI) of day-180 survival was 66.9% (62.0% - 72.2%).

Secondary endpoints included neutrophil, platelet and red cell recovery. The cumulative incidence of neutrophil recovery to >500/uL at day 42 was 76% (95% CI 71%-81%) (Figure 6).

Figure 6: Neutrophil Recovery - The COBLT Study



Results of the analyses of hematopoietic recovery are show in Table 16.

Table 16: Hematopoietic Recovery – The COBLT Study Main Protocol

Neutrophil Recovery at Day 42	76% (71%-81%)*
Platelet Recovery at Day 100 (20,000/uL level)	57% (51%-63%)
Platelet Recovery at Day 100 (50,000/uL level)	46% (39%-51%)
Erythrocyte Recovery at Day 100	65% (58%-71%)
Median time to Neutrophil Recovery	27 days
Median time to Platelet Recovery (20,000/uL level)	90 days
Median time to Platelet Recovery (50,000/uL level)	113 days
Median time to Erythrocyte Recovery	64 days

*Cumulative incidence (95% confidence interval)

7.5.5 Summary

In summary, the primary graft failure rate was 16.4% (14.4-18.6%) for subjects receiving a TNC dose $\geq$2.5 x 10^7/kg. The graft failure rates fell below 20% only for incremental TNC doses $\geq$4 x 10^7/kg and remained at approximately 5-20% until falling further at TNC doses $\geq$17 x 10^7/kg. On multivariate analysis, there was a significant association between graft failure and diagnosis (p=0.006), degree of HLA mismatch (p<0.001), and TNC dose group (P<0.001). Graft failure was more common in patients with bone marrow failure (34%) and beta thalassemia (28.6%) and

less common in the inherited metabolic disorders (8.3-10%) as compared with the hematologic malignancies (19%). Graft failure was less common in patients with 6/6 HLA match (7.9%) and with increasing TNC doses to $\geq 5 \times 10^7$/kg. The literature review also suggests that alloimmunization may increase the risk of graft failure.

The graft failure rate varied with diagnosis and ranged from 9.5% to 31.1%. When assessed by individual diagnosis, there was a significant inverse correlation between TNC dose group and graft failure for the subjects transplanted with hematological malignancies, bone marrow failure and "other" diagnoses. For Hurler syndrome and bone marrow failure, a substantial decrease in graft failure especially occurs with a TNC dose $\geq 5 \times 10^7$/kg. The literature review suggests that the higher TNC dose may also be required for patients transplanted for thalassemia.

The cumulative incidence of neutrophil recovery by day 42 was 77% (75%-79%), and the median time to neutrophil recovery was 25 days for subjects receiving a TNC dose $\geq 2.5 \times 10^7$/kg. The median time to neutrophil recovery varied by diagnosis and ranged from 19 days to 31 days. This variation was due in part to difference in TNC dose. For all subjects, the median time to neutrophil recovery was delayed substantially with TNC doses $< 2 \times 10^7$/kg. but even with TNC doses as high as 20×10^7/kg, the time to neutrophil recovery still exceeded 30 days for 10% of the subjects, a much higher rate of delayed recovery than with HPC-M or HPC-A. On multivariate analysis, degree of HLA mismatch and TNC dose were significantly associated with the time to neutrophil recovery.

Subjects in The COBLT Study receiving a TNC dose $\geq 2.5 \times 10^7$/kg had hematopoietic recovery rates similar to those for the pooled dataset overall, and the day-180 survival for these subjects met the target for the protocol.

7.6 Acute GVHD

7.6.1 Review of Dockets

1997-N-0010-DRAFT-0016, -0019, 0032: NMDP submitted summary statistics for 353 patients transplanted 2000-2005 for various diseases. Grades 2-4 GVHD occurred in 38% of patients and grades 3-4 in 22%.

An analysis of the raw dataset for 548 patients transplanted 2000-2006 was also submitted. For adults, significant factors in a proportional hazards model for grades 2-4 GVHD included gender ($p=0.003$) and preparative regimen intensity ($p=0.002$). The model for grades 3-4 GVHD included only year of transplantation ($p=0.039$). For children, there were no significant factors for grades 2-4 GVHD, and only age was significant for grades 3-4 GVHD ($p<0.001$)

1997-N-0010-DRAFT-0034: St. Louis Cord Blood Bank submitted summary statistics for 161 patients. Data was not complete for all patients. Grades 2-4 GVHD occurred in 45% of 75 evaluable patients and grades 3-4 in 23%.

1997-N-0010-DRAFT-0039: University of Minnesota submitted summary statistics for hematopoietic recovery for 257 patients undergoing HPC-C transplantation 1993-2000 for various malignant and nonmalignant conditions. The median TNC dose in the unit was 3.7 x 10^7/kg (range, 0.7-57.9). The probability of grades 2-4 GVHD was 30% (24-36%), and 12% (8-16%) for grades 3-4 GVHD. On univariate analysis, there were no factors significantly associated with grades 2-4 GVHD.

1997-N-0010-DRAFT-0042, -0043: The NYBC submitted summary statistics and a raw dataset for 562 patients undergoing HPC-C transplantation 1993-1998 for various conditions. They report that 24% of evaluable patients had grades 2-4 GVHD and 18% had grades 3-4 GVHD.

2006-D-0157-0044: Duke submitted summary statistics for 160 children transplanted for various inherited metabolic disorders. The probability of grades 2-4 GVHD was 39% (31-46%), and 10% (6-15%) for grades 3-4 GVHD.

2006-D-0157-DRAFT-0070: StemCyte submitted summary statistics for 118 patients with various diseases transplanted 2001-2005. The rate of grades 3-4 GVHD was 15%.

7.6.2 Analysis of the Pooled Dataset

In the pooled dataset, 88% of the patients had an assessment for acute GVHD reported (see Table 17 for numbers of patients in the analysis). The time to onset of each grade of acute GVHD was not available, so only a crude incidence of acute GVHD by maximum grade can be calculated. For all patients with data, 42.2% had grades 2-4 GVHD, and 19.5% had grades 3-4 GVHD (Table 17). When comparing patients who received a TNC dose $\geq$2.5 x 10^7/kg to those who received a lower TNC dose, the incidences of grades 2-4 GVHD (42.1% vs. 42.7%, p=0.88) and grades 3-4 GVHD (18.8% vs. 23.6%, p=0.12) were similar.

Table 17: Acute GVHD – Pooled Dataset

	All Subjects Transplanted (N=1381)	**Subjects with a TNC Dose ≥2.5 x 10^7/kg (N=1182)**
Number (%) with maximum grade 0	451 (32.7%)	369 (31.2%)
1	347 (25.1%)	315 (26.7%)
2	314 (22.7%)	276 (23.4%)
3	176 (12.7%)	149 (12.6%)
4	93 (6.7%)	73 (6.2%)

The incidence of grades 2-4 and grades 3-4 acute GVHD by diagnosis are displayed in Table 18. Comparisons between diagnoses are limited by the small number of cases with a GVHD assessment reported for some of the indications, such as adrenoleukodystrophy and beta thalassemia.

Table 18: Acute GVHD by Diagnosis

	All Subjects Transplanted			Subjects with a TNC Dose ≥2.5 x 107/kg		
	N	% Gr 2-4	% Gr 3-4	N	% Gr 2-4	% Gr 3-4
Hematologic malignancies	975	42.6%	21.5%	795	42.5%	21.0%
Hurler Syndromes	71	47.9%	15.5%	71	47.9%	15.5%
Krabbe Disease	40	45.0%	10.0%	39	43.6%	10.3%
X-linked Adrenoleukodystrophy	23	47.8%	26.1%	19	52.6%	26.3%
Immunodeficiency diseases	93	30.1%	12.9%	91	30.8%	13.2%
Bone marrow failure	78	51.3%	25.6%	70	52.9%	24.3%
Beta thalassemia	6	33.3%	0.0%	6	33.3%	0.0%

7.6.3 Relevant Literature

The reported rates of grades 2-4 acute GVHD range from 14 to 52% after unrelated donor HPC-C transplantation. Several risk factors for acute GVHD have been reported, including CMV serostatus, pretransplant infection, age, CD34 cell dose and HLA mismatch.[7-9] How HLA mismatching impacts the risk of GVHD varies in the literature (reviewed in reference 7) from no impact to increased rates with mismatch at combinations of loci or with increasing degree of mismatch. MacMillan et al[8] also found that the risk of grades 2-4 acute GVHD was higher after double vs single unit transplantation (58% vs 39%, $p<0.01$), although the risks of grades 3-4 acute GVHD were similar (19% vs 18%). In this report, the double unit transplant recipients had significantly higher TNC, CD34 and CD3 doses in comparison to the single unit transplant recipients. The majority of the acute GVHD in the HPC-C transplant recipients appeared to involve skin alone and was responsive to steroid therapy. Such mild GVHD had little impact on treatment-related mortality or event-free survival.[8,9]

7.7 Engraftment Syndrome

7.7.1 Review of Dockets

There were no submissions to the docket that addressed the risk of engraftment syndrome in HPC-C transplant recipients.

7.7.2 Analysis of the COBLT Dataset

Patients in the COBLT Study were assessed for the occurrence of periengraftment onset fever and rash requiring treatment with corticosteroids. This toxicity was recorded as “cytokine storm” or hyperacute GVHD, and it was reported for 76 (14.7%, 95% CI, 11.7-18.0%) of the patients. Median time to onset of the event was 10 days after transplantation (range, 5-35 days).

7.7.3 Relevant Literature

Engraftment syndrome (ES) is a poorly characterized clinical entity that occurs in the pre- or peri-engraftment period in both autologous and allogeneic HPC transplant recipients. Spitzer[10] has recommended standardizing the diagnostic criteria to include noninfectious fever, rash and noncardiogenic pulmonary edema, although early intervention with steroids frequently prevents the pulmonary complications. If left untreated, patients may also go on to develop hyperbilirubinemia, weight gain, renal insufficiency and encephalopathy. The etiology is unclear, but the clinical manifestations appear to result from stimulation of immune cells and release of inflammatory cytokines. Some have distinguished ES from pre-engraftment immune reaction (PIR) largely on the basis of time of onset,[11] but this differentiation is not widely adopted. In fact, because of the overlap in clinical features of ES and GVHD, some centers do not recognize ES as a distinct entity or may call it hyperacute GVHD instead.

ES or ES-like events have been reported in 30-78% of unrelated donor HPC-C transplant recipients.[11-15] Median reported onset is approximately 7-9 days after transplantation, as much as several weeks prior to neutrophil recovery. ES after unrelated donor HPC-C transplantation resolves rapidly with a short course of high-dose steroids, and development of ES seems to have no impact on treatment-related mortality (TRM) or overall survival (OS). The incidence of ES appears to be reduced by use of short-term methotrexate or corticosteroids in the GVHD prophylaxis regimen.

7.7.4 Summary

Engraftment syndrome (ES) is a poorly characterized clinical entity that occurs in the pre- or peri-engraftment period in both autologous and allogeneic HPC transplant recipients and may include fever, rash and noncardiogenic pulmonary edema. The incidence of ES appears to be reduced by use of short-term methotrexate or corticosteroids in the GVHD prophylaxis regimen. ES or ES-like events have been reported in 30-78% of unrelated donor HPC-C transplant recipients in the literature. In The COBLT Study, ES-like events occurred in 15% of patients, and median time to onset was 10 days after transplantation (range, 5-35 days). ES after unrelated donor HPC-C transplantation generally resolves rapidly with a short course of high-dose corticosteroids, and its occurrence seems to have no impact on TRM or OS when treated.

7.8 Infusion Reactions

7.8.1 Review of Dockets

2006-D-0157-DRAFT-0070: StemCyte submitted summary statistics for 118 patients with various diseases transplanted 2001-2005. The infusion reactions reported included hypertension (8.5%), hemoglobinuria (8.5%), hives (1.7%), nausea and vomiting (1.7%), dyspnea (1.7%), and seizure and encephalopathy (0.9%). The HPC-C was infused without washing for 50 patients and after washing for 67 patients. The safety profile was similar between the two groups except for hemoglobinuria which occurred in 18% with no wash vs 1.5% when the HPC-C unit was washed prior to infusion.

7.8.2 Analyses of The COBLT Study Dataset

The COBLT Study provides the only dataset that includes prospective monitoring for infusion reactions. The dataset includes information for 511 patients who received 523 HPC-C units. Data on TNC dose and administration information were available for 499 infusions, and 442 of these had a TNC dose $\geq 2.5 \times 10^7$/kg. To prepare for infusion, HPC-C units were washed and resuspended in 30-150 mL 8% Dextran 40 with 4% albumin. Infusions were to be completed within 30 minutes.

Table 19 summarizes the administration information that was available for 499 single unit infusions.

Table 19: HPC-C Administration Parameters from The COBLT Study

	N	Median (range)
Infusion Duration	494	35 (1-130) min
Total Volume	499	93 (20-343) mL
Vol/Kg	499	4.3 (0.3-21) mL/kg
Infusion rate	494	7.5 (0.6-105.1) mL/kg/hr
TNC Dose	499	6.2 (0.8-65.0) x 10^7/kg

Premedications were administered for 98.5% of the infusions. Subjects were monitored for predefined infusion reactions identified as occurring within 24 hours of transplantation. Events were graded according to the NCI CTC scale. The incidences of infusion reactions for all 523 infusions are listed in Table 20.

Table 20: Infusion Reactions – The COBLT Study

	All Infusions (n=523)		Subjects with a TNC Dose $\geq 2.5 \times 10^7$/kg (n=442)	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Any reaction	65.4%*	26.6%	65.4%	27.6%
Hypertension	46.5%	19.9%	48.0%	21.3%
Vomiting	15.7%	0.2%	14.5%	0.2%
Nausea	14.8%	6.1%	12.7%	5.7%
Sinus bradycardia	10.3%	0.0%	10.4%	0.0%
Fever	5.5%	0.2%	5.2%	0.2%
Sinus tachycardia	5.2%	0.8%	4.5%	0.2%
Allergy	3.1%	0.2%	3.4%	0.2%
Hypoxia	2.9%	2.7%	2.0%	2.0%
Hypotension	2.9%	0.6%	2.5%	0.0%
Hemoglobinuria	1.9%	0.0%	2.1%	0.0%
Dyspnea	1.7%	1.1%	0.9%	0.7%
Infection	1.5%	1.5%	0.9%	0.9%
Chills	1.3%	0.0%	0.9%	0.0%

*Percentage of infusions

The majority of infusions (65%) were associated with a reported reaction, and over a quarter were assessed as grades 3-4 in severity. Emergency medications for reactions were administered for 3.8% of the infusions. The most common reactions (>10%) were hypertension, nausea, vomiting, and sinus bradycardia. The most common grades 3-4 reactions (≥2%) were hypertension, nausea and hypoxia. Four events (0.8%) were reported as serious adverse reactions involving cardiopulmonary signs or symptoms, two of which cited hypertension as an infusion reaction. Narratives are not available for the serious adverse events.

Demographic, product and administration characteristics were assessed by the effect likelihood ratio test for correlations with infusion reactions using the subset of 499 single unit infusions with administration information. These factors included duration of infusion, total volume infused, volume/kg, volume/kg/hour, age, diagnosis, degree of HLA mismatch, race, gender and TNC dose. The outcomes included any adverse event, any grade 3-4 event, and any hypertension. Multivariate analyses were performed using a backward stepping approach.

The development of any adverse event correlated with the infusion duration (p=0.01) and total volume (p=0.02). The highest rates of adverse events were for infusions exceeding 150 mL (75%) and when the infusion required more than 60 minutes to complete (79%). On multivariate analysis, there was no model found with more than one significant parameter.

Table 21: Infusion Reactions – Multivariate Analyses

	Any Grade 3-4 AE		**Any Hypertension**	
	Odds Ratio	**p**	**Odds Ratio**	**p**
Total Volume (per mL change)	1.005	***0.04***	1.008	***<0.001***
Age Group[1] Teen	2.52	***0.002***	2.97	***0.02***
Child	3.73		2.48	
Infant	3.82		2.58	
Neonate	0.00		2.62	

[1] vs Adults

Having any grade 3-4 event correlated with age group (p=0.005), with the highest rates in infants (29%), children (30%) and teens (24%), and the lowest rates in neonates (0%) and adults (11%). On multivariate analysis, both total volume and age group were significantly associated with grade 3-4 adverse events (Table 21).

Developing hypertension as an adverse event correlated with infusion duration, total volume infused, degree of HLA mismatch and diagnosis. The highest rates of hypertension occurred when the infusion duration exceeded 1 hour (58%), for infusions exceeding 150 mL (66%), and in patients with marrow failure (69%) or inherited metabolic disorders (60%). On multivariate analysis, total volume infused and age group were significantly associated with development of hypertension (Table 21).

7.8.3 Relevant Literature

Adverse experiences related to infusion of HPC-C include allergic reactions, immune-mediated events and toxic effects. The specific events reported include fevers, rigors, dysgeusia, headache, dizziness, paresthesias, arrhythmia, chest pain, hypertension, bradycardia, coronary spasm, dyspnea, hypoxia, pulmonary edema, renal failure, abdominal pain, nausea, vomiting, hemolysis and anaphylaxis.[16-24] The reported incidence of HPC-C infusion reactions varies from 4% to 65%. Most of the events were stated to be mild, but as many as 4.6% of the recipients had life-threatening reactions.[22]

Toxicity may in part be due to the cells themselves, plasma proteins, or to agents added to the infusate during processing or preparation for infusion. How HPC-C units are prepared for infusion varies. The most common methods include a) thaw at the bedside and infuse immediately, b) dilute with Dextran 40 and albumin prior to infusion, and c) dilute and replace supernatant prior to infusion. Consequently, the infusion may include not only the cord blood cells, but also cell debris, free hemoglobin, plasma proteins, albumin, Dextran 40 and dimethylsulfoxide (DMSO), each of which may contribute to the toxicity of the HPC-C unit. Dextran 40 and DMSO are of particular concern.

Dextran 40 (reviewed in reference 25) is a mixture of mainly α-1,6-glucan type polysaccharides with average molecular weight 40,000 d. Its known uses include volume expansion for treatment of shock, for priming extracorporeal pumps, and for prevention of venous thromboses and pulmonary emboli. Dextran 40 is supplied as a 10% solution for IV use, and the usual dosage is 5-10 mL/kg (< 1 gm/kg) over 12 to 24 hours. For adults, the starting infusion rate is usually no greater than 100 mL/hr. The lowest molecular weight fraction is cleared by the kidneys within hours of administration, but the higher molecular weight fraction may take days to be excreted and/or metabolized, so monitoring fluid balance to avoid fluid overload is critical.[25] In addition, renal impairment may delay excretion. Known side effects of Dextran 40 include acute renal failure, pulmonary edema, congestive heart failure, bleeding disorders and anaphylactoid reactions. It is estimated that anaphylactoid reactions to Dextran 40 occur in approximately 1-5 cases per 10,000 patients treated with Dextran 40 when premedication with Dextran 1 is not used.[26]

DMSO has no approval for intravenous use in the US. Following administration, DMSO is widely distributed in the body, including across the blood brain barrier. Animal studies showed that DMSO and its metabolites are partially excreted through the kidneys, but the metabolite dimethyl sulfide is also excreted through exhalation.[27,28] Dose-toxicity data are limited. In a small phase I study of intravenous DMSO for treatment of intracranial hypertension, single daily doses of 1 gm/kg as a bolus infusion resulted in severe hypernatremia and fluid overload.[29] The latter may be due to hyperosmolar plasma expansion.[30] Other known side effects of intravenous DMSO include dysgeusia, nausea, vomiting, elevated liver enzymes, hemolysis and renal failure.[29,31-36] Encephalopathy occurs with very high doses (see Section 12.0 Overdosage). Anaphylaxis may occur, and it is not dose-dependent.

Removal of DMSO by washing the HPC-C cells prior to infusion may reduce some of the side effects, especially hypertension, but resuspension of the cells in a Dextran 40-containing medium after washing does not eliminate the potential toxicities due to that agent.[16,19,23,24]

7.8.5 Summary

Reactions related to infusion of HPC-C include allergic reactions, other immune-mediated events and toxic effects. Cell debris, free hemoglobin, plasma proteins, albumin, Dextran 40 and dimethylsulfoxide (DMSO) may contribute to the development of infusion reactions. The COBLT study provided the only dataset that included prospective monitoring for infusion reactions. Reactions were reported in a majority of infusions (65%) in the COBLT study, and over a quarter were assessed as grades 3-4 in severity. The reported incidence of HPC-C infusion reactions in the literature varies from 4% to 65%. Most of the events were stated to be mild, but as many as 4.6% of the recipients had a life-threatening reaction. Removal of DMSO by washing the HPC-C cells prior to infusion may reduce some of the side effects, especially hypertension, but resuspension of the cells in a Dextran 40 containing medium after washing does not eliminate the potential for toxicities.

7.9 Malignancies of Donor Origin

7.9.1 Review of Dockets

There were no submissions to the docket that reported development of malignancies from HPC-C.

7.9.2 Analysis of the Pooled Dataset

The pooled dataset provides no information on development of malignancies from HPC-C.

7.9.3 Relevant Literature

HPC donor-derived malignancies are generally limited to leukemias and the opportunistic lymphoproliferative disorders (PTLD) resulting from EBV infection.

Donor cell leukemia is a rare event in HPC transplant recipients, estimated to occur in 124/100,000, although rates as high as 5% have been reported in single institution studies.[37] In a review of 64 published cases of donor cell leukemia, median time from transplantation to diagnosis of leukemia was 31 months (range 2-312 months), the complete remission rate for treated patients varied by disease (53-76%), and the median survival was 5.5 months from diagnosis of donor cell leukemia.[37]

Nine cases of donor cell leukemia, myelodysplasia or myeloproliferative disorders in HPC-C transplant recipients have been published (Table 22) for an estimated incidence of 9/10,000,[†] an

[†] The denominator is based on the estimated cumulative number of HPC-C transplantations performed worldwide as of 2010 (Gracia J. Transfus Apher Sci 2010;42:257-263).

incidence slightly less than that estimated for all transplant recipients above. A single institution has reported an incidence as high as 3% in HPC-C transplant recipients.[43] Amongst the reported cases in Table 22, one was diagnosed as a lymphoid leukemia, and the remainder were myeloid in nature. Outcome data are incomplete. Follow-up information for the donor was available for 3 of the cases; these donors were reported to be alive and well, two at 1.5 and 7 years after donation.

Table 22: Donor Cell Leukemia, MDS and MPD in HPC-C Transplant Recipients

Reference	Original Diagnosis	Donor Cell Leukemia	Time to Diagnosis of Donor Cell Leukemia	Outcome
38	Histiocytosis	AML	40 mos	Died (10 mos)
39	Lymphoma	AML		
40	AML	T cell LGL		
41	ALL	MPD	5 mos	
42	AML	AML	14.5 mos	Died (11 mos)
42	CLL	MDS	6 mos	Alive (28 mos)
42	ALL	MDS	5 mos	Alive (9 mos)
43	AML	MPD	26 mos	Died
43	Lymphoma	MDS-RAEB	21 mos	Died

Abbreviations: MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; AML, acute myeloid leukemia; LGL, large granular lymphocytic leukemia; CLL, chronic lymphocytic leukemia; RAEB, refractory anemia with excess blasts

EBV-related PTLD is represented by a spectrum of disorders, usually of donor origin, ranging from a polyclonal lymphoproliferation to a highly aggressive monoclonal lymphoma. In a review of over 18,000 HPC transplant recipients, the cumulative incidence of PTLD was 1% at 10 years.[44] Risk factors for early onset (<1 year after transplantation) included unrelated donor, mismatched donor, T-cell depletion of the allograft, use of ATG or anti-CD3 antibody for prevention or treatment of GVHD, grades 2-4 GVHD and radiation in the preparative regimen. PTLD occurred in 8% of patients with 2 risk factors and 22% with 3 risk factors. Chronic GVHD was the only risk factor for late-onset PTLD. Rituximab is the first line treatment of EBV-PTLD, with 55-100% responding.[45,46]

The reported incidence of EBV-related PTLD after unrelated donor HPC-C transplantation varies from 2% to 16%.[43,47,48] The incidence is highest (>20%) in those who received a nonmyeloablative or reduced intensity preparative regimen with ATG.[48] The inciting EBV infection is a reactivation of prior infection in the recipient and is not transmitted from the HPC-C donor to recipient, as in cases were donor cells were available, no evidence of infection by EBV was found,[45,49] although this is not always the case.[50] The reported response to rituximab is 33-55%. Many patients die within weeks of diagnosis from a fulminant lymphoma, and in the case series, 0-50% of the patients were alive at the time of report. Although no comparative study has been performed, it appears that EBV-related PTLD has a worse prognosis in the unrelated donor HPC-C recipients than in patients transplanted with other HPC types.

7.9.4 Summary

Donor-derived malignancies after HPC transplantation are generally limited to donor cell leukemias and the opportunistic lymphoproliferative disorders (PTLD) resulting from EBV infection. Donor cell leukemia, myelodysplastic syndrome and myeloproliferative disorders are extremely rare events in HPC-C transplant recipients, estimated to occur in 9/10,000. EBV-related PTLD is represented by a spectrum of disorders, usually of donor origin, ranging from a polyclonal lymphoproliferation to a highly aggressive monoclonal lymphoma. The reported incidence of EBV-related PTLD after HPC-C transplantation varies from 2% to 16%.

7.10 Transmission of Serious Infection

7.10.1 Review of Dockets

There were no submissions to the docket that reported transmission of serious infections from the HPC-C donor to recipient.

7.10.2 Analysis of the Pooled Dataset

The pooled dataset provides no information on transmission of serious infections from the HPC-C donor to recipient.

7.10.3 Relevant Literature

Weinberg et al[51] assayed 362 HPC-C samples for CMV, HHV-6, HHV-7, HHV-8 and EBV by polymerase chain reaction (PCR). HHV-6 was detected in 2 (0.6%) samples, and testing for the other viruses was negative. The authors tested a further 312 samples from donors having CMV IgM-negative mothers, finding 1 positive sample by PCR, for an overall CMV detection rate of 0.15%. The results indicate that HPC-C may harbor CMV and HHV-6 that may be transmitted to the HPC-C transplant recipient.

Haut et al[50] reported on a patient who died from EBV PTLD 6 months after HPC-C transplantation. Tumor biopsies at autopsy expressed donor-specific HLA typing, confirming its donor origin. A DNA sample from the HPC-C unit that had been stored was positive for EBV (1 copy/100,000 cells). The recipient was seronegative for EBV at diagnosis of leukemia and was found to have low levels of VCA-IgG prior to transplantation, but VCA-IgM was negative. The authors concluded that the VCA-IgG in the recipient resulted from passive transfer through transfusions during prior treatment, and that the EBV infection causing the PTLD was transmitted by the HPC-C; however, no further testing was performed to ensure that the EBV in the recipient was the same strain as the EBV in the donor. No other case of transmission of infection from a HPC-C donor to the recipient was found.

7.10.4 Summary

The estimated incidence of transmission of a serious infection is 1/10,000, generally with CMV, HHV, and EBV.

7.11 Transmission of Rare Genetic Disorders

7.11.1 Review of Dockets

There were no submissions to the docket that reported transmission of rare genetic disorders from the HPC-C donor to recipient.

7.11.2 Analysis of the Pooled Dataset

The pooled dataset provides no information on transmission of rare genetic disorder from the HPC-C donor to recipient.

7.11.3 Relevant Literature

Review of the published literature revealed no reports of transmission of rare genetic disorders from the HPC-C donor to recipient.

7.11.4 Summary

On the basis of the information that is available, the estimated risk of transmission of a rare genetic disorder is less than 1/10,000.

7.12 Overdosage

7.12.1 Review of Dockets

2006-D-0157-DRAFT-0070: StemCyte submitted summary statistics for 117 patients with various diseases transplanted 2001-2005. There was one case of seizure and encephalopathy reported. The sponsor did not provide additional information about the DMSO load in this patient but cautioned that the DMSO dose should not exceed 1 gm/kg.

7.12.2 Analysis of the Pooled Dataset

The pooled dataset provides no information on overdosage.

7.12.3 Relevant Literature

The three major components of HPC-C that may contribute to clinical overdosage include the cell content, Dextran 40 and DMSO. The literature provides no reports on overdosage due to an excessive number of nucleated cells infused for either HPC-C or other HPC types; the upper

limit of the tolerable cell dose range has not been established. Additionally, there are no reports of overdosage from Dextran 40.

The initial report of a toxic overdose of DMSO included two patients who had received approximately 1.5 gm/kg/day intravenously for 2 days (total dose 3 gm/kg) as treatment of arthritis.[31] The first patient developed vomiting, liver failure, renal insufficiency and loss of consciousness. Peritoneal dialysis had no clinical effect. The patient regained consciousness in 48 hours, and all signs and symptoms of toxicity resolved within 7 days with supportive care. The second patient developed vomiting, jaundice and renal insufficiency, reversing within one week with supportive care as well.

Dhodapkar et al[52] reported a toxic overdose in two patients with myeloma undergoing autologous HPC-A transplantation. The first patient received approximately 225 mL DMSO (approximately 3.2 gm/kg) over 10 hours with infusion of the HPC-A. He became somnolent and developed oliguria. Six days later, a plasma DMSO level was measured as 388 ug/mL. The patient underwent plasma exchange with reduction in the DMSO level to 78 ug/mL and improved clinically thereafter. A second patient received 120 ml DMSO (approximately 1.7 gm/kg) and was somnolent within 6 hours of infusion. His neurological status improved gradually over the next 5-6 days.

There were no reports in the literature of a DMSO overdose related to HPC-C transplantation.

7.12.4 Summary

Three major components of HPC-C that may contribute to clinical overdosage include the cell content, Dextran 40 and DMSO. Toxic overdose of DMSO has been reported in a patient undergoing autologous transplantation; there were no reports in the literature of a DMSO overdose related to HPC-C transplantation.

8 Postmarket Experience

There is no additional postmarket safety information for review.

9 Appendices

9.1 Literature Review/References

9.1.1 Literature Search Strategies

Early Mortality
The following PubMed searches were used:
N=133 for cord blood transplant AND early mortality
N=77 for cord blood transplant AND cause of death

Infusion Reactions
The following PubMed searches were used:
N=26 for cord blood transplant AND infusion reaction
N=33 for cord blood transplant AND allergic reaction
N=32 for cord blood transplant AND hypersensitivity

Adverse Events
The following PubMed searches were used:
N=35 for cord blood transplant AND adverse events
N=13 for hematopoietic AND transplant AND reaction AND DMSO
N=77 for stem cell transplant AND adverse AND DMSO
N=4 for cord blood transplant AND reaction AND DMSO
N=46 for dmso AND toxicity AND (Humans[Mesh] AND Review[ptyp])
N=15 for stem cell transplant AND reaction AND dextran
N=4 for cord blood transplant AND reaction AND dextran
N=38 for dextran AND toxicity AND (Humans[Mesh] AND Review[ptyp])

Hematopoietic Recovery
The following PubMed searches were used:
N=32 for cord blood transplant AND graft failure AND risk factor
N=83 for cord blood transplant AND engraftment AND risk factor
N=43 for cord blood transplant AND platelet AND risk factor
N=68 for cord blood transplant AND graft failure AND cell dose

Acute Graft vs Host Disease
The following PubMed searches were used:
N=81 for cord blood transplant AND GVHD AND risk factors
N=134 for cord blood transplant AND GVHD AND cell dose

Engraftment Syndrome
The following PubMed searches were used:
N=581 for ((Engraftment syndrome) OR (pre engraftment syndrome))
N=340 for ((Engraftment syndrome) OR (pre engraftment syndrome)) AND stem cell transplant

N=76 for ((Engraftment syndrome) OR (pre engraftment syndrome)) AND cord blood transplant

Malignancy of Donor Origin
The following PubMed searches were used:
N=211 for donor origin AND malignancy AND stem cell transplant
N=26 for donor origin AND malignancy AND cord blood transplant

Transmission of Serious Infection
The following PubMed searches were used:
N=48 for transmission of infection AND cord blood transplant
N=50 for donor AND transmission of infection AND stem cell transplant
N=20 for infection transmitted by transplant AND stem cell
N=13 for infection transmitted by transplant AND cord blood

Transmission of Rare Genetic Disorders
The following PubMed searches were used:
N=0 for cord blood transplant AND transmit AND genetic
N=0 for cord blood donor AND transmit AND genetic

Overdosage
The following PubMed searches were used:
N=53 for dmso AND intravenous AND toxicity
N=48 for dmso AND intravenous AND adverse
N=10 for dmso AND intravenous AND (Humans[Mesh] AND Clinical Trial[ptyp])
N=18 for dmso AND intravenous AND (Humans[Mesh] AND Case Reports[ptyp])

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9.2 Labeling Recommendations

The major recommendations for labeling resulting from this safety review are:

- Include a black box warning for fatal infusion reactions

- Include in the instructions for dosage a minimum TNC dose of 2.5 x 10^7 /kg at cryopreservation for units with at least 4 of 6 antigens matching for HLA-A,-B and -DR, and that the DMSO dose should not be greater than 1 mL/kg/day.

- Include in the instructions for administration the recommendations for prehydration, premedication, peri-infusion monitoring, and discontinuation of the infusion if an allergic reaction occurs or if the volume load is not tolerated.

- Include a contraindication for those who are allergic to DMSO or other components in the preparation for infusion.

- Include warning and precautions that address allergic reactions and anaphylaxis, infusion reactions, graft versus host disease, engraftment syndrome, graft failure, malignancies of donor origin, transmission of serious infection, and transmission of rare genetic disease.

- Identify the most common adverse reactions (>5%) as hypertension, nausea, vomiting, bradycardia, tachycardia, fever. Highlight the increased risk of grades 3-4 infusions reactions and hypertension in pediatric patients and with large volumes of infusate.

- Include a description of the clinical manifestations of DMSO overdosage and management of DMSO overdosage.

9.3 Appendices

9.3.1 The Cord Blood Transplantation Study Protocol (The COBLT Study)

Protocol Design

This is a prospective, open-label, single-arm, multicenter Phase 2A trial. The study sites include transplant centers, cord blood banks and a coordinating center. Each bank used the same protocol for recruiting donors, collecting, processing, testing, storage, retrieval from storage, reprocessing from the frozen state, and shipping. Each participating transplant center used the same patient selection criteria, preparative regimen for patients in the same class, initial graft-versus-host disease (GVHD) prophylaxis, indications for the use of cytokines, definitions for events and complications, and methods for evaluating immune reconstitution. Data were also collected on banked cord blood units to establish indicators of quality that correlated with patient outcome.

Objectives

1. The primary endpoint for the study of umbilical cord stem and progenitor cell transplantation is 180 day survival.

2. The secondary endpoints are:

- Disease-free survival (DFS)
- Long-term patient survival
- Incidence of neutrophil engraftment
- Incidence of both primary and secondary graft failure
- Incidence of platelet engraftment
- Incidence of RBC engraftment
- Incidence and severity of acute and chronic GVHD
- Incidence of complications, including infection, VOD, and interstitial pneumonitis
- Incidence of relapse
- Incidence of other malignancies, lymphoproliferative disorders, and post-transplant MDS
- Immune reconstitution

Key Eligibility Criteria

1. Eligible disease
    - Hematological malignancy – AML, ALL, CML, MDS, lymphoma without active CNS disease and without myelofibrosis >grade 2
    - Benign disorders – Marrow failure, inborn error of metabolism, primary immunodeficiency disorders

2. The cord blood unit for transplantation is at least 3/6 matched with recipient and has a minimum of $1x10^7$ TNC/kg cryopreserved
3. Meets defined minimum organ function

4. KPS ≥70% or Lansky ≥50%
5. Age <55 years
6. No uncontrolled infections and seronegative for HIV
7. Prior allogeneic transplantation >12 months from enrollment and prior autologous transplantation >6 months from enrollment.
8. Not pregnant or breast feeding
9. Able to provide consent

Treatment Plan

Upon registration, subjects were enrolled by disease category. Following retrospective high-resolution HLA typing, subjects were stratified as follows:

1. Malignant disease, 5/6 or 6/6 high resolution HLA match, ≤18 years of age
2. Malignant disease, 4/6 high resolution HLA match, ≤18 years of age
3. Malignant disease, 3/6 high resolution HLA match, ≤18 years of age
4. Malignant disease, 2/6 or 1/6 high resolution HLA match, ≤18 years of age
5. Severe aplastic anemia, Fanconi anemia and other marrow failure syndromes
6A. Inborn errors of metabolism/storage diseases
6B. Combined immune deficiencies
6C. Other non-malignant diseases not described above
7. Malignant disease alternative conditioning regimen (busulfan and melphalan)
8. Adult patients (> 18 years of age)

Multiple disease-specific myeloablative busulfan-based or TBI-based preparative regimens were specific in the protocol. GVHD prophylaxis consisted of cyclosporine and corticosteroids. Filgrastim was administered from Day 0 to ANC >2000. High-dose corticosteroids were to be administered for fever and erythroderma between days 5 and 9 (engraftment syndrome). Standard supportive care measures and infection prophylaxis were used.

Safety Monitoring

Study visits were scheduled weekly after transplantation for 14 weeks, and thereafter at day-100, day-120, day-150, 6 months, 9 months, 12 months, 19 months, 24 months, and 36 months.

The required examinations included:

1. Daily CBC, differential through neutrophil recovery; Post-engraftment: CBC and platelet count 3 times a week until discharge; Postdischarge: CBC and platelet count weekly until PRBC and platelet transfusion independent, and at Days 100, 180,270, and 360.
2. Reticulocyte count at 4 weeks post-transplant, then weekly until reticulocyte count > 30,000/mm^3 for two consecutive weekly measurements
3. Bone marrow aspirate on Day 42 for patients who do not have an ANC >500/mm^3 by Day 42
4. CMV surveillance should be performed according to institutional policy
5. For patients with CML, cytogenetic tests should be performed on bone marrow specimens

at 3, 6, and 12 months
6. For patients with lymphoma, radiologic studies which were positive prior to transplantation should be repeated at 3, 6, and 12 months
7. IgG, IgA, and IgM immunoglobulin levels at 6, 12, 18, and 24 months
8. Chimerism studies between Days 28 and 42, Day 100 and 1 year
9. Immune reconstitution at 1, 2, 3, 6, 9 (optional), 12, 18 (optional), 24, 36, and 48 months
10. Kamofsky/Lansky history and physical examination, CBC, renal and liver function tests, cardiac function tests (echocardiogram or MUGA scan), pulmonary function tests, thyroid function tests yearly for 4 years then as clinically indicated, height, weight, head circumference, if age appropriate
11. GVHD grading update weekly through day-100
12. Core toxicities

Endpoint Definitions

1. Primary Graft Failure is failure to achieve ANC > 500/mm^3 for three consecutive measurements on different days by Day 42. The first of the three measurements may occur on Day 42. The ANC recovery must be of donor origin documented by either bone marrow or peripheral blood chimerism assays indicating at least 90% of cells of donor origin. Infusion of stem cells prior to Day 42 will be considered primary graft failure.

2. Secondary Graft Failure: Documented engraftment as defined above followed by ANC < 500/mm^3 absence of donor cells in the marrow or blood as demonstrated by a chimerism assay without subsequent improvement occurring either spontaneously or after growth factor treatment.

3. Neutrophil engraftment is defined as achieving ANC >500/mm^3 for three consecutive measurements on different days by Day 42. The first of the three measurements may occur on Day 42. The ANC recovery must be of donor origin documented by either bone marrow or peripheral blood chimerism assays indicating at least 90% of cells of donor origin. A patient receiving a stem cell infusion prior to Day 42 will be considered a graft failure.

4. Platelet engraftment will be defined as the first day of a minimum of three consecutive measurements on different days such that the patient has achieved a platelet count > 50,000/mm^3 and is platelet transfusion independent for a minimum of seven days.

5. Time to red cell engraftment is defined as the first day of two consecutive measurements on different days such that the patient has achieved an absolute reticulocyte count > 30,000/mm^3.

6. Acute GVHD usually develops within the first three months after transplantation and appears as a characteristic dermatitis often accompanied by cholestasis and enteritis. The staging of acute GVHD will follow NMDP guidelines but will include weekly capture of symptoms and characterization of alternative causes.

7. Initial symptoms of chronic GVHD frequently include nausea and anorexia with ocular and oral sicca. Rash characteristically appears with pigmentary changes progressing to sclerosis and contractures. Other organs may be involved. Symptoms may mimic those seen in patients with scleroderma and other autoimmune disorders. Chronic GVHD typically does not occur until three or more months after transplantation. Details regarding the definition and diagnosis are listed in Appendix C

8. Veno-occlusive disease is defined by the occurrence of two of the following within 30 days of transplantation with no other explanation for these signs and symptoms present at time of diagnosis: hyperbilirubinemia (total serum bilirubin >2 mg/dL), hepatomegaly or right upper quadrant pain of liver origin, and sudden weight gain (> 5% of baseline body weight) because of fluid accumulation. Reversal of hepatic blood flow can frequently be demonstrated on doppler ultrasonography.

9. Interstitial pneumonitis is defined by diffuse interstitial infiltrates on chest x-ray not caused by fluid overload. It may be caused by a virus, bacteria, fungus, or may be of unknown etiology.

10. Infections will be graded according to the following severity scale:

- Mild, no active treatment (e.g., viral syndromes)
- Moderate, requires outpatient PO antibiotic
- Severe, requires N antibiotic or antifungal or hospitalization
- Life-threatening (e.g., septic shock)
- Caused or contributed to death

For infection as a secondary endpoint, only grades 3-5 infections will be considered.

11. The term relapse is used to describe the recurrence of disease after transplantation. For the purposes of this study, relapse will be defined separately for each disease eligible for transplantation. The time to relapse is the time to the first observation of hematologic or cytogenetic changes which result in characterization as relapse. Treatment given for relapse reversal will be considered indicative of relapse even in the absence of laboratory characteristics.

12. Infusion-related toxicities were graded using the NCI CTC system. Regimen-related toxicity was graded according to Bearmans's criteria

Analytic Plan

Accrual was planned to continue until up to 360 pediatric subjects enrolled. This would allow for an estimated 300 pediatric subjects with malignant diseases and at least 75 patients in the 3/6 and 4/6 strata.

The target day-180 survival is 60%. A sample size of 75 with a true survival proportion of 60% will provide 94% power to exclude a survival probability of 40%.

Primary endpoint - The primary analysis will consist of estimating the Day 180 survival probability based on the Kaplan-Meier product limit estimator for Strata 1 to 4 combined and

each strata separately. The Day 180 survival probabilities and confidence intervals will be calculated for each of these cells. All transplanted patients will be used in the analysis.

Secondary endpoints - Similar calculations will be performed for the secondary endpoints, e.g. neutrophil engraftment, red cell engraftment, platelet engraftment, overall survival, disease-free survival, acute GVHD, etc. The primary analysis of neutrophil graft failure will be conducted conditional on patients surviving at least 14 days.

Secondary analyses - Overall relapse rates will be estimated by Kaplan-Meier product limit curves using log-rank tests to compare strata. Adjustments will be made as necessary for covariates including age of recipient, disease risk status, interval between diagnosis and transplant, disease type, gender of donor, post-transplant chimerism, pre-transplant Kamofsky score, or other measure of performance status by use of proportional hazard or other multivariate models as appropriate. A secondary analysis of neutrophil graft failure will be conducted conditional on patients surviving at least 28 days. A secondary analysis will be performed on patients who fail to engraft. Incidence rates of both acute and chronic GVHD will be estimated using Kaplan-Meier product limit curves. Multivariate models will be employed to adjust for covariates. The interaction of cell dose and degree of HLA mismatch on transplant outcomes will be examined using appropriate statistical models. The secondary endpoint of infectious complications will be analyzed with respect to the number, the severity, and the subsequent complications of infectious episodes while controlling for important prognostic factors as previously described. Rates of other complications such as veno-occlusive disease and interstitial pneumonitis will be examined. Type and severity of adverse events will also be analyzed, including incidence of other malignancies, lymphoproliferative disorders, and post-transplant myelodysplasia.

9.3.2 The Cord Blood Transplantation Study Expanded Access Protocol (EAP)

Protocol Design

This is a prospective, open-label, single-arm, multicenter expanded access protocol for use of the cord blood units banked for The COBLT Study. Eligible subjects have a disease that warrant cord blood transplantation but are not eligible for the main protocol. Treatment is not standardized; all subjects are co-enrolled on an IRB-approved treatment plan or treatment protocol that vary by patient and/or institution. Patients are followed for 3 years. Safety and outcomes data are provided at specified time points on standardized data collection forms.

Objectives

Specific objectives were not stated in the expanded access protocol

Key Eligibility Criteria

1. Serious or life-threatening illness where cord blood transplantation is the only satisfactory treatment available.

2. Not eligible for The COBLT Study main protocol
3. The cord blood unit for transplantation is at least 3/6 matched with recipient
4. Able to provide consent
5. Co-enrolled on an IRB-approved treatment plan or treatment protocol

Treatment Plan

The preparative regimen, GVHD prophylaxis and supportive care measures were stipulated in the individual IRB-approved treatment plans or protocol and were not standardized in the expanded access protocol.

Safety Monitoring

Safety monitoring proceeded according to the individual IRB-approved treatment plans or protocol. Standardized registry safety and outcomes data forms were to be completed pretransplantation, at days 28 and 42, and after transplantation at day 100 and 6, 12, 24 and 36 months.

Safety Analytic Plan

The anticipated sample size is 60 subjects.

Primary endpoint - The primary analysis will consist of estimating the Day 180 survival probability based on the Kaplan-Meier product limit estimator. The analysis will include the confidence interval for this probability.

Secondary endpoints - Similar calculations will be made for the secondary endpoints , e.g. neutrophil engraftment, red cell engraftment, platelet engraftment, survival, and acute GVHD

Secondary analyses - A secondary analysis of neutrophil graft failure will be conducted conditional on patients surviving at least 28 days. A secondary analysis will be performed on patients who fail to engraft. Incidence rates of both acute and chronic GVHD will be estimated using Kaplan-Meier product limit curves. Multivariate models will be employed to adjust for covariates. The interaction of cell dose and degree of HLA mismatch on transplant outcomes will be examined using appropriate statistical models. The secondary endpoint of infectious complications will be analyzed with respect to the number, the severity, and the subsequent complications of infectious episodes while controlling for important prognostic factors as previously described. Rates of other complications such as veno-occlusive disease and interstitial pneumonitis will be examined. Type and severity of adverse events will also be analyzed, including incidence of other malignancies, lymphoproliferative disorders, and posttransplant myelodysplasia.

CLINICAL EFFICACY REVIEW
NONMALIGNANT INDICATIONS

Application Type	BLA
Division / Office	DCEPT / OCTGT
Reviewer	John E. Hyde, Ph.D., M.D.
Supervisory Reviewer	Wilson W. Bryan, M.D.
Review Completion Date	November 3, 2011
Established Name	Hematopoietic progenitor cells – cord
Therapeutic Class	Allogeneic cord blood hematopoietic progenitor cell therapy
Formulation	Cell suspension for infusion
Indication(s)	Hurler syndrome Krabbe disease X-linked adrenoleukodystrophy Primary immunodeficiency diseases Bone marrow failure Beta thalassemia
Intended Population(s)	Adult and pediatric

Template Version: March 6, 2009

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Table of Abbreviations

AAP	American Academy of Pediatrics
ALD	(X-linked) Adrenoleukodystrophy
AMN	Adrenomyeloneuropathy
BMF	Bone marrow failure
BMT	Bone marrow transplant
BRMAC	Biological Response Modifiers Advisory Committee
CI	Confidence interval (95%, unless otherwise specified)
CIBMTR	Center for International Blood and Marrow Transplant Research
COBLT	Cord Blood Transplantation (Study)
CTGTAC	Cell, Tissue, and Gene Therapies Advisory Committee
Docket	Collection of FDA dockets for cord blood
FA	Fanconi anemia
GVHD	Graft versus host disease
Hgb	Hemoglobin
HLA	Human leukocyte antigen
HPC-C	Hematopoietic progenitor cells – cord (umbilical cord blood)
HSCT	Hematopoietic stem cell transplant
IFAR	International Fanconi Anemia Register
IOM	Institute of Medicine
IST	Immunosuppressive therapy
IVIG	Intravenous immune globulin
MPS	Mucopolysaccharidosis
MRI	Magnetic resonance imaging
NMDP	National Marrow Donor Program
NYBC	New York Blood Center
PBSC	Peripheral blood stem cells
R-UCB	Related umbilical cord blood
SAA	Severe aplastic anemia (acquired)
SCID	Severe combined immunodeficiency
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
TNC	Total nucleated cells
UCB	Umbilical cord blood (unrelated, unless otherwise specified)
U-UCB	Unrelated umbilical cord blood
VLCFAs	Very long chain fatty acids

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Hurler Syndrome Indication

This Reviewer recommends that UCB not be approved with an indication for Hurler syndrome on the grounds that there is lack of substantial evidence of efficacy.

Based on this Reviewer's assessment of the data available in the Docket and the literature, there is not substantial evidence that UCB has efficacy for improving survival in Hurler syndrome. The finding of enzyme elevation due to UCB is poorly documented and of uncertain clinical meaningfulness, and it is an insufficient basis for approval. There is lack of substantial evidence of an effect of UCB on other aspects of Hurler syndrome.

See Section 6, Efficacy Summary, Hurler Syndrome, for further discussion of the efficacy evidence.

Krabbe Disease Indication

This Reviewer recommends that UCB not be approved with an indication for Krabbe disease on the grounds that there is lack of substantial evidence of efficacy.

Based on this Reviewer's assessment of the data available in the Docket and the literature, there is not substantial evidence that UCB has efficacy for improving survival in Krabbe disease. The finding of enzyme elevation due to UCB is poorly documented and of uncertain clinical meaningfulness, and it is an insufficient basis for approval. There is lack of substantial evidence of an effect of UCB on other aspects of Krabbe disease.

See Section 6, Efficacy Summary, Krabbe Disease, for further discussion of the efficacy evidence.

X-Linked Adrenoleukodystrophy Indication

This Reviewer recommends that UCB not be approved with an indication for ALD on the grounds that there is lack of substantial evidence of efficacy.

Based on this Reviewer's assessment of the data available in the Docket and the literature, there is not substantial evidence that UCB has efficacy for improving survival in adrenoleukodystrophy (ALD). There is lack of substantial evidence of an effect of UCB on other aspects of ALD.

See Section 6, Efficacy Summary, Adrenoleukodystrophy, for further discussion of the efficacy evidence.

Primary Immunodeficiency Indication

This Reviewer recommends that UCB be approved for improving survival in SCID. However, in this Reviewer's assessment, there is insufficient information to support a broad indication for all primary immunodeficiency diseases.

Based on this Reviewer's assessment of the data available in the Docket and the literature, substantial evidence has been provided that UCB has efficacy for improving survival in SCID, and the risks are acceptable. There was insufficient information in the Docket to evaluate evidence of efficacy for other primary immunodeficiency diseases.

See Section 6, Efficacy Summary, Primary Immunodeficiency Diseases, for further discussion of the efficacy evidence.

Bone Marrow Failure Indication

This Reviewer recommends that UCB not be approved with an indication for bone marrow failure on the grounds that there is lack of substantial evidence of efficacy.

Based on this Reviewer's assessment of the data available in the Docket and the literature, there is not substantial evidence that UCB has efficacy for improving survival in Fanconi anemia (FA) or severe aplastic anemia (SAA). There is lack of substantial evidence of an effect of UCB on other aspects of these diseases. There was insufficient information in the Docket to evaluate the evidence of efficacy for other bone marrow failure conditions.

See Section 6, Efficacy Summary, Bone Marrow Failure, for further discussion of the efficacy evidence.

Beta Thalassemia Indication

This Reviewer recommends that UCB not be approved with an indication for beta thalassemia on the grounds that the benefit-risk profile is not acceptable.

Based on this Reviewer's assessment of the data available in the Docket and the literature, substantial evidence has been provided that UCB can alter hemoglobin expression and make some patients transfusion independent. However, there is lack of substantial evidence that UCB has efficacy for improving survival in beta thalassemia, and, in fact, there appears to be an increased risk of mortality following UCB.

See Section 6, Efficacy Summary, Beta Thalassemia, for further discussion of the efficacy evidence.

1.2 Risk Benefit Assessment

Primary Immunodeficiency Indication

Although some of the mortality following UCB for SCID is undoubtedly treatment related, underlying mortality due to disease is extremely high, and the risk is readily offset by much greater intermediate- and longer-term survival. Although patients with SCID due to adenosine deaminase (ADA) deficiency can be expected to benefit from UCB compared to *no* treatment, there remains a question about the acceptability of the risk of UCB in ADA-deficient SCID patients who are responsive to enzyme replacement therapy.

Beta Thalassemia Indication

Although this Reviewer considers there to be substantial evidence for the efficacy of UCB in reversing transfusion dependence in beta thalassemia, the substantial mortality following UCB (see Section 6.7.4) is a significant concern that, in this Reviewer's assessment, makes the benefit-risk profile unacceptable, unless and until a subset of beta-thalassemic patients can be identified for whom additional benefit, such as improved longer-term survival, might be demonstrated to offset the acute risks, or for whom the treatment-related mortality could be substantially diminished.

2 Introduction and Regulatory Background

2.1 Product Information

This review is not for a specific product, but is applied to cord blood products as a whole (see also Product Comparability under Section 2.6). In general, HPC-C is a minimally manipulated placental/cord blood product containing live human cord blood cells for unrelated allogeneic use. The cord blood is collected for banking from newborns with maternal consent. It is cryopreserved for storage and shipping. The end user may dilute or wash the cells after thawing prior to intravenous administration.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Available Treatments for Proposed Indications

Indication	FDA-Approved Therapies	Other Available Treatments
Hurler syndrome	Aldurazyme (laronidase)	HSCT
Krabbe disease	(none)	HSCT
Adrenoleukodystrophy	(none)	(b) (4) HSCT
Primary immunodeficiency diseases	IVIG (multiple brands) Adagen (pegademase bovine) – for ADA-SCID	HSCT
Bone marrow failure	Atgam (antithymocyte globulin) Actimmune (interferon γ) – for osteopetrosis	Thymoglobulin (antithymocyte globulin), Anadrol-50 (oxymethalone), Neupogen (filgrastim), cyclosporine, HSCT
Beta thalassemia	For iron overload: Desferal (deferoximine), Exjade (deferasirox)	RBC transfusion, HSCT

2.3 Availability of Proposed Active Ingredient in the United States

UCB has been used in the US since sibling cord blood was used to treat a patient with Fanconi anemia in 1988, but as of the date of this review, no UCB product has been approved under a BLA. Although the FDA is embarking on a program to regulate these products and require that they be BLA-approved, the products have been available on the market through the FDA's exercise of enforcement discretion.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On January 20, 1998, the FDA issued a notice in the Federal Register (63 FR 2985) titled *Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Blood Hematopoietic Stem/Progenitor Cell Products; Request*

for Comments. In this notice, the FDA requested the submission of proposals and data to support establishment controls, process controls, and product standards designed to ensure the safety and effectiveness of minimally manipulated unrelated allogeneic hematopoietic stem/progenitor cell products derived from peripheral and cord blood for hematopoietic reconstitution. Submitted comments were to include supporting clinical and nonclinical laboratory data and other relevant information. The comments and data received were placed in a public docket [Docket No. FDA-2006-D-0157] (formerly Docket No. 06D-0514). The initial comment period of two years (until January 20, 2000) was extended, at the request of industry, for 90 days until July 17, 2000 (65 FR 20825, April 18, 2000).

The Biological Response Modifiers Advisory Committee (BRMAC) was convened on February 27, 2003, 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 the public docket. On the basis of the assessment of submitted information, discussion of the BRMAC, and review of published literature on this subject, the FDA determined that the data were sufficient to provide recommendations for establishment and processing controls and product characteristics for these products and to establish the safety and effectiveness of HPC-Cs for allogeneic transplantation in the treatment of hematologic malignancies.

In 2007, the FDA announced the availability of *Draft Guidance for Industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies* dated December 2006 (Federal Register notice of January 17, 2007 (72 FR 1999)). A meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) was held on March 30, 2007, to discuss the draft guidance. The committee discussed access to HPC-Cs 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.

The *Final Guidance for Industry: Minimally Manipulated Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications* was published on October 20, 2009 (74 FR 53753). The HPC-C licensure guidance provides recommendations to cord blood manufacturers applying for licensure of their HPC-Cs for the specified indications of hematologic malignancies, Hurler syndrome (MPS I), Krabbe disease (globoid leukodystrophy), X-linked adrenoleukodystrophy, primary immunodeficiency diseases, bone marrow failure, and beta thalassemia.

Table 2: History of Development of Regulatory Policy for Cord Blood

1997	Human Cells, Tissues, and Cell- and Tissue-Based Products (HCT/P) Regulations Initiated
1998	FR notice: Request for Proposed Standards – Minimally manipulated unrelated allogeneic cord blood and PBSCs intended for hematopoietic reconstitution
2003	Convened Advisory Committee (BRMAC) on cord blood scientific issues
2007	Draft Guidance on BLA requirements published and comments gathered
2007	Advisory Committee (CTGTAC) convened
2009	Final BLA guidance and Draft IND guidance issued. FR notice announces intention to end enforcement discretion.
2011	INDs or BLAs required for distribution in US of allogeneic unrelated cord blood after October 20, 2011

A description of the prior human experience is available at www.regulations.gov under Docket numbers FDA-1997-N-0010 (Legacy Docket number 97N-0497) and FDA-2006-D-0157 (Legacy Docket number 06D-0514), which contain the data used to establish efficacy in the specified indications.

On October 20, 2009, the FDA announced through a Federal Register (FR) notice that it will end the period of phased-in implementation of IND and BLA requirements for minimally manipulated unrelated allogeneic placental/umbilical cord blood (HPC-C). The FR notice established a two-year implementation period, scheduled to end October 20, 2011, by which date all distribution of HPC-C for clinical use in the US must be done under an approved BLA or active IND.

2.6 Other Relevant Background Information

Background on Diseases

Because of the numerous indications involved in the application, discussion of background for the various disease entities in this section would result in too fragmented a presentation. Therefore, background on each indicated disease is presented in the corresponding subsections of Section 6.

Product Comparability

UCB is a product that has high variability inherent in the means by which it is produced. The cord blood guidance (FDA 2009) stipulated that any UCB product meeting the product characteristic requirements provided in that guidance is eligible to receive the indications it listed, without providing further data to support efficacy. In effect, all products satisfying those standards are regarded as “comparable” (in essence, pharmaceutically equivalent) to any (to-be-) marketed product approved under the conditions of that guidance.

However, related-donor bone marrow, unrelated-donor bone marrow, and peripheral blood stem cells have recognized differences from each other and from UCB regarding likelihood of engraftment, rates of engraftment, and incidence of various complications. None of these other products will be considered "comparable" to UCB in this review, and any substantial evidence of efficacy for those other products is not viewed as direct substantial evidence of efficacy for UCB.

Combination Therapy Issues

For patients receiving UCB transplantation, with the exception of certain patients with primary immunodeficiency, a preparative regimen is required to avoid rejection of the hematopoietic graft. This may consist of radiation or combination chemotherapy. For the pediatric inborn error cases in the Duke dataset, for example, the vast majority received conditioning with busulfan, cyclophosphamide, and antithymocyte globulin. Conditioning regimens are not recorded in the other two datasets in the Docket.

For malignant diseases, the preparative regimen can reasonably be viewed as the primary therapy in which the objective is to eliminate a neoplastic cell line; the efficacy depends critically on how successfully this is achieved, and the hematopoietic stem cell therapy (HSCT) plays more of the role of "rescue" therapy, although it is also replacing hematopoietic functions that have been affected by the disease, and a "graft vs. leukemia" effect may play a role in efficacy. For the nonmalignant proposed indications, the HSCT can be viewed as the primary therapy, because the objective is to provide a hematopoietic function that is absent or seriously deficient due, in most cases, to an inborn disease (acquired bone marrow failure being an exception). Efficacy is derived directly from the ability of the HSCT to provide those functions, but success is still importantly influenced by the effectiveness of the preparative regimen in facilitating engraftment.

Use as a preparative regimen for HSCT is an approved indication for IV busulfan (Busulfex), used in conjunction with cyclophosphamide, only for treatment of CML. Labeling for cyclophosphamide does not explicitly describe its use for HSCT. Although the Busulfex labeling described one preparative regimen, others have been used. For some conditions, notably Fanconi anemia, reduced-intensity regimens are recommended. The regulatory status of the conditioning regimens should be kept in mind for the review and the regulatory action for UCB products. Ideally, an assessment of the effectiveness of UCB transplantation should take the preparative aspect of the combined therapy into account, but the necessary information is not available. A full evaluation of the safety and efficacy of the drug products or devices used in the preparatory regimens for the various indications is beyond the scope of this review. Any regulatory action regarding the current application should be taken with an awareness of potential implications regarding explicit or implicit approval of off-label uses for the agents used in preparatory regimens.

3 Ethics and Good Clinical Practices

The material being reviewed in support of efficacy for a cord blood BLA is primarily the material that was submitted to the three separate FDA dockets associated with regulation of allogeneic cord blood cell transplantation, supplemented with data from publications. The information submitted to the dockets from those outside the FDA was provided voluntarily in response to public solicitations by the FDA, and there was no requirement that docket submissions be limited to information that was collected under an IND or that would meet standards expected for a BLA application. Consequently, the information submitted to the dockets is accepted "as is."

Deficiencies in the submitted data are described below. It is important to identify the deficiencies for purposes of understanding the limitations that apply to conclusions that might be drawn from the data. However, because submitters were not subject to BLA requirements, deficiencies cannot be viewed as having implications regarding regulatory integrity or as calling for any official corrective action relating to the submitters.

3.1 Submission Quality and Integrity

Organization

This review is for the non-malignant indications for cord blood that are listed in the Cord Blood Guidance (FDA 2009), and is intended to be applicable to any BLA that restricts requested indications to those listed in that Guidance, that references the dockets in support of those indications, and that presents no other evidence and analysis in substantiation of efficacy. The material submitted to the dockets was a series of documents with no meaningful indexing or overarching organization. Because this review is without reference to a specific BLA, and rests only on submissions to the dockets and on published literature, there was no Integrated Summary of Efficacy, Reviewer's Guide, complete study reports, or other materials provided to assist in organizing the efficacy data and to provide argument as the adequacy of the efficacy data to support approval.

Dataset Quality and Integrity

See Section 5.1 for a description of the relevant docket documents. The following discussion applies to the three datasets that were regarded as the primary sources of clinical data (Tier 1 datasets).

Common Issues

Incompleteness

All three datasets lack information on diagnostic criteria that were used, patient status (although cancer stage was provided by the NMDP and NYBC datasets, and Lansky score was provided in the Duke dataset); there are no laboratory data, imaging results,

or genotyping data. Only the Duke dataset included information on the preparative regimen used. All three datasets included outcome information consisting of engraftment information, complications (such as GVHD), and mortality, but no disease-specific outcomes such as transfusion independence, immunologic testing, infection frequency, hemoglobin type, extent of chimerism, physical exam findings, or neurologic evaluation (although enzyme values were provided in the Duke dataset).

Lack of Case Report Forms
None of the datasets is accompanied by case report forms for deaths and discontinuations.

Possible Duplicate Reporting
The Duke dataset is the report of the experience at a single treating institution, and the cord blood units used came from banks at other sites, with a substantial number coming from the NYBC and through the NMDP. Although the source of the unit was identified in the Duke dataset, there is insufficient information in each of the datasets to identify clearly whether or not a patient may have information reported in more than one of these datasets. Concordance of ages and survival times for certain patients suggests, but does not establish, that there may be duplicate reporting in at least a few cases. See Section 5.2 for the strategy used to reduce duplication.

Lack of Data Standards
The datasets did not comply with SDTM standards nor did they employ common coding or variable names, so that pooled analyses required additional manipulation of the datasets in most cases, and was not feasible for some other types of data.

Issues with the NMDP Dataset

The NMDP dataset lacked information on prefreeze viability of the units for 81% of patients. Two infants had cause of death listed as “RECUR/RESDL LEUK,” although one had Krabbe disease and one had another inborn error of metabolism; this raises questions about either the primary disease categorization or the accuracy of the reporting of reasons for death.

Issues with the NYBC Dataset

The NYBC dataset lacked information on gender, race, and product attributes. Age is only given as an integer, even for patients under 1 year of age.

Issues with the Duke Datasets

The Duke datasets had no data definition file; however, the meaning of most variables could be inferred from the variable names.

This Reviewer easily identified isolated errors (such as gender of "N" when all others were "F" or "M" (pt (b) (6) or a value of 19 on a scale of 0 to 10 (pt (b) (6). In the electronic dataset that accompanied the docket submission, the date of transplant appears three times but was inconsistent for one patient (pt (b) (6). Patient numbers were not consecutive, raising a question of selection bias, although the missing numbers might correspond to BMT patients. A separate dataset for enzyme data (which also includes BMT patients) was provided in printout form (docket document 2006-D-0157-DRAFT-0054) but without patient numbers to permit cross-linking to the main Duke dataset. However, matching by transplant date did allow a presumptive correspondence. Using that correspondence, it was noted that patient (b) (6) was coded as Hurler syndrome in the main dataset, but the one patient with the same transplant date was coded as Hunter syndrome in the enzyme dataset. It appears that even basic range and value validation checks were not performed for the Duke dataset, and it is reasonable to question the accuracy of these data in general.

Significant data quality problems were identified in the Duke dataset:

1) For the reported follow-up times, the value listed for overall survival days for those patients who had not died was provided – not as a specific value – but as an Excel spreadsheet function reporting the number of days between the transplant date and the current date (i.e., the date on which the spreadsheet was being viewed). In comparing the electronic dataset to the printout of the dataset in the dockets, the survival times could be made to agree by substituting 4/17/2007, the date that appears on the docket printout, for the current date function in the Excel spreadsheet. Further, patient (b) (6) diagnosed with ALD, has a cause of death listed, but is not treated as having died for purposes of reporting a survival time. Thus, it appears that the survival times did not represent a recorded date on which the patients were known to be alive. Rather, it appears as though any patients not listed as having died were treated as if still alive as of the date of the printout. The survival times listed in that dataset therefore cannot be considered a reliable representation of known follow-up times for patients who are not listed as dead.

2) Review of the literature uncovered a report of a patient with beta thalassemia who received UCB transplantation at Duke in 1998 (Hall and Martin et al. 2004). No patient with a diagnosis of beta thalassemia was found in the Duke dataset. Further, review of the literature uncovered an article reporting on the Duke experience in which a patient with ALD died after beginning the conditioning regimen but before receiving a transplant (Beam and Poe et al. 2007). There is sufficient information in the article to determine that the patient was not included in the Duke dataset. The Duke dataset cannot be considered a complete record of patients who began the process of cord blood transplantation at that site, and not all deaths after starting treatment have been reported.

3.2 Compliance with Good Clinical Practices

Good Clinical Practice (GCP) compliance cannot be evaluated from the data and datasets submitted to the dockets. Although the dataset from the NMDP was represented as being collected under IND 7555, no protocol, informed consent forms, or related materials were submitted to the dockets for the NMDP dataset, or for either of the other two datasets. In some cases, e.g., the Duke dataset, accompanying information in the dockets gives some information about how data were collected, but the details that would typically be provided for a prospective study are lacking. For other documents that provided only summary results, no information is provided to address compliance with GCP.

Because the data were provided to the dockets apart from any BLA submission by parties not acting in the role of a BLA applicant, no clinical site inspections were requested.

3.3 Financial Disclosures

No financial disclosures were provided for the Docket documents.

5 Sources of Clinical Data

"The Docket"

The material being reviewed in support of efficacy for a cord blood BLA is primarily the material that was submitted to the three separate FDA dockets associated with regulation of allogeneic cord blood cell transplantation: Dockets FDA-1997-N-0010 (Legacy Docket number 97N-0497), FDA-2006-D-0157 (Legacy Docket number 06D-0514), and FDA-2009-D-0490). This collection of dockets will be referred to simply as "the Docket" in this review. Information in addition to those three datasets was also considered in the review. The Docket submissions of potential relevance are described in Section 5.1.

Literature

This Reviewer searched the literature for publications not provided in the Docket in an effort to identify appropriate external (historical) control data for comparing to the UCB experience reported in the Docket and to identify other publicly available information about experience with cord blood transplantation for the candidate indications. Data from publications that were only available online (such as publications from CIBMTR.org that were not available in a journal publication) were not relied upon as sources of data for this review.

Additional details of the literature search strategy, along with the cited references, are given in Section 9.1.

5.1 Tables of Studies/Clinical Trials

The Docket included numerous submissions that did not provide clinical data, and those were not considered further for this review. The documents that did contain clinical data are itemized below. The Docket did not provide any indexing or organization that was relevant to an efficacy review. Therefore, this Section provides a structured listing of the clinical data in the Docket. To further organize the submission, this Reviewer categorized the documents into Tiers, reflecting perceived relevance to the evaluation of the efficacy of UCB.

Tier 1: Detailed data on UCB transplantation

1. NMDP Dataset
   - Patient listings of 581 patients who received a single unit from Feb 2000 through Dec 2006. Includes data on recipient, product, and outcomes (survival, engraftment, GVHD).

- Excel dataset is provided in Docket document 1997-N-0010-0032. Excel spreadsheet of summary tabulation for each variable (1997-N-0010-0033) is serviceable as a data definition document.

- An analysis of 1-year survival and predictive factors for a subset of 548 patients, not broken down by disease, is provided in 1997-N-0010-0016, and summary and printout of cord blood transplants from Feb 2000 to Dec 2005 collected under IND 7555 (n=353) are provided in 1997-N-0010-0019, and -0021.

2. NYBC Dataset
   - Patient listing of 562 consecutive patients given cord blood from the NYBC program. These patients are the same as those reported by Rubinstein (Rubinstein and Carrier et al. 1998) but updated through May 2001 and with some corrections. The dataset provides limited patient demographics and only a little information on the attributes of the product infused.

   - It is provided as summary tables for the variables and as a printed tabulation spanning two docket documents (1997-N-0010-DRAFT-0042, and -0043). The variable summaries are serviceable as a data definitions document. An electronic dataset was described in the cover letter and made available to FDA, but it is not present as a docket document. On spot-checking, the electronic dataset appears to correspond to the printout in the docket.

3. Duke Datasets
   - Patient listings of 160 patients given UCB transplants at Duke University, primarily for pediatric inborn errors of metabolism. A separate dataset provides pre- and post-transplant enzyme levels on a subset of these patients and for some BMT patients.

   - Docket document 2006-D-0157-DRAFT-0055 is a printout of the main dataset. An electronic dataset was described in a related docket document and was made available to the FDA, but was not present as a docket document. The electronic dataset appears to correspond to the docket printout, with a notable exception regarding follow-up times as discussed under Section 3.1. There is no data definitions document.

   - Document 2006-D-0157-DRAFT-0054 (and also -0082) contains the printout of the pre- and post-transplant enzyme values. There is no accompanying data definitions document. No electronic dataset was located by this Reviewer, but one was created by pasting from the printout into an Excel spreadsheet.

   - Documents 2006-D-0157-DRAFT-0044, -0045, -0046, -0052, -0082 contain Duke report, tables, and graphs regarding factors affecting survival and engraftment in

158 pediatric patients (apparently the first 158 patients in the Duke dataset). The report presents summary data that are not disease-specific, but some of the affiliated tables and graphs show results by disease.

4. Stemcyte Case Reports
   - 2006-D-0157-DRAFT-0078 is a publication (Jaing and Lee et al. 2006) of a case report of UCB transplantation in a patient with SCID.
   - 2006-D-0157-DRAFT-0079 is a draft article on a case series of five UCB transplants for beta thalassemia.
   - 2006-D-0157-DRAFT-0080 is a publication (Jaing and Hung et al. 2005b) of a single case report of UCB transplantation for beta thalassemia in Taiwan. (This patient is also included in the case series.)
   - 2006-D-0157-DRAFT-0081 is a publication (Jaing and Hung et al. 2005a) of a case series of five UCB transplants for beta thalassemia. It closely resembles the draft case series article above (-0079), but there are some minor differences.

Tier 2: Less detailed data regarding UCB transplantation

5. 1997-N-0010-DRAFT-0021: Analysis by Thermogen on transient warming and viability, with reference to a publication (Rubinstein and Carrier et al. 1998) on general factors affecting engraftment of UCB and event-free survival. The publication does not provide much detail on death alone. Analyses are not broken down by disease.

6. 1997-N-0010-DRAFT-0034: St. Louis Cord Blood Bank analysis of effect of storage time on engraftment and survival; analyses are not broken down by disease.

7. 1997-N-0010-DRAFT-0035, -0037: NYBC analyses of factors affecting engraftment speed, transplant-related events, and leukemic relapse. This is based on an experience in 1019 patients, and so is not the same as the dataset in item 2, above.

8. 1997-N-0010-DRAFT-0039: Univ. of Minnesota analysis of factors affecting engraftment, GVHD, and 2- and 4-year survival.

9. 1997-N-0010-DRAFT-0062, -0063: Dr. Creer PowerPoint slides on effects of TNC and CD34+ counts on engraftment and survival.

10. 2006-D-0157-0007: CIBMTR summary tabulations regarding 42-day engraftment and 1- and 2-year survival for non-malignant conditions. Some analyses were done by specific disease.

11. 2006-D-0157-DRAFT-0064, -0065: NYBC analysis of engraftment and survival to 1 year from single UCB transplant by broad disease categories. This is based on experience in 1,618 patients, and so is not the same as either item 2 or item 7, above.

12. 2006-D-0157-DRAFT-0069, -0070, -0072, -0077: Stemcyte-submitted publication (Chow and Nademanee et al. 2007) on factors affecting UCB transplant engraftment and survival in 283 patients. First two documents are drafts that contain some tables not included in published version (last two documents).

Tier 3: Detailed data regarding HSCT other than UCB

13. NMDP data on 1178 peripheral blood stem cell (PBSC) transplants
    1997-N-0010-0018, -0020, -0023, -0029: data dictionary
    1997-N-0010-0022: printed dataset of PBSC cases # 1-1178
    1997-N-0010-0024, -0025, -0026, -0027, -0030, -0031: Excel datasets
    1997-N-0010-0028: report
    1997-N-0010-DRAFT-0073, -0074, -0075, -0078, -0080: dataset printouts

Tier 4: Less detailed data regarding HSCT other than UCB

14. 1997-N-0010-DRAFT-0105, -0015: NMDP-submitted publication (van Rood and Oudshoorn 2008) of a special report on BMT that presents an analysis of factors affecting survival.

5.2 Review Strategy

Scope of the Review

This review is limited to an evaluation of the evidence supporting efficacy of those indications listed in the guidance for cord blood (FDA 2009). This review is not intended to include a review of safety; safety data from the Docket are addressed in a separate Docket safety review.

Scope of Diseases Considered

This efficacy review is an evaluation of the evidence supporting efficacy for those non-malignant indications listed in the guidance for cord blood (FDA 2009). Some of those indications identified specific diseases (Hurler syndrome, Krabbe disease, adrenoleukodystrophy, and beta thalassemia), whereas others identified broad categories of disease that could include numerous different conditions as candidate indications (primary immunodeficiency and bone marrow failure). For the latter groups of indications, the review efforts were directed towards those conditions that were substantially represented in the data submitted to the docket.

For the primary immunodeficiency diseases, the datasets submitted to the Docket contained the numbers of cases shown in Table 3.

Table 3: Immunodeficiency Diseases Represented in Docket Datasets

Disease	Cases in Datasets
SCID	47
Wiskott-Aldrich Syndrome	14
Kostmann disease	4
Lymphocyte adhesion disorder	4
Chronic granulomatous disease	3
Chediak Higashi syndrome	2
Combined immunodeficiency (not SCID)	1
Common variable immunodeficiency	1
Nezelof syndrome	1
Other/unknown	4

Consequently, the review for primary immunodeficiency focused on SCID. The other diseases were considered to be too sparsely represented in the Docket datasets or in any of the other submissions to the Docket to have a reasonable prospect of generating substantial evidence of efficacy.

For bone marrow failure diseases, the datasets submitted to the Docket contained the conditions listed in Table 4. (While osteopetrosis might be categorized as an inborn error of metabolism, it was included in this listing because bone marrow failure is a significant aspect of the disease.)

Table 4: Bone Marrow Failure Diseases Represented in Docket Datasets

Disease	Cases in Dataset
Fanconi anemia	39
Severe aplastic anemia	37
Osteopetrosis	16
Amegakaryocytic thrombocytopenia	4
Diamond-Blackfan anemia	4
Dyskeratosis congenita	2
Shwachman-Diamond syndrome	1

The review for bone marrow failure diseases focused on Fanconi anemia and severe aplastic anemia. The other conditions listed were considered to be too sparsely represented in the Docket datasets or in any of the other submissions to the Docket to have a reasonable prospect of generating substantial evidence of efficacy.

Scope of Materials Reviewed

For the material submitted to the Docket, the main focus of the review was on the materials identified as Tier 1 data in Section 5.1, which are the datasets that contained individual patient data from patients who had received UCB and significant case reports. Summary information on patients who had received UCB (Tier 2 data) was also

considered, but, due to its nature, was not subjected to extensive analysis. Datasets and other types of information regarding HSCT other than UCB (Tier 3 and 4 data) were not subjected to detailed review.

Material outside the Docket that was reviewed in detail consisted of published reports of natural disease history for the diseases under consideration, as well as any reports of investigations or other significant clinical experience using UCB for those diseases.

Pooling/Duplicates

Since the numbers of patients for the non-malignant indications were generally rather small, and because any control groups were external to those datasets anyway, the three major UCB datasets were pooled to improve precision of estimates of survival for the non-malignant indications. It is possible that this approach may result in counting some patients twice, because duplicate reporting between Duke, which is a transplant center, and the other two dataset submitters, which are cord blood providers, cannot be ruled out (see Section 3.1). The datasets were inspected visually to identify cases with identical or nearly identical attributes, including transplant date, demographics, product attributes, and survival time. The following presumptive duplicates were identified, and the duplicates were eliminated for purposes of the efficacy analyses:

Table 5: Presumptive Duplicate Cases

Duke Pt #	Diagnosis	Other Record
(b) (6)	Hurler	NYBC (b) (6)
	Hurler	NYBC
	Hurler	NYBC
	Hurler	NYBC
	Hurler	NMDP
	Hurler	NMDP
	Hurler	NMDP
	Hurler	NMDP
	Krabbe	NYBC
	Krabbe	NMDP
	ALD	NYBC
	ALD	NMDP

Controls

The data provided in the Docket reflected essentially only uncontrolled experience with UCB transplantation. To meet the regulatory requirement to base approval on well controlled investigations, this Reviewer searched the literature for historical data in an attempt to identify appropriate control populations. See Section 9.1 regarding search strategy, and the control data presented in subsections of Section 6. The FDA ICH E10 document (FDA 2001) discusses considerations pertaining to selection and quality of external control data. Other discussion on the limitations of historical controls and database evaluation to assess efficacy can be found in Temple 1990.

Selection of Endpoints

The principal clinical efficacy outcome provided by the three major Docket datasets was time to death, and there was little additional information to help assess clinical effectiveness. Consequently, the primary efficacy endpoint for most of the nonmalignant indications was taken to be time until death. Death is an objective outcome that has the advantage in historically controlled comparisons of being readily interpretable across studies. Time to death also is relevant for most of the proposed indications, because most involve significantly increased mortality. Time to death is nonetheless subject to weaknesses relating to completeness of follow-up and reasons for loss to follow-up; the latter can be difficult to assess for both the docket data and historical control data.

While there are other aspects of response to therapy that would be clinically meaningful for the various diseases, their assessment was not, with a few exceptions, accommodated by the information in the docket datasets. For Hurler syndrome and Krabbe disease, information on pre- and post-transplant enzyme levels was provided, although with no additional documentation of clinical status. Enzyme levels are of uncertain clinical meaningfulness, and were viewed as secondary endpoints

For the indications in which there are well documented case reports, there was an opportunity to try to assess additional outcomes. The two conditions for which such reports were provided were SCID and beta thalassemia. For SCID, the case report documents freedom from infection and significantly improved immune function in addition to improved survival. For beta thalassemia, case series provide information on elimination of transfusion dependence, and hemoglobin electrophoresis results are provided for one of these cases.

For all indications, additional outcome data were available concerning proportions of patients achieving engraftment and times to engraftment for neutrophils and platelets. While these might be regarded as reflecting an aspect of effectiveness, engraftment factors are addressed in a separate Clinical Safety Review, because delayed or failed engraftment presents significant risks to the patient.

General Organization of the Efficacy Review and Modifications to the Review Template

To help keep information unified in the face of the numerous indications under consideration, all discussion of clinical trials is located in subsections of Section 6, rather than under Section 5.3. For the indication of bone marrow failure, for which the two specific entities of Fanconi anemia and severe aplastic anemia are considered, each condition is given its own complete major subsection. Within each indication under Section 6, baseline treatment data are included under Demographics. The subsections 6.X.6 on Other Endpoints are omitted, as there are no additional experimental or exploratory endpoints for any of the indications. Also, subsections 6.X.9 on Discussion of Persistence of Efficacy and/or Tolerance Effects are omitted.

Section 4 is omitted as not relevant, because this review is for Docket efficacy data and not a specific BLA. Sections 7 and 8 were omitted because the Docket safety data are addressed in a separate safety review. Sections 9.2 and 9.3 are omitted because the review is not for a specific BLA.

5.3 Discussion of Individual Studies/Clinical Trials

See the discussions for each indication in the subsections of Section 6.

6 Review of Efficacy

Efficacy Summary

Hurler Syndrome

The Docket datasets provided information on survival following UCB transplant for Hurler syndrome, but did not provide any control data for comparison. One reasonable candidate for an historical control was identified from the literature. Based on the data submitted to the Docket, there is early mortality with UCB transplantation in Hurler syndrome, with a break-even point that appears to occur somewhere between 5 and 9 years after transplant, compared to historical controls. However, the follow-up data in the Docket datasets are very sparse at 9 years. In addition, there is an inability to evaluate the comparability of Docket patients and historical controls due to limited individual patient data for both Docket and historical control patients regarding baseline attributes and concurrent therapy. Further, the Docket dataset that provides the majority of the evidence for this disease (Duke dataset) has data quality issues regarding length of follow-up that make the conclusions from those data unreliable. Therefore, in this Reviewer's assessment, the available data do not provide substantial evidence that UCB transplant improves survival in Hurler syndrome.

Although the survival curve for UCB appears very similar to that for bone marrow transplant in Hurler syndrome, the similarity is clearest only for the period that includes the high early mortality, but the small numbers of UCB patients followed for at least a decade means there is little evidence by which to judge the similarity to BMT in that extended time frame.

Changes in enzyme levels were reported in the Docket, but the data were not well documented, and the clinical meaningfulness of an elimination of blood enzyme levels is unclear. No other clinical outcome data were provided in the Docket datasets. Evidence from published data regarding the effect of UCB on other aspects of Hurler syndrome is limited by the lack of objective comparisons to controls and by susceptibility to possible selection or reporting bias.

No clear relationship was seen between UCB dose and survival in Hurler syndrome over the range of doses used in the Docket dataset.

Krabbe Disease

The Docket datasets provided information on survival following UCB transplant for Krabbe disease, but did not provide any control data for comparison. One reasonable source of historical control data was identified from the literature. Based on the data submitted to the docket, the overall survival experience following UCB for Krabbe disease appears to overlap that of candidate historical controls; variability of the

phenotype and uncertainty about the phenotypes of patients in the Docket datasets make control selection challenging. There is an inability to evaluate the comparability of Docket patients and historical controls due to limited individual patient data for both Docket and historical control patients regarding baseline attributes and concurrent therapy. Further, the Docket dataset that provides the majority of the evidence for this disease (Duke dataset) has data quality issues regarding length of follow-up that make the conclusions from those data unreliable. The literature seems to indicate no benefit from UCB transplant in Krabbe disease once symptoms develop, but suggests that presymptomatic transplantation is effective in improving survival. Interpretation of the evidence for the latter conclusion is limited by difficulty in determining phenotype prior to symptom onset, uncertainty about the comparability of the UCB and control groups, and the apparently post hoc nature of the subgroup analysis. Also, more recent observations suggest that UCB-transplanted patients with Krabbe disease are still severely affected. Therefore, in this Reviewer's assessment, the available data do not provide substantial evidence that UCB transplant improves survival in Krabbe disease.

Changes in enzyme levels were reported in the Docket, but the data were not well documented, and the clinical meaningfulness of an elimination of blood enzyme levels is unclear. No other clinical outcome data were provided in the Docket datasets. Evidence from published data regarding the effect of UCB on other aspects of Krabbe disease is limited by lack of objective comparisons to controls and by susceptibility to possible selection or reporting bias.

No clear relationship between UCB dose and survival in Krabbe disease was observed over the range of doses used in the Docket dataset.

X-Linked Adrenoleukodystrophy (ALD)

The Docket datasets provided information on survival following UCB transplant for ALD, but did not provide any control data for comparison. A small number of candidate historical control groups were identified from the literature. The phenotype in ALD is variable, and, without knowledge of the age at onset of symptoms and the degree of MRI abnormalities in the study population, it is difficult to assess the prognosis of the patients who were transplanted and to identify an appropriate historical control. While there is some suggestion that overall survival following UCB transplantation for ALD patients in the Docket database is better than that of untransplanted patients who have had onset of neurologic symptoms, it appears to be worse than survival in diagnosed untransplanted patients who have not developed MRI abnormalities. Overall, based on the data submitted to the Docket, the survival experience following UCB for ALD appears to overlap that of candidate historical controls, including the most recent available natural history experience. There is an inability to evaluate the comparability of Docket patients and historical controls due to limited individual patient data for both Docket and historical control patients regarding baseline attributes and concurrent therapy. Further, the Docket dataset that provides the majority of the evidence for this disease (Duke dataset) has data quality issues regarding length of follow-up that make

the conclusions from those data unreliable. In a report of an epidemiologic study suggesting better outcomes with HSCT vs. No HSCT in ALD, the Docket survival experience more closely resembled the No HSCT group. Therefore, in this Reviewer's assessment, the available data do not provide substantial evidence that UCB transplant improves survival in ALD.

No clinical outcome data other than survival were provided in the Docket datasets. Evidence from published data regarding the effect of UCB on aspects of ALD other than survival is limited by lack of objective comparisons to controls and susceptibility to possible selection or reporting bias.

No clear relationship between UCB dose and survival in ALD was observed over the range of doses used in the Docket dataset.

Primary Immunodeficiency

Primary immunodeficiency covers a heterogeneous group of diseases. Only severe combined immunodeficiency (SCID) was considered to be represented in the Docket in sufficient numbers to have a reasonable prospect of providing sufficient data to support efficacy. Therefore, only SCID was reviewed for this indication group.

Severe Combined Immunodeficiency (SCID)

The Docket datasets provided information on survival following UCB transplant for SCID, but did not provide any control data for comparison. Two sources of candidate historical control data were identified from the literature. The approximately 2/3 survival for several years following UCB for SCID is in striking contrast to the near uniform early fatality in SCID seen in two historical control groups. The Docket data and historical control data are limited in the ability to evaluate comparability of the treated and control populations because of the limited information regarding baseline characteristics and concurrent therapy. The presence of some patients older than 2 years raises some questions about the diagnostic criteria or the relevance of the historical controls. However, the apparent effect remained statistically and clinically striking when subjected to various sensitivity analyses. In light of the dramatic size of the treatment effect on an objective and clinically significant endpoint, this Reviewer feels that the comparisons of the Docket data to the historical data can be regarded as an adequately controlled clinical investigation.

A single reasonably detailed case report from the literature (that was also submitted to the Docket) provided evidence of prolonged survival and improved immune status in a SCID patient compared with the known natural history of the disease.

Therefore, in this Reviewer's assessment, the available data provide substantial evidence in the form of a controlled investigation, with supporting information provided by a detailed case report, that UCB transplant improves survival in SCID.

No clear relationship was seen between cell dose and survival over the range of doses used.

Bone Marrow Failure

Bone marrow failure covers a heterogeneous group of diseases. Only Fanconi anemia (FA) and severe aplastic anemia (SAA) were considered to be represented in the Docket in sufficient numbers to have a reasonable prospect of providing sufficient data to support efficacy. Therefore, only FA and SAA were reviewed for this indication group. Each is presented separately below:

Fanconi anemia (FA)

The Docket datasets provided information on survival following UCB transplant for FA, but did not provide any control data for comparison. One source of historical data was identified, but its ability to provide an appropriate control group was limited. Based on the data submitted to the Docket, the 72% one-year mortality following UCB transplant in FA well exceeds the mortality in the general FA population, and there is little UCB follow-up beyond 2 years. Although the UCB-transplanted FA patients undoubtedly reflect a select subgroup of FA regarding prognosis, prognosis could not be evaluated from the docket data. A published epidemiologic analysis of the historical data suggested HSCT (not necessarily UCB) was associated with a 5-fold increased hazard for mortality in the subset of FA patients with who had had onset of hematologic features of the disease, but the observational nature of study limits its interpretability. Published literature in Fanconi anemia generally confirms a similarly high mortality following UCB transplant. Based on the data available, no evidence was identified that demonstrates a survival benefit for UCB transplant in FA. Therefore, in this Reviewer's assessment, the available data do not provide substantial evidence that UCB transplant improves survival in FA.

No clinical outcome data other than survival were provided in the Docket datasets.

From analysis of the docket datasets, survival appeared to be related to TNC dose, with patients who received a dose < 2.5×10^7 TNC/kg experiencing noticeably worse survival, although those with doses above that level did not fare substantially better than the group as a whole. Due to the high treatment-related mortality inherent in the conditioning regimen that is an intrinsic part of UCB therapy in this disease, the finding of a dose response cannot be regarded as sufficient to demonstrate evidence of efficacy in this situation.

Severe aplastic anemia

The Docket datasets provided information on survival following UCB transplant for FA, but did not provide any control data for comparison. Several candidate historical control groups were found, but there was variation in reported survival rates. There is an inability to evaluate the comparability of Docket patients and the various historical controls due to limited individual patient data for both Docket and historical control patients regarding baseline attributes and concurrent therapy. Based on the limited data submitted to the docket, the overall survival experience appears to overlap that seen in older control data, and tends to be lower than survival proportions seen in more recent control experience, including cohorts of patients unresponsive to immunosuppressive therapy. The evidence from the published literature regarding the effect of UCB on survival or other effects in SAA is limited by the lack of controls and possible selection or reporting bias. A recent published report of survival experience following UCB for SAA from a large series is not appreciably different from the survival experience observed in the Docket data. The authors of that report recommended that prospective studies are needed before UCB can be recommended for SAA. Therefore, in this Reviewer's assessment, the available data do not provide substantial evidence that UCB transplant improves survival in SAA.

No clinical outcome data other than survival were provided in the Docket datasets.

From an analysis of the Docket datasets, survival appeared to be related to TNC dose, with patients who received a dose < 2.5×10^7 TNC/kg experiencing worse survival, although those with doses above that level did not fare substantially better than the group as a whole. Due to the high treatment-related mortality inherent in the conditioning regimen that is an intrinsic part of UCB therapy in this disease, the finding of a dose response cannot be regarded as sufficient to demonstrate evidence of efficacy in this situation.

Beta Thalassemia

The Docket datasets provided only very limited data (n=8) on survival following UCB transplant for beta thalassemia, and they did not provide any control data for comparison. Search of the literature identified only a few candidate historical groups and a few substantial reports of experience with UCB in beta thalassemia. Therefore, the ability to evaluate the comparability of UCB treated groups and historical controls was limited. The evidence from published literature regarding the effect of UCB on survival showed a range of results, but outcomes appeared to be unfavorable compared to the expected usually excellent short- to intermediate-term prognosis for pediatric patients with beta thalassemia. A recent review reported outcomes with UCB that appeared to be worse than those with other forms of HSCT, leading the authors to conclude that the use of UCB for beta thalassemia was "suboptimal" for hemoglobinopathies and discouraged its use outside of well-designed clinical trials.

Published series generally report the ability of UCB to eliminate transfusion dependence, although that endpoint is not explicitly defined. Reasonably detailed case reports in the literature also document the ability of UCB to eliminate transfusion dependence and to improve the hemoglobin profile toward normal.

In this Reviewer's assessment, there is substantial evidence of the ability of UCB to improve the hemoglobinopathy and alleviate transfusion dependence in beta thalassemia major. However, the survival experience following UCB appears to be worse than any available historical controls, which brings into question the benefit-risk profile.

6.1 Hurler Syndrome

Mucopolysaccharidosis I (MPS I) is a lysosomal storage disorder caused by deficiency of alpha-L-iduronidase (IDUA). It is autosomal recessive and caused by a mutation of the gene for IDUA located on chromosome 4p16.3. Incidence is estimated at 1 per 100,000 live births (Muenzer and Wraith et al. 2009). Diagnosis is made by enzyme assay of alpha-L-iduronidase in leukocytes or cultured fibroblasts. Molecular diagnosis is complicated by genetic heterogeneity. The phenotype is variable, and MPS I is subclassified as Hurler syndrome (MPS I-H) for the most severe cases, Hurler-Scheie (MPS I-HS) for moderate cases, and Scheie (MPS I-S) for the mildest cases. The classification is based on clinical presentation. About 50% to 80% of MPS I cases are Hurler syndrome.

The classical features of Hurler syndrome are coarse facial features, corneal clouding, mental retardation, hernias, skeletal and joint abnormalities, and hepatosplenomegaly (Neufeld and Muenzer 2001). Diagnosis is usually made in the first year of life. Untreated, average age at death is generally reported as 5 years, and survival beyond 10 years is uncommon. Aldurazyme (laronidase) is an approved enzyme replacement therapy for the disease.

Hurler-Scheie syndrome differs from Hurler syndrome in that the former usually is diagnosed between two and six years of age, has less coarse facial features, often includes a small mandible, and features toe walking due to Achilles tendon contractures. The condition progresses less rapidly, usually does not involve mental retardation, and patients usually survive into their twenties. Scheie syndrome is milder and lifespan is longer. Diagnosis of Scheie syndrome may be delayed until teenage years, and presenting symptoms are usually joint stiffness and corneal clouding.

6.1.1 Methods

Efficacy was evaluated by computing estimates for post-transplant survival obtained from pooling the three datasets described in Section 5.1. Results were compared to historical control survival data obtained from the literature. The literature was reviewed for additional reports of experience with unrelated cord blood use for Hurler syndrome.

Diagnostic information other than the diagnosis of Hurler syndrome was not provided. Thus, eligibility criteria for the series and the criteria for classification of the phenotype are unknown. Most (67%) of the cases came from the Duke dataset, in which diagnosis of Hurler-Scheie also appeared, indicating that a distinction between the two was made in that dataset. Apart from post-transplant enzyme levels, information on disease-specific outcomes that might have been of interest, such as mental ability, physical ability, or organomegaly, were not provided. As noted in Section 5.1, there are questions about the accuracy of the follow-up times for censored observations in the Duke dataset.

6.1.2 Demographics

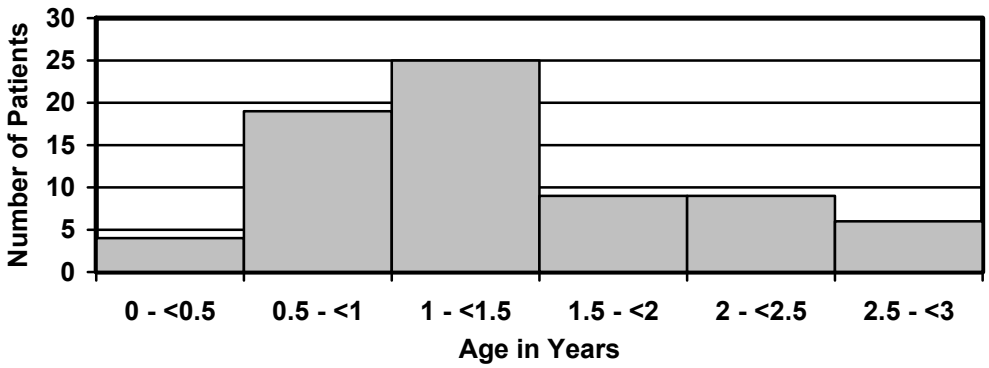
Basic demographic data for the Hurler patients in the pooled datasets are shown below, together with basic treatment data. Demographic information other than age was not provided in the NYBC dataset.

Table 6: Demographics and Treatment Data for Hurler Syndrome Patients – Docket Data

Total N	72
Age in Years	
Mean (SD)	1.4 (0.7)
Median (range)	1.3 (0 – 2.9)
Gender	
Male	46% (33)
Female	49% (35)
Unknown	6% (4)
Race	
Caucasian	81% (58)
African/American	3% (2)
Hispanic	10% (7)
Asian Indian	1% (1)
Unknown	6% (4)
Dosing* ($x10^7$ TNC/kg prefreeze)	
Median	10.9
10^{th}, 25^{th}, & 75^{th} percentiles	5.4, 7.1, 14.4
Dose < 2.5	0% (0)
HLA Match	
6/6	14% (10)
5/6	43% (31)
4/5	35% (25)
3/6	6% (4)
Unknown	3% (2)
Data source	
Duke[1]	67% (48)
NMDP[2]	28% (20)
NYBC[3]	6% (4)

[1] Duke count includes 4 cases also reported by NMDP, and 4 cases also reported by NYBC
[2] Excludes 4 cases also reported by Duke
[3] Excludes 4 cases also reported by Duke
* Dose was unknown for 2 patients (3%)

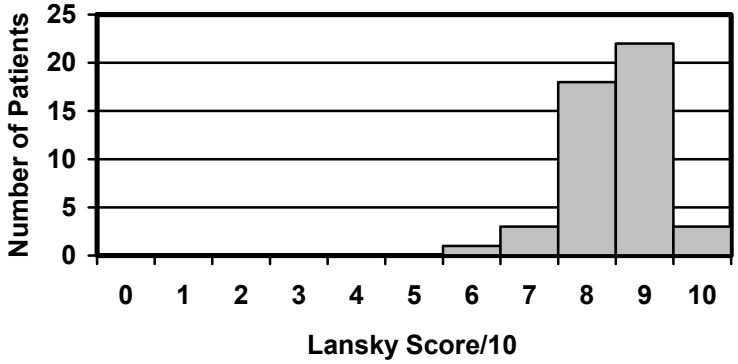
Figure 1: Age Distribution for Hurler Syndrome Patients – Docket Data



The age distribution appears to be as expected for patients early in the course of Hurler syndrome. The older patients may represent those for whom UCB transplant was delayed until a year or more after diagnosis, but might also be an indication that some patients with Hurler-Scheie syndrome have been included. Knowing age at diagnosis could have been helpful in determining how well patients fit the classic Hurler syndrome phenotype.

The Lansky score (Lansky and List et al. 1987) is a general play-performance score originally designed for pediatric cancer patients. The score was recorded only in the Duke dataset. The score ranges from 0 to 100 in multiples of 10 (in the Duke dataset, the score was divided by 10). Briefly, on this scale 100 is fully active, 90 is minor restriction in strenuous activity, 80 is active but tires more quickly, 70 is greater restriction and less time spent in play, and 60 is minimal play but busy with quieter activities. The distribution for Hurler patients in the Duke data is shown in Figure 2 below:

Figure 2: Lansky Score Distribution for Hurler Syndrome Patients – Docket Data



(Lansky score only for patients reported in Duke dataset. One value coded as 19 was treated as missing.)

6.1.3 Subject Disposition

No protocol was provided for this study, and there is no information available about screening, eligibility criteria, or diagnostic criteria. Two patients in the Duke dataset were diagnosed as "Hurler's Scheie" and "Hurler Scheie" with ages given as 0.97 and 2.9 years. They were not included in this analysis. Of the 72 total Hurler syndrome patients, 19 are reported to have died. The causes of death were:

Table 7: Causes of Death in Hurler Syndrome Patients – Docket Data

	N
Respiratory	7
Hemorrhagic	3
Multisystem	2
Renal failure	2
Misc.*	5

* Veno-occlusive disease-1, hyperammonemia-1, acute GVHD-1, Infection, unspecified-1, other, unspecified-1.

For one patient (Duke, (b) (6), an event of autologous recovery was listed as occurring about three months after transplant, but the follow-up information was unclear: neither a death nor an overall survival time is reported. The demographics above were reported for all available patients, but the survival analysis excludes patient Duke (b) (6) (equivalent to treating her as censored at time 0).

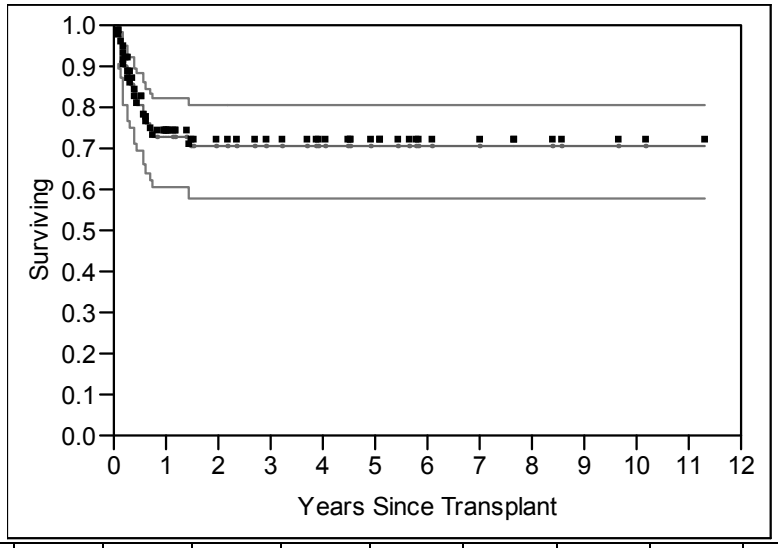
Two patients in the NMDP dataset received a second transplant, one at 39 days due to no engraftment, one at 10 months for an unknown reason. Both were recorded as alive at last report.

6.1.4 Analysis of Primary Endpoint(s)

Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown below for the 71 analyzable Hurler syndrome patients. There is 27% mortality by the end of the first year. After the first year, additional mortality is very low. The loss to follow-up is greatest in the first year, with progressive censoring through year 6. Median follow-up was 1.1 years; 75th quartile of follow-up was 4.5 years.

Figure 3: Survival for 71 Hurler Patients Following UCB Transplant – Docket Data



Year	0	1	2	3	4	5	6	7	8	9	10
Survival	1.00	0.73	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70
No. at Risk	71	40	28	24	20	15	9	8	5	3	2

Staba published a report of 20 Hurler syndrome patients who received UCB transplant at Duke University (Staba and Escolar et al. 2004). It presumably represents a subset of the 48 patients in the Duke dataset. In that experience she reported overall event-free survival of 85% at a median follow-up of 2.5 years. She reported that growth velocity was normal in the majority of patients and that "all children had either stable or improved neurocognitive function after transplantation." There was a developmental lag post-transplant, but "by 72 months [of age] they appeared to be gaining cognitive skills at slightly slower rate (slope = 0.95) than the mean for unaffected children."

The long-term mortality is important in evaluating the efficacy of UCB transplant on survival in order to determine if there is a survival "payoff" for the early mortality risk. To refine the assessment, two modifications were made:

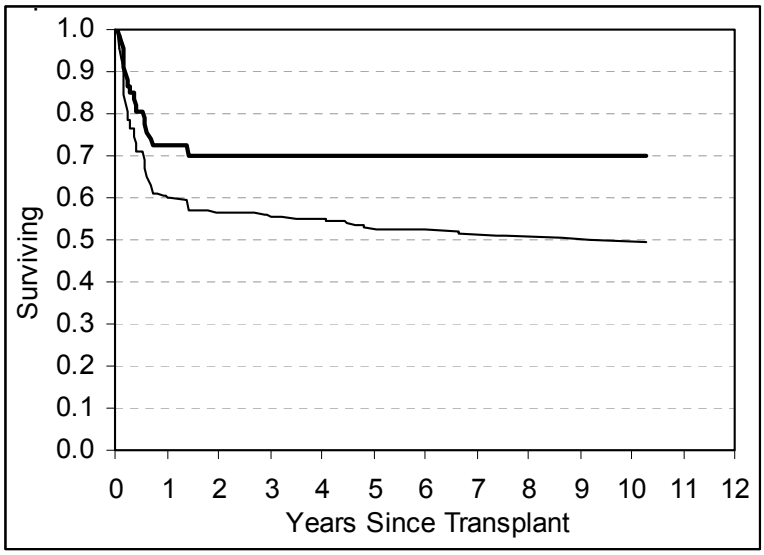
First, the Duke data were adjusted in an attempt to discount for the apparent overstatement for follow-up time for censored patients (that used the date of the dataset rather than time of a last visit as the follow-up time, see Section 3.1). As an approximation, it was assumed that patients might be seen only quarterly for the first year, semiannually in the second and third years, and annually thereafter. A simple conservative approximation to the implied step function is to replace the stated follow-up time, T, by the function T * 2/3 for T < 3 years and T-1 for T ≥ 3 years. Time to death was not adjusted for those who died.

Second, the usual method for estimating the standard error for the Kaplan-Meier curve has the characteristic that no change occurs following the last observed death, even if

this is followed by substantial censoring. That overstates the confidence in the estimates following the last death. A hybrid technique (Borkowf 2005) provides more accurate confidence intervals in this situation.

These modifications result in the survival curve shown below (including only the lower end of the 95% confidence interval). The estimated survival is very similar to that without adjustment, but the confidence limits extend almost 10% lower by the right end of the curve:

Figure 4: Survival for 71 Hurler Patients Following UCB Transplant with Adjustment to Duke F/U Times – Docket Data



Year	0	1	2	3	4	5	6	7	8	9	10
Survival	1.00	0.72	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70
No. at Risk	71	35	27	21	17	9	8	5	3	2	1

Survival curves with Duke follow-up time for censored observations discounted (see text). Heavy line is survival estimated by Kaplan-Meier method; light line is lower end of 95% confidence limits using Borkowf hybrid technique.

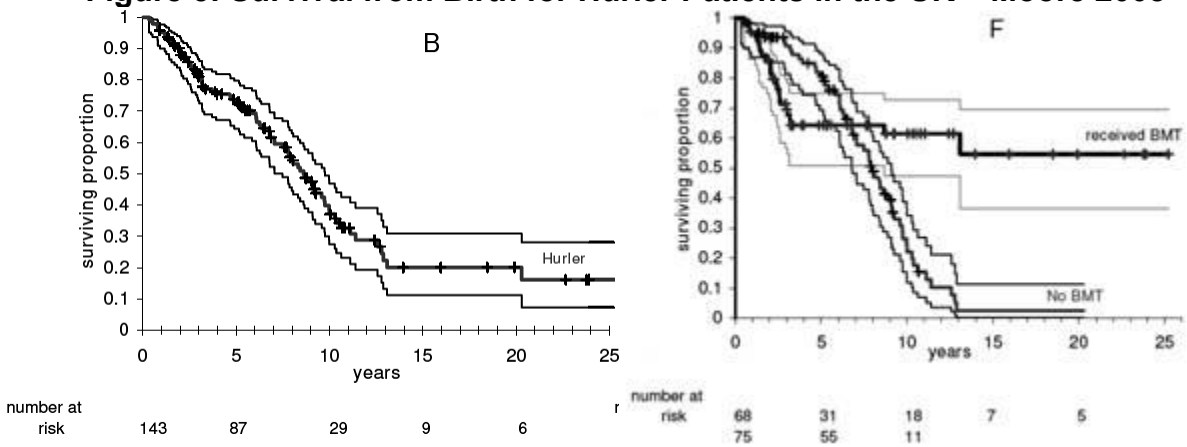
Historical Experience

Wraith (Wraith and Rogers et al. 1987) reviewed 27 cases of Hurler syndrome seen in Australia between 1950 and 1986. He reported the average age at death was 6.25 years, with a range of 1.3 to 10.9 years. The data are given only as summary statistics without survival curves, and it is not stated whether any received HSCT.

More extensive historical control data come from an analysis by Moore (Moore and Connock et al. 2008). The authors obtained information from a longitudinal dataset maintained for over 20 years by the Society for Mucopolysaccharidosis Disease (UK). Since most MPS I patients are seen at only a few centers in the U.K., the Society

estimates that it has data on most, if not all, MPS I patients in that country. Moore reviewed cases entered between 1981 and 2005 and included only those with births up to 2003, in order to allow for delay in diagnosis. Of the 196 patients in the database, 143 were categorized as Hurler syndrome. Overall survival for these cases is shown as display B in Figure 5 below. Because 65 Hurler syndrome patients received BMT, Moore also computed a survival curve for those 65, as well as a survival curve for all Hurler patients, but treating BMT as a censoring event. These curves are shown as display F in the Figure 5 below:

Figure 5: Survival from Birth for Hurler Patients in the UK – Moore 2008



Source: Moore and Connock et al. 2008

A log rank test of the BMT vs. No BMT experience estimated a hazard ratio of 0.58 with p = 0.0004

> *Reviewer's Comment: The assumption of proportional hazards clearly does not apply when survival curves cross, so the hazard ratio number is hard to interpret. Although the test rejects the hypothesis of equal hazards, the question of which one is "better" requires consideration of more than just the hazard ratio estimate*.)

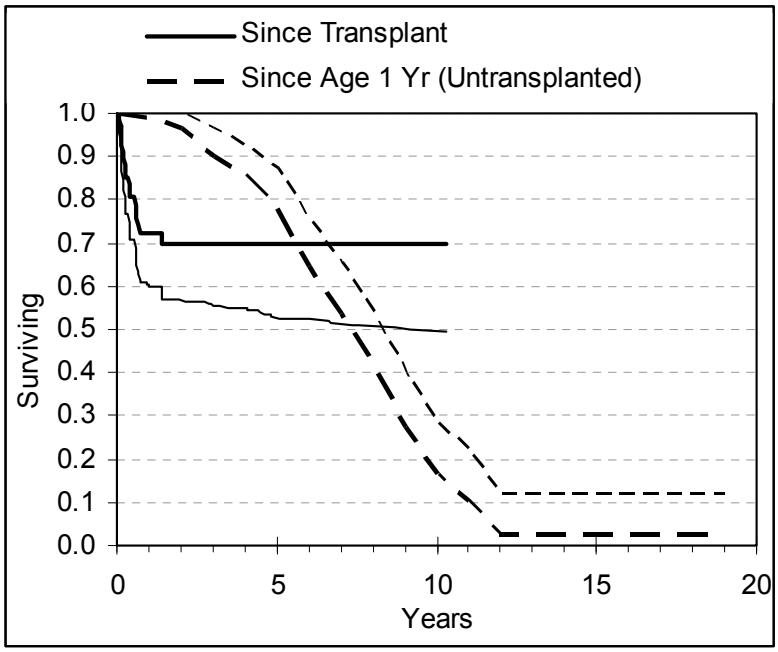
The Moore and Connock paper also showed an overall survival curve for Hurler-Scheie patients. This is not reproduced here, but it is noteworthy that the 10-year survival was about 95%, and 20 year survival was better than 80%. Thus, it is important to be sure that only Hurler syndrome patients are included in the active treatment experience if the Moore control experience for Hurler syndrome is to be used. As mentioned previously, the Duke dataset had evidence that it made the distinction, but only the term "Hurler syndrome" appeared in the NYBC and NMDP datasets. The diagnostic criteria used for making the diagnosis and deciding on the phenotype were not stated for any of the Docket datasets. Without knowing diagnostic or eligibility criteria, it is not known how well these patients fit the diagnosis. Of note, only one of the 16 patients surviving beyond 5 years from transplant came from other than the Duke report (NYBC). For the

historical control patients, it would be valuable to know what the phenotype determination was at the average age at which transplant might have occurred and whether there was any revision of the phenotype designation as the clinical course unfolded.

Since the decision to have BMT is assumed not be randomized in the UK data, the No BMT experience reported by Moore may be subject to selection bias, and the censoring used in calculating the survival curves is unlikely to be uninformative censoring. Given the dates, the exposure to laronidase in the population was probably none to minimal, and Moore reports that only Hurler-Scheie and Scheie patients had received it. The data for the No BMT experience are reasonably consistent with the natural history reported by Wraith and Rogers et al. 1987 as described above. The Moore data appear to be the most complete and detailed historical data available.

Since the control data from the U.K. used by Moore are only published in the form of a graphic, it is not possible to do a log-rank comparison of the docket data vs. the historical controls. In order to compare the active treatment and historical control experiences more directly, the Moore control experience was visually extracted by making measurements on an enlargement of the published graphic. Moore's graph (Figure 5) shows a small probability of death in the first year. Post-transplant experience should be compared to natural history *conditioned on* survival until the age at which transplant occurs. Because patients received UCB at a median age slightly greater than 1 year, the control data were adjusted to represent the natural history of survival for time elapsed since reaching 1 year of age, to approximate the expected survival after the median age of transplant. The superposition of this construction and the post-transplant UCB experience is shown in Figure 6:

Figure 6: Docket UCB Transplant Experience Compared to Historical Controls for Hurler Syndrome



Year	0	1	2	3	4	5	6	7	8	9	10
Survival	1.00	0.72	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70
No. at Risk	71	35	27	21	17	9	8	5	3	2	1

Survival following UCB transplant with adjusted follow-up times for Duke dataset (as described in text and shown previously) with overlay of control experience modified to show survival after age 1 year. Lighter solid line is *lower* end of 95% CI (two-sided) for UCB transplant; lighter dashed line is *upper* end of 95% CI for control.

Source: UCB (Transplant) data from Docket, control (Untransplanted) data modified from Moore and Connock et al. 2008

Although lack of individual patient data for the historical controls preclude the usual statistical comparisons, the visually extracted data from the control survival curve can be taken as a set of fixed values for use in a one-sample comparison (Hyde 1977). Using the discounted survival times for the Docket data, the expected number of deaths in patients given UCB is estimated to be 7.4 based on the historical experience, whereas 19 deaths were observed, giving an estimated hazard ratio for UCB vs. control of 2.6. Without discounting survival times the estimated hazard ratio is 2.0. (A nominal one-sample test of significance finds $p < 0.001$, but this is anticonservative because it ignores the uncertainty in the control group.)

Reviewer's Comments:
As was the case for the comparison of BMT to historical controls, the assumption of proportional hazards is not supported because the UCB and control survival curves cross. The reason that apparently similar curves (BMT and UCB) produce opposite relative hazard ratios compared to control (BMT hazard < 1 but UCB hazard > 1) is due to the difference in risk exposure: the relatively longer periods of observation for

the BMT patients produce a hazard ratio estimate that is an averaged hazard ratio weighted more toward the later part of the curve where the hazard ratio is lower, whereas the hazard ratio averaging for UCB is more heavily weighted toward the early post-transplant experience due to the shorter follow-up of UCB patients.

Based on the data submitted to the Docket, there is early mortality with UCB transplantation in Hurler syndrome, with a break-even point that appears to occur somewhere between 5 and 9 years after transplant, compared to historical controls. However, the follow-up data in the Docket datasets are very sparse at 9 years. In addition, there is an inability to evaluate the comparability of Docket patients and historical controls due to limited individual patient data for both Docket and historical control patients regarding baseline attributes and concurrent therapy. Further, the Docket dataset that provides the majority of the evidence for this disease (Duke dataset) has data quality issues regarding length of follow-up that make the conclusions from those data unreliable.

Although the survival curve for UCB appears very similar to that for bone marrow transplant in Hurler syndrome, the similarity is clearest only for the period that includes the high early mortality, but the small numbers of UCB patients followed for at least a decade means there is little evidence by which to judge the similarity to BMT in that extended time frame.

6.1.5 Analysis of Secondary Endpoint(s)

For patients treated at Duke, a dataset was provided that reported enzymes values before and after transplantation with UCB. However, there was no information regarding the specimen, assay, units of measurement, or timing of assessments.

Table 8: Enzyme Results for Hurler Syndrome Patients – Duke Dataset

	Pretransplant (N=41)	Post-transplant (N=35)	Difference (N=32)
Mean (SEM)	0.5 (0.2)	63 (5)	61 (4)
Median (Range)	0 (0 – 5)	56 (12 – 170)	58 (25 – 106)

While it appears that enzyme levels were significantly higher following UCB transplantation, the clinical significance of the finding is unclear.

The potential to substantiate claims for clinical benefits other than survival was not evaluated because no other disease-specific outcome data were included in the Docket datasets.

6.1.7 Subpopulations

Of the 72 patients with Hurler syndrome, gender and race data were not recorded for 4 (6%).

In a univariate proportional hazards analysis, survival outcome appeared to be related to age, with an estimated increase in hazard of 68% per year (p = 0.048). The results were essentially the same with adjustment for dose. The effect seemed to be driven by a much higher mortality in the subgroup of 6 patients aged 2.5 years or greater, in which 5 of the patients died within a year of transplant. In a multivariate analysis incorporating age, gender, race, and dose (but omitting the 4 patient with incomplete data), the estimated effect of age was slightly lower (57% per year), and it was not statistically significant (see below).

By proportional hazards analysis, neither gender nor race appeared to be related to survival outcome, either in univariate analyses, or in a multivariate analysis (n = 65) incorporating age, gender, race, and dose, (p = 0.11 for age, p = 0.79 for gender, p = 0.80 for race, and p = 0.94 for dose in the multivariate analysis).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A univariate proportional hazards model found no significant relationship between dose (as prefreeze TNC/kg) and survival (nominal p = 0.97) with an estimated 0.2% *increase* in hazard for each increase in dose of 10^7 TNC/kg. The results were similar with an analysis including adjustment for age. There was no patient with a dose < 2.5 x 10^7 TNC/kg, so a subgroup analysis for that dose range could not be done. An analysis comparing patients with doses above and below the median dose of 10.9 x 10^7 TNC/kg showed nearly identical survival curves.

6.1.10 Additional Efficacy Issues/Analyses

Published Reviews and Opinions

In a review of cord blood banking by an AAP Work Group (Work Group on Cord Blood Banking 1999), the summary of indications for allogeneic stem cell transplantation included Hurler syndrome in the category of “controversial; may be effective in selected patients.” Those conclusions were reflected in the 2005 IOM report on cord blood (Meyer and Hanna et al., 2005). However, the Work Group review did not provide references to specific data in support of that determination. The IOM report cited evidence from Staba and Escolar et al. 2004. More recent reviews of the uses of cord blood are found in Smith and Wagner 2009 and Prasad and Kurtzberg 2010. Prasad reported the status of UCB in severe phenotypes of MPS I as standard of care, and provided a list of references in support: Boelens and Rocha et al. 2009, Martin and Carter et al. 2006, Prasad and Mendizabal et al. 2008, and Staba and Escolar et al. 2004. The Cochrane Collaboration has not reviewed the use of stem cell

transplantation in Hurler syndrome. Search of the literature identified additional primary reports of outcomes experience with UCB in Hurler syndrome: Dusing and Thorpe et al. 2007a, Dusing and Thorpe et al. 2007b, Church and Tylee et al. 2007, and Dusing and Rosenberg et al. 2005. The evidence from these publications is described below.

Published experience with UCB in Hurler syndrome

Staba and Escolar et al. 2004 (n=20)

This is a report of 20 patients with Hurler syndrome transplanted with unrelated cord blood at Duke between 1995 and 2002, and so presumably represents a subset of the patients already considered in the review of the Duke dataset. It offers some additional diagnostic and outcome information that was not in the docket datasets. All patients had undetectable or "extremely low" concentration of α-L-iduronidase, consistent with Hurler syndrome; two were homozygous and seven were compound heterozygous for mutations associated with the severe phenotype of MPS I. The median follow-up was just under 2.5 years, but ranged from 1 to 7.5 years. Survival through the first year was 85% and deaths beyond 1 year were reported. After the first year, growth velocity was "normal in the majority of patients." The authors reported that "all children had either stable or improved neurocognitive function after transplantation," and "by 72 months [of age] they appeared to be gaining cognitive skills at slightly slower rate (slope = 0.95) than the mean for unaffected children." There was no clinically significant cardiac dysfunction, but several patients required orthopedic procedures. Although development was compared to normal controls in the form of normative charts, the report did not provide a comparison to objective untransplanted Hurler syndrome control data.

Dusing and Rosenberg et al. 2005 (n=2)

This reported on two patients who received UCB for Hurler syndrome at Duke and had motor assessments through 10 months post-transplant. They observed that both children gained new skills but gross motor skills were less advanced than fine motor skills. There were no pretransplant evaluations for comparison. The report did not provide objective untransplanted Hurler syndrome control data for comparison.

Martin and Carter et al. 2006 (n=21)

This a report of 69 patients with lysosomal and peroxisomal storage disorders who received UCB transplantation under the COBLT study sponsored by NHLBI. Almost all (67) were transplanted at Duke. The population included 21 patients with Hurler syndrome, who are presumably a subset of the patients already considered in the review of the Duke dataset. The report presents summaries of engraftment, survival, toxicity, and GVHD, but results are not broken down by disease. For the entire group, survival was 80% at 6 months and 72% at one year. Survival was not statistically significantly associated with age, cell dose CD34+ dose, performance status, or HLA match number, but it was significantly worse in non-Caucasians and in those who

received units as part of an expanded access program. The article does not provide efficacy information specifically for Hurler syndrome patients.

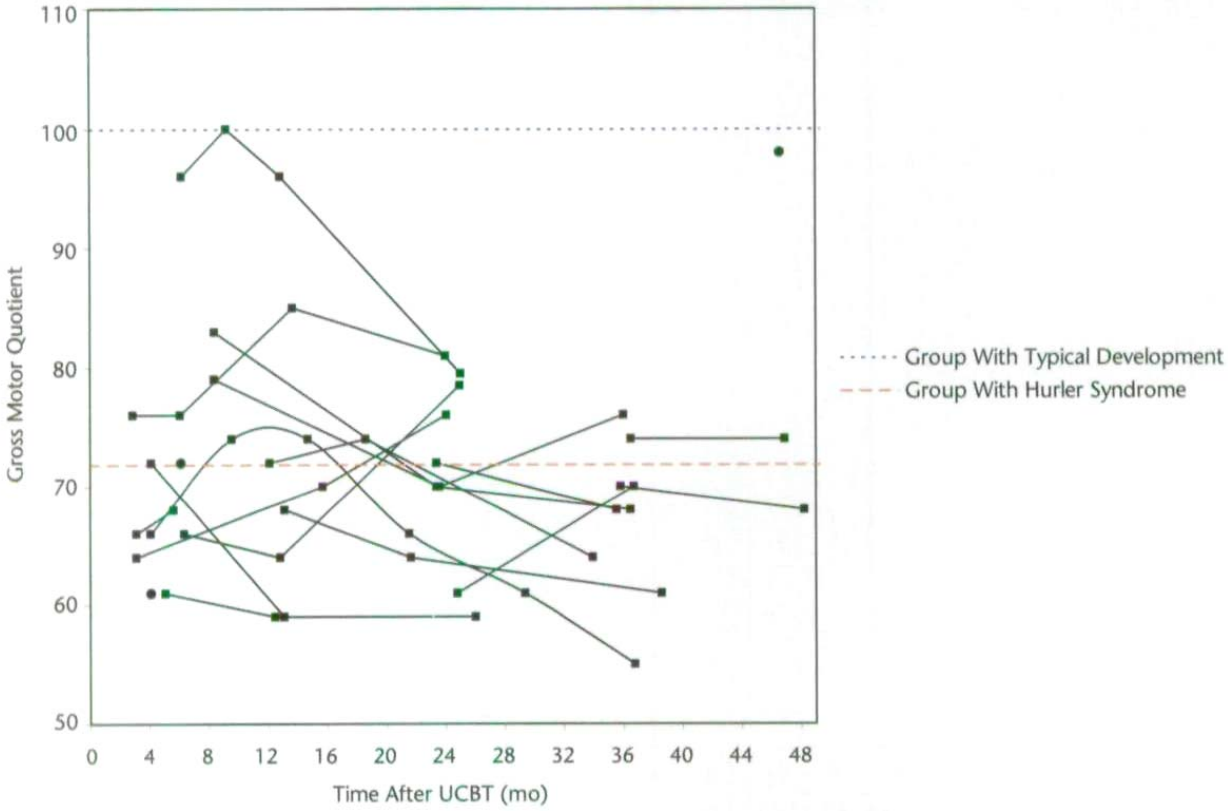
Dusing and Thorpe et al. 2007a (n=18)

This reported on 18 Hurler syndrome patients who received UCB transplant and had longitudinal gait assessments. The patients were seen at Univ. of North Carolina and apparently were transplanted at Duke. A group of 438 normal children were used as controls. The Hurler syndrome patients were selected on the ability to walk 50 ft without assistive devices; 13 of them were receiving physical therapy at the time of at least one assessment, most of them weekly. The authors found the Hurler syndrome patients had slower gait speed and shorter step length than normals at ages 2 and 3 years, but were similar to normal controls at 4 years. In post hoc analyses, time since transplant, but not age, was associated with normalization of these two parameters. The authors acknowledged that lack of an untreated Hurler syndrome control group limited the ability to assess the effect of UCB on the parameters, and lack of a non-Hurler syndrome UCB group limited the ability to assess how much of the early deficits were attributable to the disease vs. the transplantation experience.

Dusing and Thorpe et al. 2007b (n=21)

This reported on 21 Hurler syndrome patients who received UCB at Duke at a mean age of 17 months. It included 15 patients from the previous report (Dusing and Thorpe et al. 2007a); 2 had received UCB before symptoms developed. Patients were assessed for up to 4 years following UCB, with an average of 2.6 assessments per patient. Motor performance score was expressed as a percentage of normal scores based on 2,003 typically developing children. Using the Peabody Developmental Motor Scales, the authors found the Hurler syndrome patients' average gross motor quotient was 72% of normal and did not show any trend toward improvement, relative to development in normal children, between 0 and 4 years after transplant (see Figure 7). Of the subscores, locomotion showed a trend toward relative improvement, stationary skills showed a trend to relative worsening, and object manipulation skills showed no relative trend, compared to the development in normal children (none of these trends was statistically significant). The authors acknowledged that information on the natural history of gross motor abilities in Hurler syndrome is limited, and the findings were not compared to children with Hurler syndrome who had not received UCB. Lack of a non-Hurler syndrome UCB group limited the ability to assess how much of the early deficits was attributable to the disease vs. the transplantation experience.

Figure 7: Gross Motor Development in Children with Hurler Syndrome Following UCB Transplantation – Dusing 2007



Changes in gross motor quotient (GMQ) after umbilical cord blood transplantation (UCBT). Solid lines represent 18 children with Hurler syndrome who were assessed multiple times using the Peabody Developmental Motor Scales, second edition (PDMS-2). Each square marker represents the GMQ at the assessment time after UCBT. The solid circles represent an additional 3 children who had only a single assessment. The large dashed red line represents the average GMQ for the children with Hurler syndrome, as derived from the hierarchical linear models. The small dashed blue line represents the mean GMQ on the PDMS-2 for children who were developing typically.
Source: Dusing and Thorpe et al. 2007b

Church and Tylee et al. 2007 (n=6)

This article examined 39 patients with Hurler syndrome from Manchester and Dublin at least one year following UCB or bone marrow transplant to assess α-L iduronidase activity and urinary glycosaminoglycans. Of the 6 patients who had UCB, all had full donor chimerism (>95% donor cells). The group of 19 patients with full chimerism had the highest enzyme levels, and enzyme level was inversely related to the urinary dermatan sulphate/chondroitin sulphate ratio. The authors noted "It is notoriously difficult to determine clinical outcome in these patients after transplant. However, we believe that before our data can be used to influence current transplant practice, including donor selection criteria, clinical outcome scores should be correlated with different variables, including biochemical outcome such as we detail."

Prasad and Mendizabal et al. 2008 (n=45)
This is a report of 159 patients who received UCB transplantation at Duke, including 45 patients with Hurler syndrome. This appears to consist of patients whose data were also submitted to the Docket and therefore does not appear to provide additional evidence regarding survival. Most results are presented for the study population as a whole. However, the Hurler-specific data showed a 75% survival between 2 and 10 years, with a median follow-up of 5.8 years; the survival experience for Hurler syndrome was similar to that already reported above in Figure 3.

The report did offer some outcome information in additional to survival. There was 89% engraftment with high (>90%) donor chimerism. Other results for the Hurler syndrome patients are reported in the paragraph cited below:

> In this series, 45 patients with severe phenotype Hurler syndrome (MPS I) underwent transplantation and have now been followed for a median of 5.6 years (range, 1-11 years). All of the surviving patients have experienced disease stabilization and most continue to gain cognitive skills. All children of sufficient age attend school, with 81% placed in age-appropriate classes. Most of the patients with average IQ have required an aide in the classroom to help them attend to tasks. All but 2 children experienced stabilization or improvement of corneal clouding. Orthopedic problems have progressed in many children, with some requiring surgical correction. A total of 3 children had surgery for carpal tunnel syndrome, 4 for back or spine, 2 for hip problems, and 2 for knee problems. A total of 2 children have been treated with growth hormone for short stature and 2 (1 boy, 1 girl) have developed precocious puberty. A total of 2 children have also developed Hurler-associated retinal disease. (Prasad and Mendizabal et al. 2008)

The article does not state how the diagnosis of Hurler syndrome was established or criteria used to determine eligibility for transplant, and no comparisons to specific untreated Hurler control data were provided.

> *Reviewer's comment: Because the transplantation center is Duke, this report is presumed to include the same patients reported in the Duke database, and therefore provides no additional evidence regarding survival beyond what was reviewed in Section 6.1.4. The Duke dataset included 48 patients with Hurler syndrome, was dated 4/17/07, and was received in the Docket on 5/18/07; the article was submitted to the journal on 3/15/08, almost a year later. It is unclear why only 45 patients are reported in the article.*

Boelens and Rocha et al. 2009 (n=93)
This article is a retrospective report on 93 patients with Hurler syndrome who received UCB transplantation. It is a composite of the Duke and Eurocord experience and included 47 patients from Duke, with the remaining patients coming from 18 international centers and one other U.S. site (Minneapolis). The article states that 40 patients were previously published. Median patient age was 1.3 years. At 3 years, overall survival was 77% and event-free survival (EFS, defined by time to autologous

reconstitution, graft failure, retransplant, or death) was 70%. Six had autologous reconstitution and 5 had graft failure. Survival rates beyond 3 years are not reported. Of 58 patients with chimerism data at last follow-up, 97% had full donor chimerism. EFS was positively related to shorter interval from diagnosis to transplant, conditioning regimen using busulfan and cyclophosphamide. There was a trend toward better EFS with HLA match, but HLA match did not predict acute or chronic GVHD. Neither cell dose nor prior enzyme replacement therapy predicted survival. Acute GVHD was associated with a higher ($> 7.6 \times 10^7$) cell dose.

Reviewer's Comment:
Evidence from published data regarding the effect of UCB on other aspects of Hurler syndrome is limited by the lack of objective comparisons to controls and by susceptibility to possible selection or reporting bias. Additional experience from publications does confirm early mortality rate but has limited duration of follow-up (~3 years).

6.2 Krabbe Disease

Krabbe disease (globoid cell leukodystrophy) is an autosomal degenerative neurologic disease caused by deficiency of the enzyme galactocerebrosidase (GALC). It is due to a mutation of the GALC gene on chromosome 14q31. Diagnosis is made by enzyme assay in leukocytes or cultured fibroblasts. The incidence is estimated at 1 in 100,000 live births (Duffner and Jalal et al. 2009).

The phenotype is highly variable and clinical course seems to correlate strongly with age of onset, whereas level of enzyme activity and (generally) mutation do not correlate with phenotype (Duffner and Jalal et al. 2009). Over 60 mutations have been identified, but only a few have been associated with the most severe form of the disease; one mutation (C502T, a large deletion) appears associated with the early infantile onset form and may account for a third of such cases (Kemper and Knapp et al. 2010).

The early infantile onset form presents in the first six months of life with developmental delay, hypotonia, absent reflexes, optic atrophy, and microcephaly. Patients deteriorate rapidly, developing seizures and tonic extensor spasm, and typically die by two years of age (Wenger and Suzuki et al. 2001). Late infantile and juvenile forms present later in life and are more variable in progression, but patients usually die two to seven years after diagnosis. Based on about 400 cases referred to his lab for diagnosis, Wenger estimated that 85% to 90% of cases are infantile onset type (Wenger and Rafi et al. 2000). However, of the cases in the Krabbe Family Database, only 71% had onset in the age range 0 to 6 months (Duffner and Jalal et al. 2009).

Loes and Peters et al. 1999 evaluated MRI findings in 22 patients with Krabbe disease, 5 of whom had more than one serial assessment. Three patients, age range 16 months to 8 years) were asymptomatic. Patients were classified as early onset or late onset based on whether symptoms presented at 2 years of age or younger. They found that cerebellar white matter and deep gray matter abnormalities were seen only in early onset disease and the posterior corpus callosum and parieto-occipital white matter abnormalities were more common in older onset patients. Pyramidal tract involvement was seen in both groups.

> *Reviewer's comment: The paper did not distinguish between early infantile and late infantile forms, and the presence of 6 patients with onset listed as 6 months makes that division difficult. The paper did not evaluate the ability of presymptomatic MRI to predict clinical course. The paper did not provide any calculation of sensitivity or specificity, and any such estimates based only on the patients in the report would have been subject to training set bias.*

Husain and Altuwaijri et al. 2004 correlated neurophysiologic studies with MRI findings in 26 patients of whom 20 were early infantile onset. They observed that nerve conduction abnormalities may be seen before other neurophysiologic findings in early

onset disease, but nerve conduction abnormalities were less common and less predictable in late onset disease. They did not propose that such studies could predict phenotype in asymptomatic patients. The report by Zafeiriou and Anastasiou et al. 1997 underscores the difficulty in correlating MRI with phenotype.

Escolar and Poe et al. 2006 developed a 4-point staging system based on a categorization of specific clinical findings in order to predict post-transplant outcomes (predominantly cord blood). They found that patients with Stage 3 or 4 (moderate to severe neurologic involvement or advanced disease) had higher mortality or more severe disability following transplant, and they recommended that only patients in Stages 1 or 2 be considered for transplant.

There is no approved drug or biologic therapy for Krabbe disease. No specific therapy appears to be effective for infantile forms once a patient has become symptomatic, but a published report (Escolar and Poe et al. 2005) has suggested that UCB before onset of symptoms can be beneficial. In 2006, New York state began a screening program for Krabbe disease (Duffner and Caggana et al. 2009; Kemper and Knapp et al. 2010).

6.2.1 Methods

Efficacy was evaluated by computing estimates for post-transplant survival obtained from pooling the three datasets described in Section 5.1. Results were compared to historical control survival data obtained from the literature. The literature was reviewed for additional reports of experience with unrelated cord blood use for Krabbe disease.

Diagnostic information, other than the stated diagnosis of Krabbe disease, was not provided in the Docket datasets. Thus, eligibility criteria for the series and the criteria used for classification of the phenotype, particularly the early infantile onset phenotype, are unknown. Although the Lansky scores (see below) recorded in the Duke dataset give some indication of patient status, there is no explicit representation of whether or not a patient had neurologic symptoms at the time of UCB transplantation. Other than post-transplant enzyme concentrations, information on disease-specific outcomes that might have been of interest, such as neurologic changes, was not provided. Almost all (95%) of the cases came from the Duke dataset, for which there are questions about the accuracy of the follow-up times for censored observations (see Section 5.1).

6.2.2 Demographics

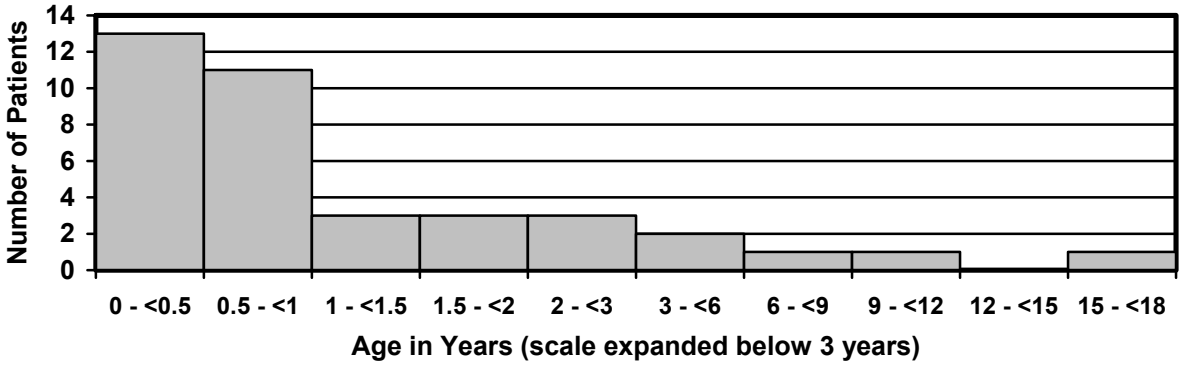
Basic demographic data for the Krabbe disease patients in the pooled datasets are shown in the table below, together with basic treatment data. Demographic information other than age was not provided in the NYBC dataset.

Table 9: Demographics and Treatment Data for Krabbe Patients – Docket Data

Total N	38
Age in Years	
Mean (SD)	1.8 (3.2)
Median (Range)	0.7 (0.05 – 16.7)
Gender	
Male	58% (22)
Female	39% (15)
Unknown	3% (1)
Race	
Caucasian	79% (30)
African or African/American	11% (4)
Hispanic or French/Hispanic	5% (2)
Unknown	5% (2)
Dosing (x10^7 TNC/kg prefreeze)	
Median	16.5
10^{th}, 25^{th}, & 75^{th} percentiles	6.0, 9.2, 21.8
Dose < 2.5	3% (1)
HLA Match	
6/6	3% (1)
5/6	37% (14)
4/5	58% (22)
3/6	3% (1)
Data source	
Duke[1]	95% (36)
NMDP[2]	3% (1)
NYBC[2]	3% (1)

[1] Duke count includes one case each also reported by NMDP and NYBC
[2] Excludes cases also reported by Duke

Figure 8: Age Distribution for Krabbe Disease Patients – Docket Data



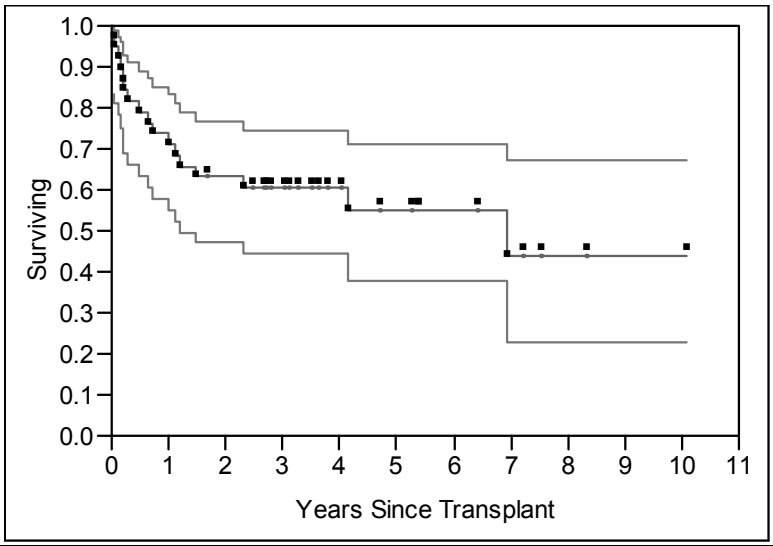
The Lansky score is a play-performance score (see discussion under 6.1.2). It was only recorded in the Duke dataset. The distribution of scores for those 36 patients is shown in Figure 9 below.

6.2.4 Analysis of Primary Endpoint(s)

Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown in Figure 10 below for the 38 Krabbe disease patients from the pooled Docket datasets. Mortality is 29% in the first year. The mortality rate is lower, but still progressive, in subsequent years. Censoring is heaviest between 2 and 4 years. The median follow-up was 2.8 years.

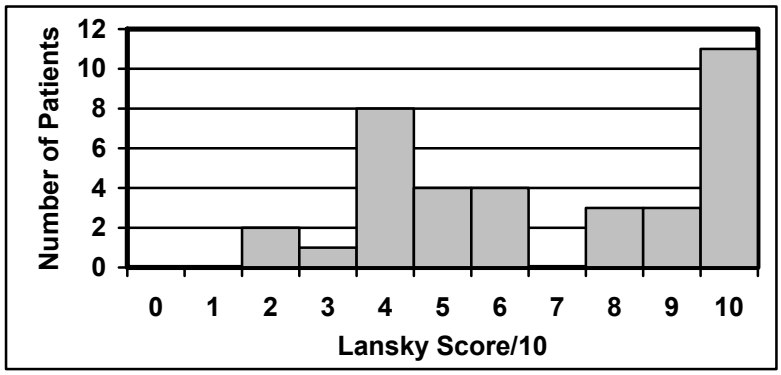
Figure 10: Survival Following UCB Transplant in 38 Krabbe Disease Patients – Docket Data



Year	0	1	2	3	4	5	6	7	8	9	10
Survival	1.00	0.71	0.63	0.60	0.60	0.55	0.55	0.44	0.44	0.44	0.44
No. at Risk	38	27	23	18	12	9	6	4	2	1	1

Current treatment recommendations in the literature (Prasad and Kurtzberg 2010) stress the importance of performing HSCT before onset of symptoms. Although symptoms are not recorded in the databases, the subset with Lansky score ≥ 80 (only available for the Duke dataset) was analyzed separately, as an approximation to selecting an asymptomatic or minimally symptomatic population. Note that this subset includes 6 patients who were at least 2 years old. The survival experience for the group is shown in Figure 11 below:

Figure 9: Lansky Score Distribution for Krabbe Disease Patients – Docket Data



(Lansky score only for the 36 patients in Duke dataset.)

It is noteworthy that there are 8 patients (21% of the total) who are older than two, of whom 3 were older than 6 years. This would be unusual for infantile onset Krabbe disease other than for a patient in the most advanced stage, who would seem to be an unlikely prospect for transplantation. Further, just under half of the Duke dataset patients had a score of 80 (active but tires more quickly) or better. The rest fell in the range of 20 (often sleeping) to 60 (minimal active play) with a mode of 40 (mostly in bed). All 6 of the patients aged 2 years or older in the Duke dataset had a Lansky score of 60 or better. Thus, it appears likely there was a substantial representation of phenotypes other than infantile onset type.

6.2.3 Subject Disposition

No protocol was provided for this study, and there is no information available about screening, eligibility criteria, or diagnostic criteria. Of the 38 total Krabbe disease patients, 17 are reported to have died. Causes of death are listed in Table 10 below:

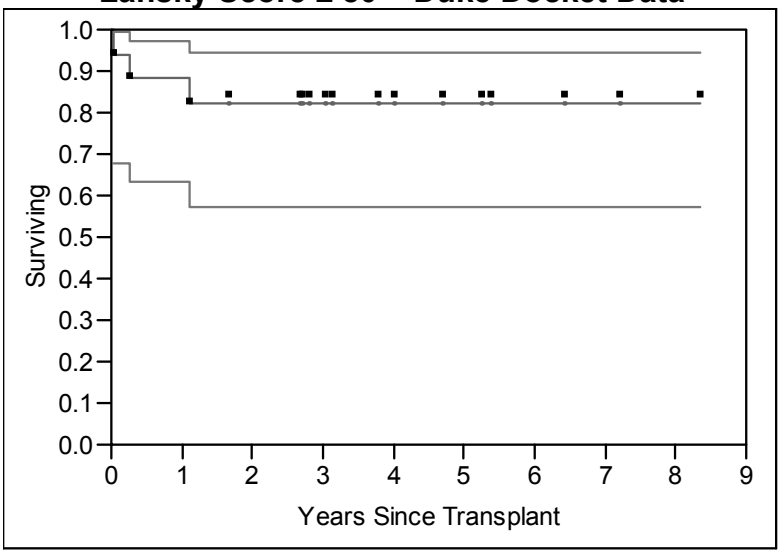
Table 10: Cause of Death for Krabbe Disease Patients – Docket Data

	N
Respiratory	8
Sepsis	2
Progression of Krabbe Disease	2
Misc.*	5

* Hemorrhage-1, GVHD-1, multi-organ failure-1, “PD” [progression of disease?]-1, “RECUR/RESDL LEUK”-1

Two of the causes of death classified as respiratory were noted to be secondary to progression of Krabbe disease. One patient (whose death was attributed to “recur/residual leukemia”) received a second transplant due to lack of engraftment.

Figure 11: Survival Following UCB Transplant in 17 Krabbe Disease Patients with Lansky Score ≥ 80 – Duke Docket Data



A subset of 25 of the Duke patients was analyzed in the publication by Escolar (Escolar and Poe et al. 2005). Because the publication also included an historical control group, it is discussed in the following section.

There were 8 patients in the dataset who were age 2 years or older and who presumably represented milder phenotypes. A separate plot for these 8 is not shown, but half of them died, all within the first year following transplant. Follow-up for the 4 survivors ranged from 3.0 to 5.4 years.

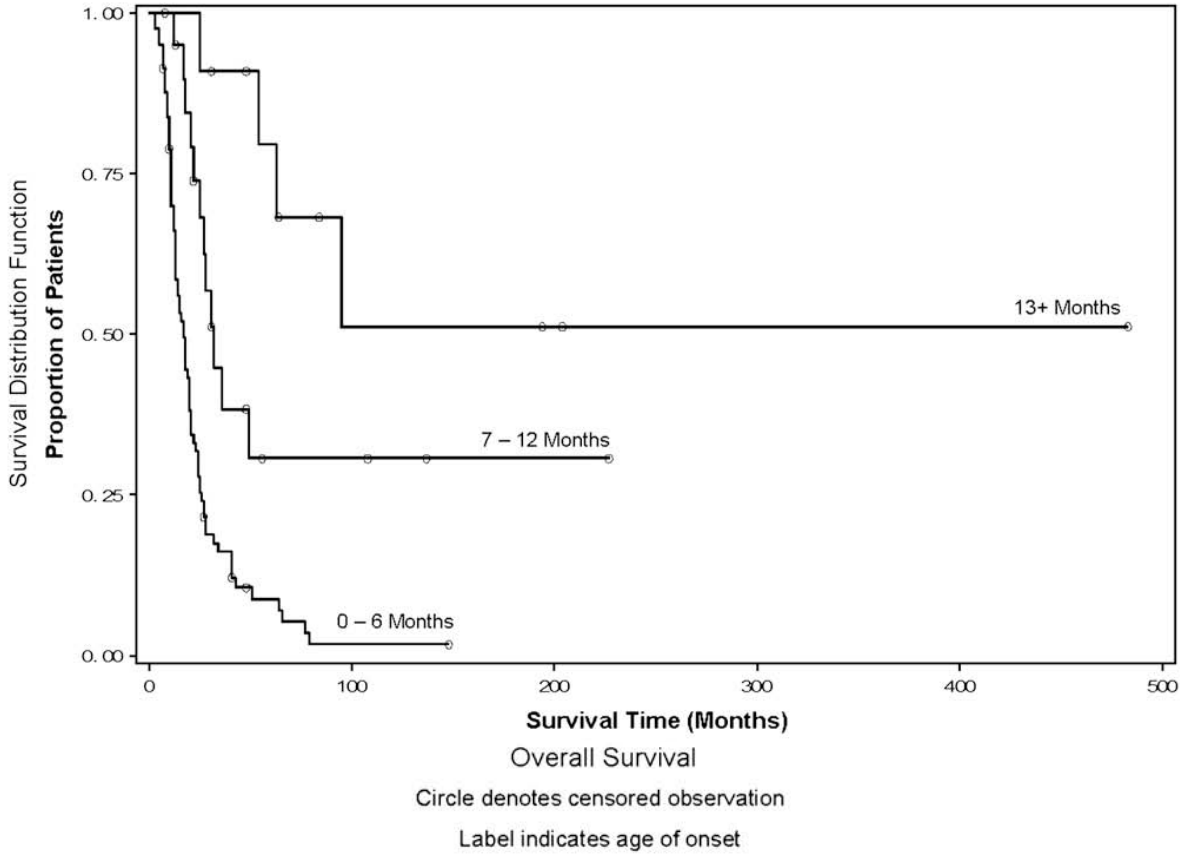
Historical Experience

One of the earliest historical series is presented in a publication that reviewed 32 Swedish cases from 1953 through 1967 (Hagberg and Kollberg et al. 1969). Individual patients' timelines were presented graphically, but were not subjected to statistical analysis. Of the 32 cases, all but one had onset of symptoms by 6 months. The median time of death was about 1 year; two survived beyond age 2, but all were dead before age 3 years.

The largest collection of historical data on Krabbe disease is that obtained by the Hunter's Hope Krabbe Family Database, which began in 1997 (Duffner and Jalal et al. 2009). The data were collected from questionnaires sent to families. As of June 2006, a total of 334 questionnaires had been received. There were 114 cases with information about age of symptom onset. (The authors noted that age at diagnosis was greater and percent of deaths was lower in the excluded cases, but that overall survival functions were not significantly different.) These 114 cases included 81 cases with symptom onset on or before 6 months, 22 cases with symptom onset from 7 through 12

months, and 11 cases with onset at 13 months or later. An analysis of survival by age of symptom onset showed evident differences between these groups (Figure 12, below). The survival analysis did not include patients who had received HSCT. The authors noted the survival experience appeared to be somewhat better than that reported by Hagberg, which they felt could be attributable to improvements in routine care.

Figure 12: Survival by Age of Symptom Onset in Krabbe Disease from Hunter's Hope Krabbe Family Database

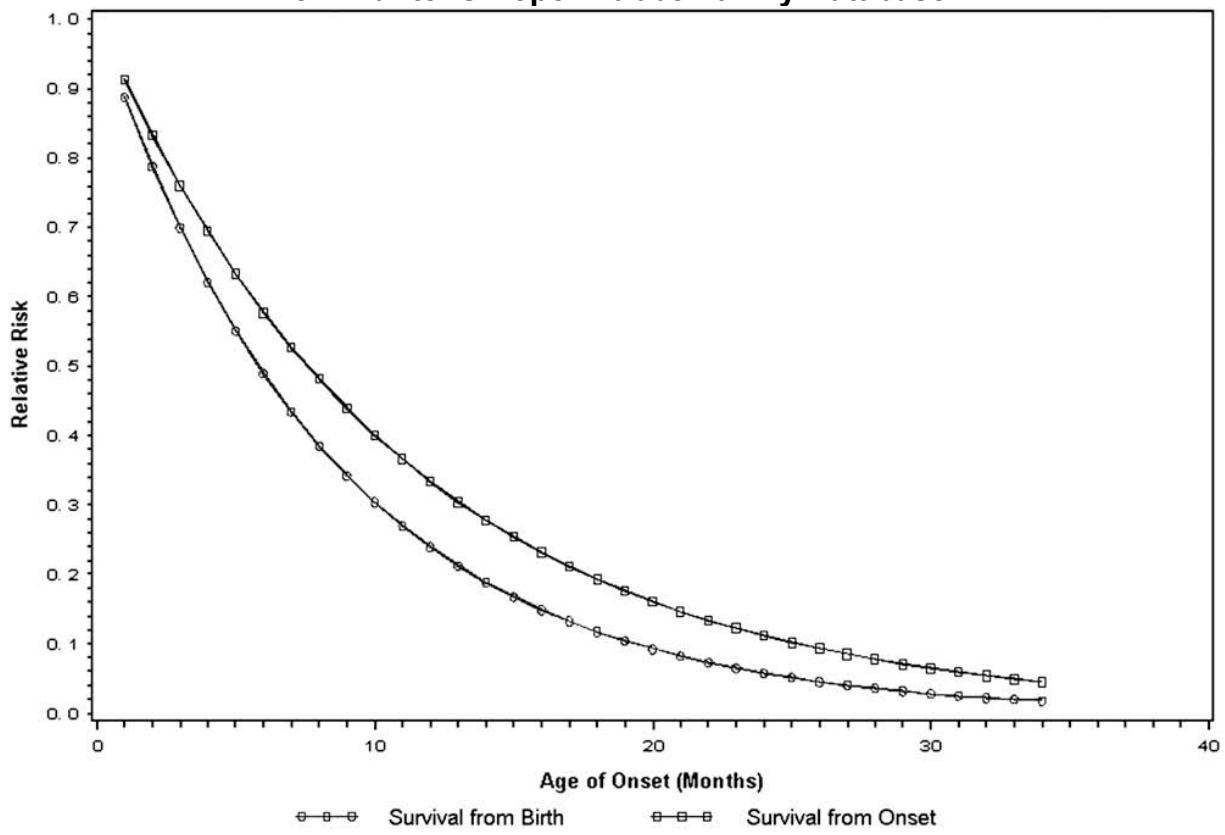


Overall survival (Kaplan–Meier curve). Survivals (in months) differed significantly according to age at onset of symptoms. Age at onset 0-6 mo (n = 81): mean survival = 24.10 mo (standard error of the mean [SEM] = 2.82), median = 17. Age at onset 7-12 mo (n = 22): mean survival = 88.81 mo (SEM = 24.10), median = 32. Age at onset 13+ mo (n = 11): mean survival = 278.75 mo (SEM = 89.02, median > 483 (note that median could not be estimated because less than half of the cases were expected to have died, but the median is known to be greater than the given value, which is the longest survival time of those who did die in this category). Pairwise comparisons (log-rank tests) were also significant: Age of onset 0-6 vs. 7-12 mo., P = 0.0003; 0-6 vs. 13+ mo., P = 0.0001; and 7-12 vs. 13+ mo., P = 0.0400.

Source: Duffner and Jalal et al. 2009

A modeled analysis of relative risk of death as a function of age of onset likewise found a strong association, as shown in Figure 13 (relative risk was calculated relative to the risk for patients whose symptoms began in the first month).

Figure 13: Relative Risk of Death by Age of Onset for Krabbe's Disease from Hunter's Hope Krabbe Family Database



Source: Duffner and Jalal et al. 2009

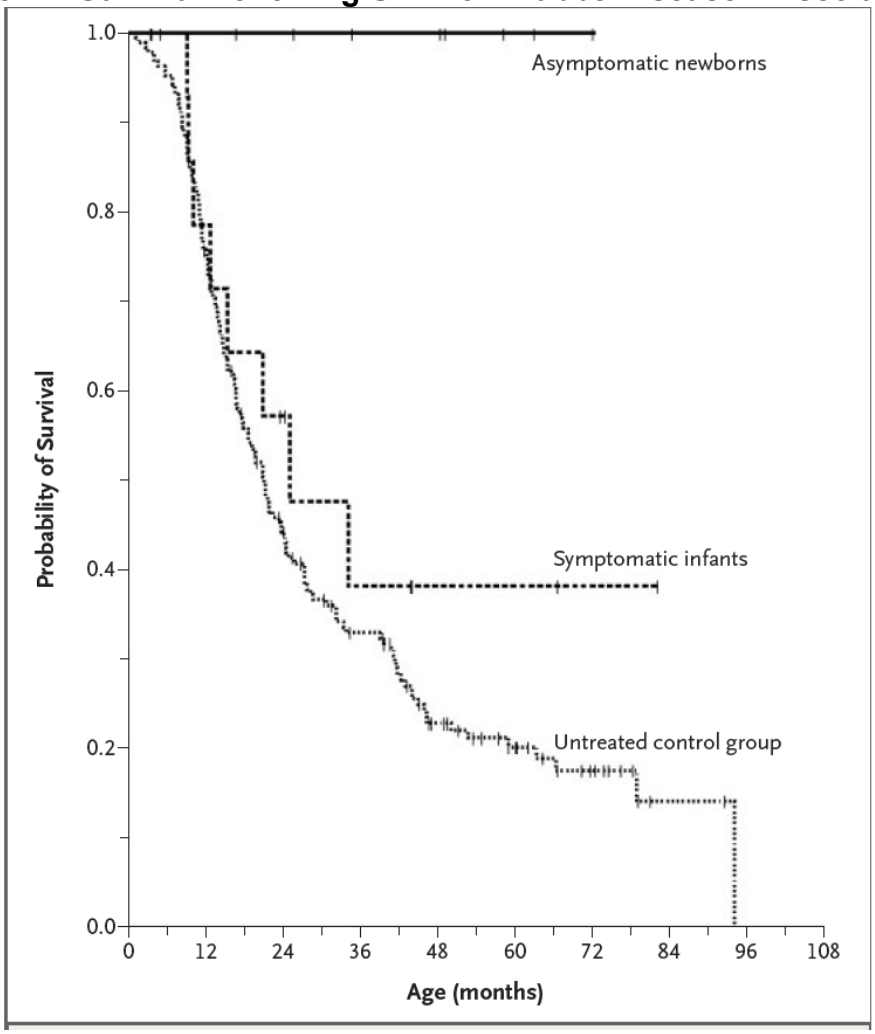
These analyses underscore the high variability in phenotype and the importance of age of symptom onset in estimating prognosis. Although the group of patients with onset at age 6 months or earlier has high mortality, a visual estimate from Figure 12 shows that about 16% survive for 4 years (48 months).

The overall experience for the 38 patients in the Docket dataset yielded an estimate of 60% survival at 4 years and about 44% survival at 100 months (~ 8 years), which would put it between the two later onset curves in Figure 12. In the absence of knowing the age of symptom onset for the Docket data, but considering the ages reported for age at transplant, the UCB transplant experience in the Docket datasets probably reflects a mixture of phenotypes and does not appear strikingly different from the historical data.

As mentioned above, a subset of the Krabbe disease patients in the Duke dataset was analyzed in a published report (Escolar and Poe et al. 2005) that forms the primary basis for the current therapeutic recommendations in the literature. In that analysis, 11 asymptomatic newborns ages 12 to 44 days, and 14 symptomatic infants ages 142 to 352 days, received UCB transplantation. Follow-up ranged from 4 months to 6 years. All 11 asymptomatic newborns survived through a median follow-up of 36 months. The publication also presented a control survival curve obtained for an analysis of 190

patients from the Hunter's Hope Krabbe Family database that were collected through 1/28/05. Further details on selection of the control group were not provided. The survival curves from the publication are shown in Figure 14 below.

Figure 14: Survival Following UCB for Krabbe Disease – Escolar 2005



Kaplan–Meier Estimates of the Probability of Overall Survival among Patients with Krabbe's Disease.

Shown are Kaplan–Meier estimates of survival among all 11 asymptomatic newborns with Krabbe's disease who underwent transplantation of umbilical-cord blood from unrelated donors, as compared with 6 of 14 infants who underwent transplantation after the development of clinical symptoms (P=0.01) and 190 untreated affected babies (P=0.001). P=0.28 for the comparison between the symptomatic infants and the control group. The tick marks indicate the most recent follow-up for each patient.

Source: Escolar and Poe et al. 2005

Reviewer's Comments:

The Duke dataset in the Docket includes only 9 patients with ages listed as 44 days (0.121 years) or less. The next two older patients were 55 and 117 days. Two of

the nine were transplanted after the date of the article, and one of these died a month after transplant. The NMDP dataset also show a death in a neonate two weeks after transplant. Thus, the favorable experience reported by Escolar cannot be confirmed exactly with the Docket datasets, and, with the additional early deaths added to the experience, the estimated treatment effect is diminished. Additional follow-up information on these patients is provided in the publication by Duffner and Caviness, Jr. et al. 2009, which is described below in the review of published experience.

The symptomatic patients were transplanted between the ages of about 5 and 12 months. Any analysis of post-transplant survival is an analysis of survival conditional on the fact that the patient has survived at least until the age of transplant. Therefore, the survival of a patient following transplant should be compared with the natural history only for patients who have survived to the age at which the transplant occurred, rather than being compared to all patients. The detailed control data are not available to permit the conditional survival probability to be computed for each transplant, but if one rescales the control survival curve upward, so that it has a probability of 1.0 at about 8 months, it approximately represents survival conditional on being alive at the average age of transplant in the symptomatic group. With that adjustment, the control curve overlaps the symptomatic infant curve very closely through about 3 years, in which case there is not even a trend toward a survival benefit in that group.

The comparison of the asymptomatic newborn experience with the control has the advantage of a clear and objective endpoint, but suffers from other deficiencies of an external control comparison, most significantly, the difficulty in establishing the comparability of study populations. The Hunter's Hope database could be subject to ascertainment bias, and the data come from family reports, rather than medical records. The Hunter's Hope analysis presented previously also showed a wide variability in survival with phenotype. In the small group of patients who were transplanted at Duke before symptom onset, the clinical phenotype is undetermined. Absent a randomized comparison to provide statistical comparability, or a series that is consecutive, minimally- or non-selective, and sufficiently large such that the usual epidemiologic distribution of phenotype frequency might be relied upon to provide a reasonable assurance of comparability of the populations, an outcome such as that observed in the Escolar publication (which is less dramatic with additional experience included – see Reviewer's comments above) is still subject to the concerns raised by the use of an external control population. The lack of even a suggestion of survival benefit for the symptomatic patients provides some grounds for additional concern about effectiveness. In addition, 90% of the data for this disease come from the Duke dataset, which has integrity issues regarding length of follow-up.

6.2.5 Analysis of Secondary Endpoint(s)

For patients treated at Duke, an affiliated dataset was provided that reported enzyme values before and after transplantation with UCB. However, there was no information regarding the specimen, assay, units of measurement, or timing of assessments.

Table 11: Enzyme Results for Krabbe Disease Patients – Duke Dataset

	Pretransplant (N=35)	Post-transplant (N=31)	Difference (N=30)
Mean (SEM)	0.2 (0.2)	3.3 (0.3)	3.0 (0.4)
Median (Range)	0.1 (0.0 – 5.5*)	3.1 (0.9 – 6.9)	3.0 (-3.1* – 6.9)

* One patient had a pretransplant value of 5.5, which differed markedly from the others; that patient's post-transplant value was 2.4.

While it appears that enzyme levels were significantly higher following UCB transplantation, the clinical significance of the finding is unclear.

The potential to substantiate claims for clinical benefits other than survival was not evaluated because no other disease-specific outcome data were included in the Docket datasets.

6.2.7 Subpopulations

Of the 38 patients with Krabbe disease, gender was not recorded for 1 (3%), and race was not recorded for 2 (5%).

In a univariate proportional hazards analysis, survival outcome appeared to be related to race grouping, with Hispanic+French/Hispanic having the highest hazard, African+African/American in the middle, and Caucasian having the lowest hazard ($p < 0.01$). However, the differences became statistically insignificant ($p = 0.13$) with dose added as a factor, or in a multivariate analysis adding age, gender, and dose (see below).

By proportional hazards analysis, neither age nor gender appeared to be related to survival outcome, either in univariate analyses, or in a multivariate analysis ($n = 36$) incorporating age, gender, race, and dose ($p = 0.72$ for age, $p = 0.94$ for gender, $p = 0.16$ for race, and $p = 0.25$ for dose in the multivariate analysis).

6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A univariate proportional hazards model found no significant relationship between dose (as prefreeze TNC/kg) and survival (nominal $p = 0.21$), with an estimated 3.5% decrease in hazard for each increase in dose of 10^7 TNC/kg. The results were similar with an analysis adjusting for age. There was only one patient with a dose < 2.5 x 10^7 TNC/kg (this was a 16 year old who received a dose of 2.4 and survived through 3 years of follow-up). An analysis comparing patients with TNC doses above and below

the median dose of 16.5 x 10^7 TNC/kg showed a trend toward improved survival at doses above the median, but the difference was not statistically significant (nominal log-rank p = 0.14).

6.2.10 Additional Efficacy Issues/Analyses

Published Reviews and Opinions

Krabbe disease is not mentioned explicitly in the 2005 IOM report on cord blood banking, although metabolic storage disorders are in the category for which the report considered allogeneic stem cell transplantation as "controversial; may be effective in selected patients." The Cochrane Collaboration has not reviewed the use of stem cell transplantation in Krabbe disease. The Prasad review in 2010 (Prasad and Kurtzberg 2010) reported UCB as standard of care, and cited the following as evidence: Escolar and Poe et al. 2005, Martin and Carter et al. 2006, and Prasad and Mendizabal et al. 2008. Search of the literature identified the follow additional primary report of experience with UCB in Krabbe disease: Duffner and Caviness, Jr. et al. 2009.

Published experience with UCB for Krabbe disease

Escolar and Poe et al. 2005 (n=25)
This is the article presenting the results of UCB transplantation discussed above in Section 6.2.4.

Escolar and Poe et al. 2006
The authors developed a 4-point staging system based on a categorization of specific clinical findings in order to predict post-transplant outcomes (predominantly cord blood). They found that patients with Stage 3 or 4 (moderate to severe neurologic involvement or advanced disease) had higher mortality or more severe disability following transplant, and they recommended that only patients in Stages 1 or 2 be considered for transplant.

Martin and Carter et al. 2006 (n=16)
This a report of 69 patients with lysosomal and peroxisomal storage disorders who received UCB transplantation under the COBLT study sponsored by NHLBI. Almost all (67) were transplanted at Duke. The populations included 16 patients with Krabbe disease, who are presumably a subset of the patients already considered in the review of the Docket datasets. The article does not provide efficacy information specifically for Krabbe disease patients. However, it did report on an analysis showing that, for the entire group, survival was not statistically significantly associated with age, cell dose, CD34+ dose, performance status, or HLA match number, but it was significantly worse for non-Caucasians and those who received units as part of an expanded access program.

Prasad and Mendizabal et al. 2008 (n=36)

This is a report of 159 patients who received UCB transplantation at Duke, including 36 patients with Krabbe disease. This appears to consist of patients whose data were also submitted to the Docket and therefore does not provide additional evidence regarding survival. Most results are presented for the study population as a whole. However, a graphic of Krabbe-specific survival data appeared very similar to that shown in Figure 10. The article does not state how the diagnosis of Krabbe disease was established and no comparisons to specific untreated Krabbe disease control data are provided.

Duffner and Caviness, Jr. et al. 2009

This is report of a workshop on outcome of presymptomatic infants transplanted for Krabbe disease. Abstracts presented at the workshop provided reports of follow-up. Although the type of stem cell transplantation is not identified, those reported from Duke were presumably all or mostly UCB. The publication is of note because it provides outcome information other than survival. Results are quoted below:

> Duke/UNC have evaluated 16 presymptomatic children transplanted at Duke and elsewhere for early infantile Krabbe disease. Of these, two have died in transplant. Of the remainder, all are spastic, although three are reported to be mild. Five require gastrostomies (although are able to eat by mouth), all are below the 3% for height and weight and most are below the 3% for head circumference. Receptive language is normal; however, all have abnormal expressive language because of impaired articulation. All have abnormal gross motor control, with 50% walking with assistive devices and only 25% able to walk independently. The investigators reported that all are considered to be normal cognitively. (There was a discussion at the meeting as to the difficulty in assessing intelligence accurately in children with such severe motor and language deficits.)
>
> A composite group of nine children from other PBMTC [Pediatric Bone Marrow Transplantation Consortium] transplant centers in the United States and Canada was also presented. … Six infants with a positive family history of early infantile Krabbe disease and low GALC activity were transplanted before symptom onset. One died of complications of transplant. Of the remaining five, all have delayed development and abnormal neurologic examinations. Three of the four children beyond 3 years of age are unable to walk without assistance because of slowly progressive spasticity. Three of four have acquired microcephaly, four of four have weights below the 3%, and three of four have heights <5%. Progressive neurological deterioration is present in three of four. (The child with stable, albeit delayed development, is only 3 years old.) (Duffner and Caviness, Jr. et al. 2009)

The discussion in Duffner and Jalal et al. 2009 is worth noting:

> Of concern in the age of bone marrow transplantation is that, even within families with the later-onset phenotype, there may be wide differences in presentation and course. Phelps et al. [14] [Phelps and Aicardi et al. 1991], for example, described two siblings, one of whom was confined to a wheelchair and institutionalized whereas her sibling remained neurologically normal despite comparable enzyme activity and computed tomography findings. Therefore, preemptively transplanting the sibling of an affected child with the same genetic abnormality may be unjustified. The situation becomes even more complex if newborns are screened for Krabbe disease at birth. Because neither the level of galactocerebrosidase activity nor the genetic mutation reliably predicts phenotype and there may be wide phenotypic variability even within families, the

decision on whether to recommend treatment is daunting [15]. Until we gain a better appreciation of the natural history of these later-onset phenotypes, decisions regarding aggressive treatment will necessarily be based on inadequate data.

In contrast, the decision regarding hematopoietic stem cell transplantation is more straightforward in the early infantile phenotype, which is known to have little clinical heterogeneity and there is the certain knowledge that, in the absence of transplantation, neurologic devastation and death are inevitable. Unfortunately, bone marrow transplantation is ineffective unless the child with the early infantile phenotype has the transplantation before developing symptoms. There is thus an urgent need for both physicians and families to be able to recognize the earliest signs and symptoms of the disease, as well as to be aware of the age at which these symptoms begin to manifest. (Duffner and Jalal et al. 2009)

Reviewer's Comment:
The recommendation in the last paragraph is based on the findings described above in the publication (Escolar and Poe et al. 2005). The cautions expressed in the first paragraph may be applicable to the presymptomatic early infantile onset case as well, unless one has certainly that the asymptomatic patients actually would have developed the early infantile onset phenotype.

Evidence from published data regarding the effect of UCB on other aspects of Krabbe disease is limited by lack of objective comparisons to controls and by susceptibility to possible selection or reporting bias.

With the newborn screening taking place in New York, and maybe beginning in additional states, there could be an opportunity to develop evidence that could resolve the question: if a program of wholesale neonatal transplantation appears clearly to alter the population distribution of the phenotype, that might be regarded as evidence of an effect of UCB transplantation on the disease.

6.3 X-Linked Adrenoleukodystrophy (ALD)

X-linked adrenoleukodystrophy (ALD) is an X-linked peroxisomal disorder cause by abnormal beta oxidation that results in accumulation of very long chain fatty acids (VLCFAs). The incidence is estimated be 1 in 100,000 to 1 in 20,000 (Moser 1997). The disease involves a mutation in the ATP-Binding Cassette, Subfamily D, Member 1 gene (ABCD1), which encodes a transporter important for moving VLCFAs into peroxisomes. VLCFAs accumulate in the affected organs, which are the CNS, adrenal cortex, and testes. The disease has been classified into a number of phenotypes, with a wide range in severity that may even vary dramatically within a family (Moser and Moser et al. 1991; Moser 1997; Moser and Loes et al. 2000). Neither mutation nor biochemistry predicts phenotype.

The childhood cerebral form usually presents in boys between 4 and 8 years, initially with behavior problems, then with neurologic deterioration including cognitive abnormalities, blindness, and quadriparesis. Once symptoms develop, progression is typically rapid, with total disability in 6 months to 2 years, and death in 5 to 10 years.

A milder form, adrenomyeloneuropathy (AMN) usually presents in young adult males as spinal cord dysfunction, but may present as progressive cerebellar disorder. An Addison-disease-only phenotype may be the expression in about 10% of patients. Carrier females can also have some mild manifestations of the disease.

There is no approved drug or biologic therapy for ALD. Lorenzo's oil has been studied in ALD, and is thought to be of some benefit in delaying progression in patients with early or mild disease (Moser and Moser et al. 2007).

6.3.1 Methods

Efficacy was evaluated by computing estimates for post-transplant survival obtained from pooling the three datasets described in Section 5.1. Results were compared to historical control survival data obtained from the literature. The literature was reviewed for additional reports of experience with unrelated cord blood use in ALD.

In the Docket datasets, diagnostic information other than the diagnosis of ALD was not provided. Thus, eligibility criteria for the series and the criteria for classification of the phenotype are unknown. Although the Lansky scores recorded in the Duke dataset give some indication of patient status, there is not an explicit representation of whether or not a patient had neurologic symptoms at the time of UCB transplantation. Information on disease-specific outcomes that might have been of interest, such as neurologic findings, was not provided. A slight majority (52%) of the cases came from the Duke dataset. As noted in Section 5.1, there are questions about the accuracy of the follow-up times for censored observation in that dataset.

6.3.2 Demographics

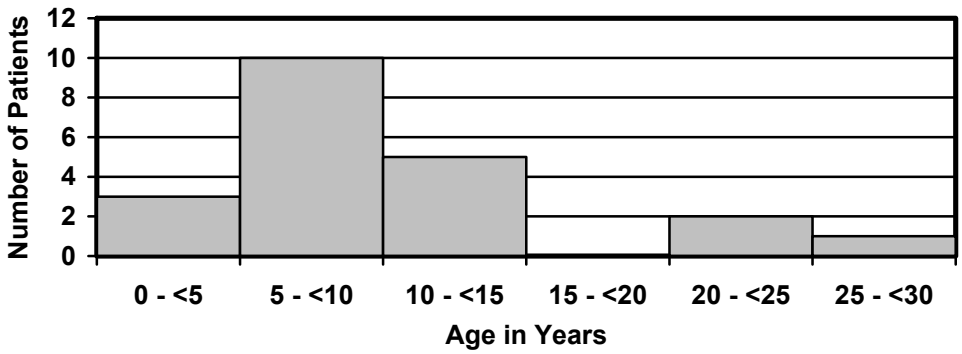
Basic demographics for the ALD patients in the pooled datasets are shown below, together with basic treatment data. Demographic information other than age was not provided in the NYBC dataset.

Table 12: Demographics and Treatment Data for Patients with ALD – Docket Data

Total N	21
Age in Years Mean (SD)	
Mean (SD)	10.0 (6.5)
Median (Range)	8.2 (2.4 – 26.3)
Gender	
Male	67% (14)
Unknown (presumed male)	33% (7)
Race	
Caucasian	52% (11)
Asian	10% (2)
African/American	5% (1)
Hispanic	5% (1)
Unknown	29% (6)
Dosing (x10^7 TNC/kg prefreeze)	
Median	4.0
10^{th}, 25^{th}, & 75^{th} percentiles	1.7, 2.6, 7.8
Dose < 2.5	24% (5)
HLA Match	
6/6	14% (3)
5/6	38% (8)
4/6	48% (10)
Data source	
Duke[1]	52% (13)
NMDP[2]	10% (2)
NYBC[2]	29% (6)

[1] Duke count includes one case each also reported by NMDP and NYBC
[2] Excludes cases also reported by Duke

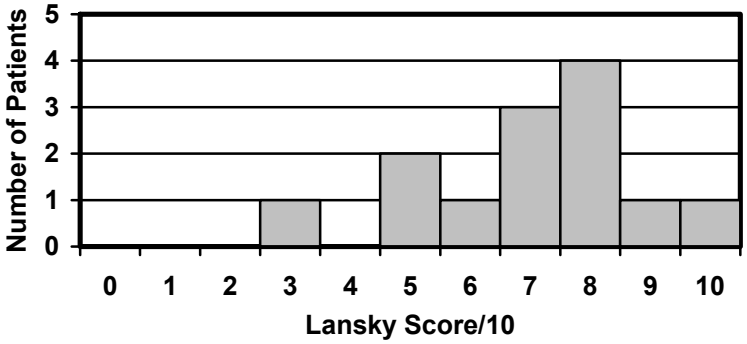
Figure 15: Age Distribution for ALD Patients – Docket Data



The presence of three patients who were 20 years or older raises some concern about the accuracy of the reporting of the diagnosis, and whether these might be more appropriately classified as AMN.

The Lansky score is a general play-performance score described above in Section 6.1.2. The score was recorded only in the Duke dataset. Except for one patient with a score of 30 (in bed, needs assistance for quiet play), the scores ranged from 50 (gets dressed but lies around much of the day) to 100 (fully active). These scores indicate there was a fairly broad range in clinical status at the time of transplant.

Figure 16: Lansky Score Distribution of Pooled Docket ALD Patients



(Lansky scores were available only for the 13 patients in Duke dataset.)

6.3.3 Subject Disposition

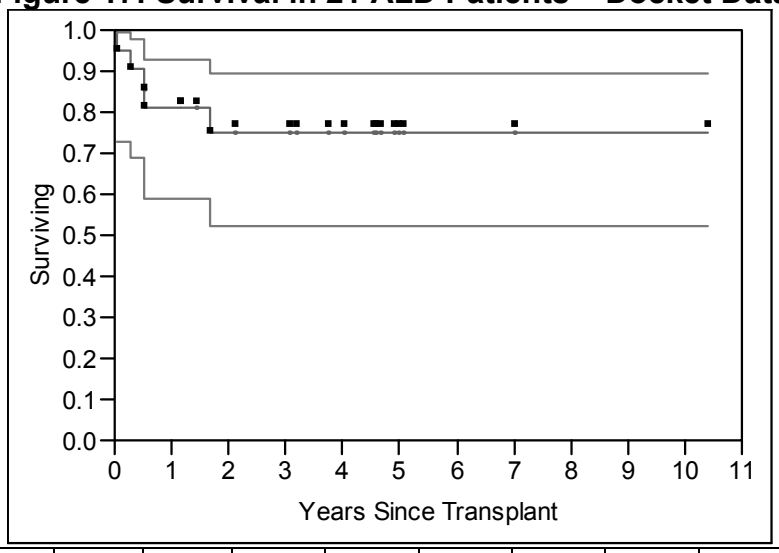
No protocol was provided for this study, and there is no information available about screening, eligibility criteria, or diagnostic criteria. Of the 21 ALD patients, 5 are reported to have died. Two deaths were attributed to neurologic deterioration or progression of ALD, and there was one death each attributed to GVHD, veno-occlusive disease, and pneumonia. (One patient in the Duke dataset had a cause of death listed as infection, but the patient was not reported to have died – for purposes of the analysis the patient was treated as survived, under the assumption that the infection was a misplaced non-fatal event.)

6.3.4 Analysis of Primary Endpoint(s)

Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown in Figure 17 below for the 21 ALD patients from the Docket datasets. There is 19% mortality by the end of the first year. The estimated fraction surviving at 5 years is 75% with a lower confidence limit of 52%, but the number at risk is very low at 5 years and beyond.

Figure 17: Survival in 21 ALD Patients – Docket Data

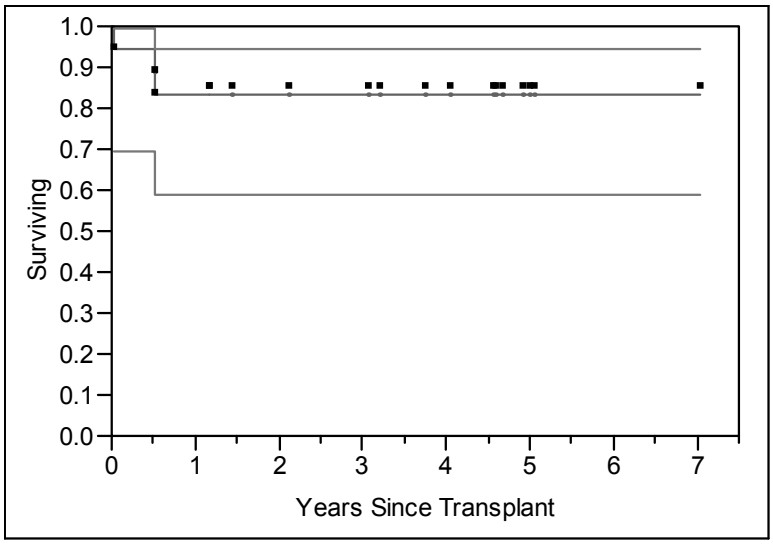


Year	0	1	2	3	4	5	6	7	8	9	10
Survival	1.00	0.81	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
No. at Risk	21	17	13	12	9	3	2	2	1	1	1

The longest survival, censored at 10.4 years following transplant, was seen in the 26 year old patient, the second longest, censored at 7.0 years following transplant, was seen in a 9 year old. Survival at 5 years and beyond came only from the Duke dataset, for which is there is concern about the validity of the follow-up times reported for censored observations.

The three patients older than 20 were not typical for the childhood cerebral phenotype, so an additional analysis was done for only the 18 patients 14 years and younger, as shown in Figure 18:

Figure 18: Survival in 18 ALD Patients ≤ 14 Years – Docket Data

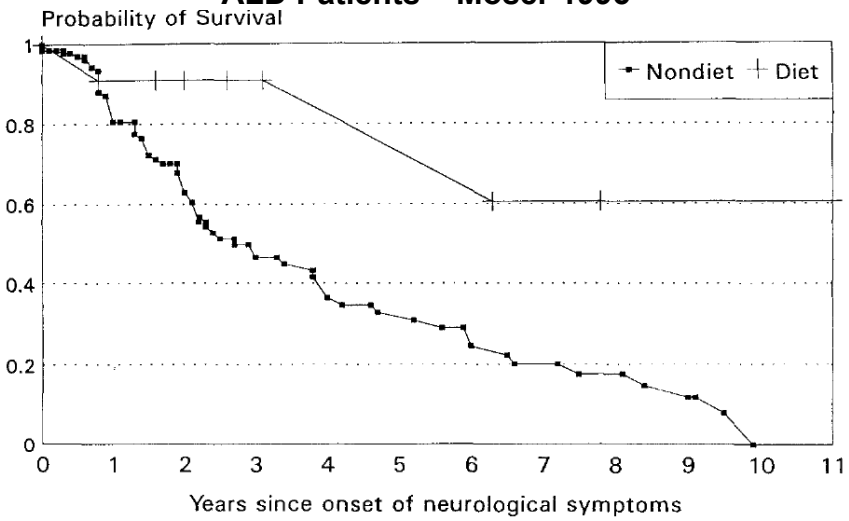


Although the estimated survival probabilities are somewhat higher, there is no demonstrably different experience in this younger subgroup than in the group as a whole.

Historical Experience

Historical data are available from a number of sources. One of the earliest substantial reports that provided a survival analysis came from a review of cases from the files at Johns Hopkins University (Moser 1995). The population consisted of 139 patients with the childhood cerebral phenotype who had not received Lorenzo's oil (the "Nondiet" group in Figure 19). The analysis showed progressive failure over a course of 10 years following the onset of neurologic symptoms. The 5-year survival was about 30%.

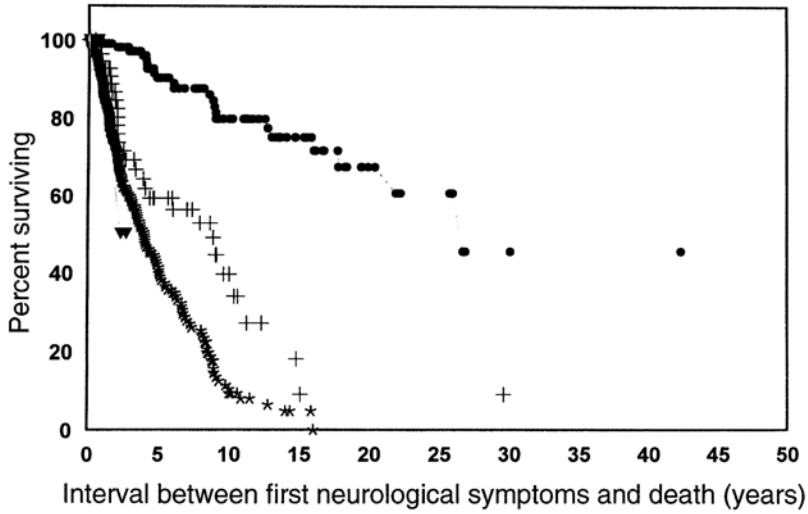
Figure 19: Survival Following Onset of Neurologic Symptoms in 139 Untreated ALD Patients – Moser 1995



Probability of survival from onset of neurologic symptoms to death. Untreated [Nondiet] (n=139) and treated [Diet] (n=11) symptomatic adrenoleukodystrophy patients.
Source: Moser 1995

In a subsequent publication, Moser presented a larger series of 257 patients with the childhood cerebral phenotype along with data on other phenotypes (Moser 1997). However, the source and selection of these data are not made clear in the publication. It is difficult to estimate from the graph in the publication (see Figure 20), but the 5-year survival in the childhood cerebral form appears to be approximately 40%.

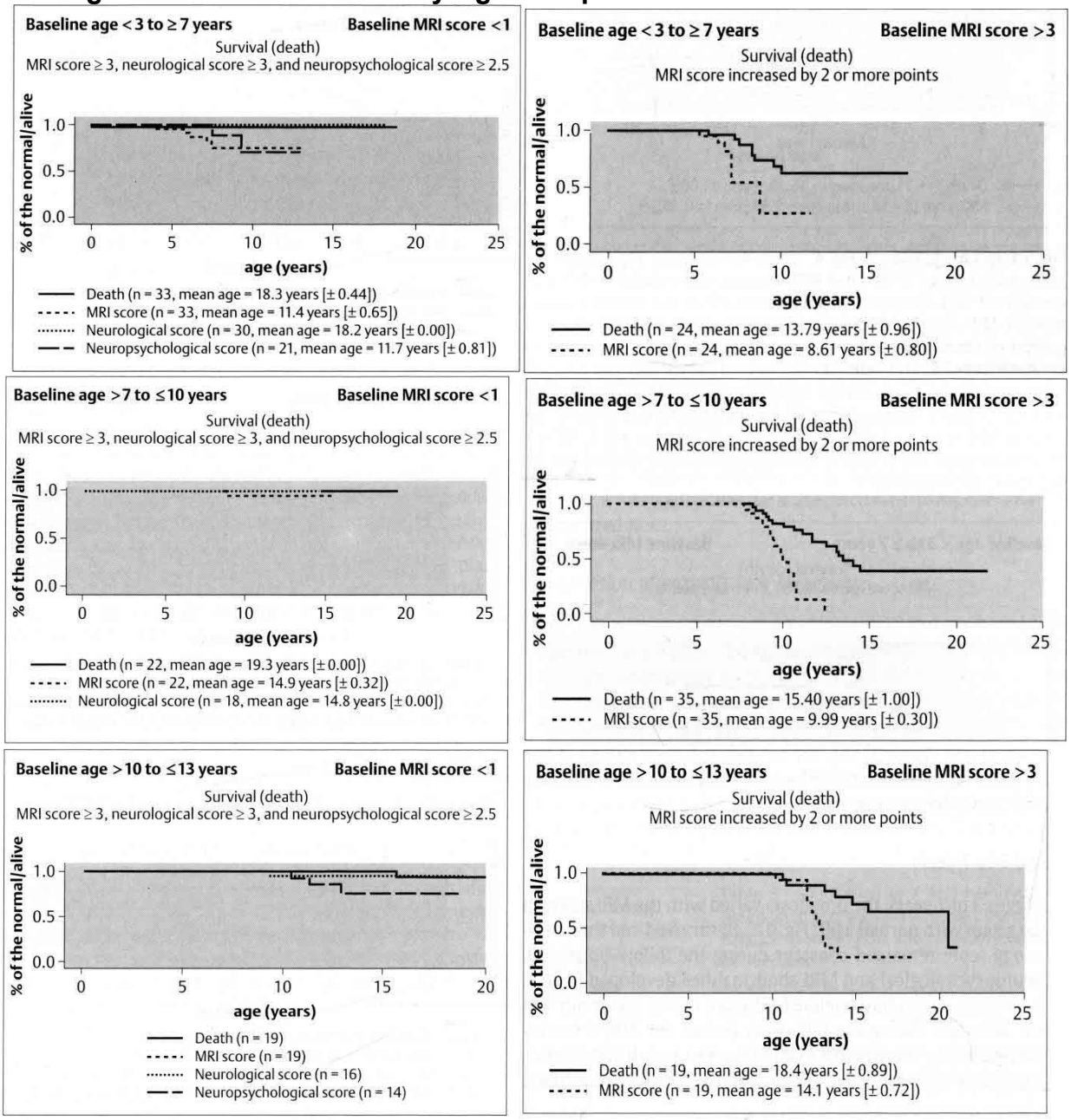
Figure 20: Survival Following Onset of Neurologic Symptoms in ALD Patients – Moser 1997



Survival from time of first neurological symptom (untreated males only). Note the rapid rate of progression of cerebral forms irrespective of age at onset. Filled circles = AMN (*n* =116); filled triangles = adult cerebral (*n* = 3); plus signs = adolescent cerebral (*n* = 60); asterisks = childhood cerebral (*n* = 257).
Source: Moser 1997

In a review of 372 cases from the records at the Kennedy Krieger Institute at Johns Hopkins, Moser undertook an extensive analysis of survival looking at the effect of age and MRI findings on prognosis (Moser and Loes et al. 2000). In that population, 8% had received BMT. Post-transplant data were excluded from the analysis. Selected graphics from that publication covering the age range of 3 to 13 years are shown in Figure 21 below. Those graphics are reproduced here because they exhibit the overall survival experience, as indicated by the solid lines. (The graphics also include information on other endpoints, but these are not considered further here because no comparable endpoints were included in the Docket datasets.)

Figure 21: Survival in ALD by Age Group and MRI Status at First Contact



Left graphs: survival (solid lines) in designated age groups and with normal MRI at first contact.
Right graphs: survival (solid lines) in designated age groups who had moderate to severe abnormality on MRI at first contact.
Analyses exclude post-transplant experience.
[Notes: Times to progression of MRI, neurologic, and neuropsychiatric scores are also plotted but are not considered further here. Age group labels for the two top graphs appear to have a typographic error, and should instead read ">3 to ≤ 7 years."]
Source: Moser and Loes et al. 2000

Most recently, Mahmood presented survival curves for a series of 283 boys with childhood cerebral ALD from the Kennedy Krieger Institute who had not received HSCT (Mahmood and Raymond et al. 2007). For that group, the 5-year survival after onset of symptoms was 66%. He also presented an analysis of survival for 19 patients who received HSCT compared with a group of 30 non-transplanted patients with similar MRI scores. For the subset of 30 patients with early stage disease, the 5-year survival after first abnormal MRI was 54%.

Figure 22: Survival from Onset of Symptoms in ALD – Mahmood 2007

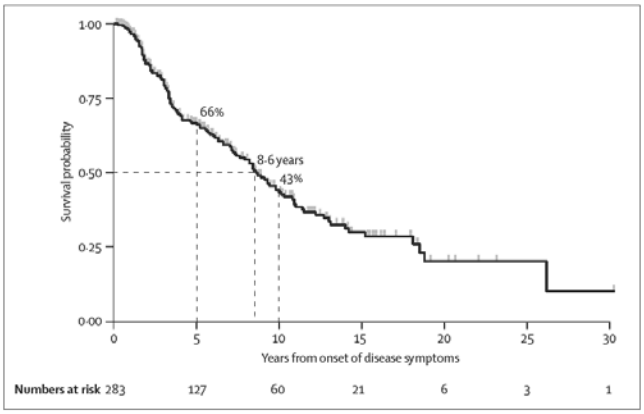


Figure 2: Kaplan-Meier estimate of survival for 283 boys with childhood cerebral X-linked adrenoleukodystrophy after development of neurological symptoms (cognitive, behavioural, or neurological symptoms)

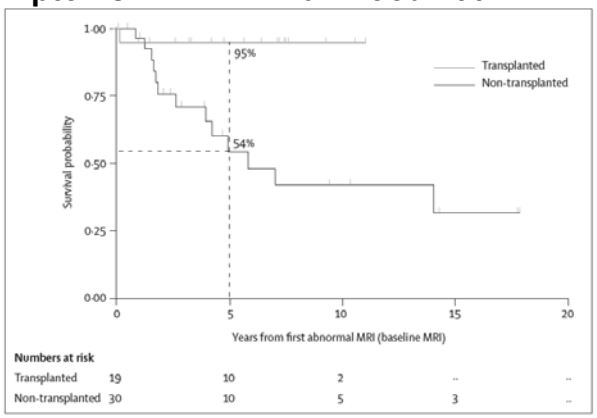


Figure 4: Kaplan-Meier estimates of survival for 19 transplanted patients with early stage cerebral adrenoleukodystrophy and for 30 non-transplanted patients with early stage cerebral adrenoleukodystrophy (ie, neurological deficit score of 0 or 1 and MRI severity score less than 9) Survival was different in these two groups (χ^2=7·47, p=0·006).

Source: Mahmood and Raymond et al. 2007

Reviewer's Comments:
The ALD phenotype is variable, and without knowledge of the timing of onset of symptoms and degree of MRI abnormalities in the Docket population, it is difficult to identify an appropriate external control.

The lower limit of the estimated 5-year survival from the Docket dataset is about 52% (Figure 17), so that the confidence interval does not exclude the estimated 5-year survival of 66% following onset of symptoms (Figure 22, left display) or 54% following first MRI abnormality in early disease (Figure 22, right display) from the most recently published historical experience. While there is some suggestion that overall survival following UCB transplantation for patients in the database is better than that of patients who have had onset of neurologic symptoms in some of the older series, survival following UCB transplantation appears to be worse than survival in diagnosed patients who have not developed MRI abnormalities (Figure 21, left displays). Although the recent analysis by Mahmood estimated higher survival in patients who underwent HSCT compared to no HSCT (Figure 22, right display), the UCB survival outcomes from the docket datasets are not that similar to those report by Mahmood for HSCT; in fact, for the first few years where the follow-

up experience is more complete, the UCB results seem closer to those of the untreated group.

6.3.5 Analysis of Secondary Endpoint(s)

The potential to substantiate claims for clinical benefits other than survival was not evaluated because no disease-specific outcome data were included in the Docket datasets.

6.3.7 Subpopulations

Of the 21 patients with ALD, gender was not recorded for 7 (33%), but all can be presumed to be male. Race was not recorded for 6 (29%).

By proportional hazards analysis, neither age nor race appeared to be related to survival outcome, either in univariate analyses, or in a multivariate analysis (n = 15) incorporating age, race, and dose (p = 0.51 for age, p = 0.27 for race, and p = 0.16 for dose in the multivariate analysis).

6.3.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A univariate proportional hazards model found no statistically significant relationship between dose (as prefreeze TNC/kg) and survival (nominal p = 0.86) with an estimated 2.2% *increase* in hazard for each increase in dose of 10^7 TNC/kg. There were only 5 patients with a dose < 2.5 x 10^7 TNC/kg. There was one death in that subset, and the survival curve appeared similar to that of those who got the higher doses. An analysis comparing patients with TNC doses above and below the median dose of 4.0 x 10^7 TNC/kg showed a slight trend toward worse early survival, but with improved late survival, for doses above the median, but the difference was not statistically significant (nominal log-rank p = 0.14).

6.3.10 Additional Efficacy Issues/Analyses

<u>Published Reviews and Opinions</u>

Neither the review of cord blood banking by an AAP Work Group nor the 2005 IOM report commented explicitly on the effectiveness of UCB for ALD, but they both categorized stem cell transplantation for metabolic storage disorders as “controversial; may be effective in selected patients.” A 2010 review by Prasad (Prasad and Kurtzberg 2010) regarded UCB as standard of care for adrenoleukodystrophy, and cited the following sources as evidence: Martin and Carter et al. 2006, Beam and Poe et al. 2007, and Prasad and Mendizabal et al. 2008. The Cochrane Collaboration has not reviewed the use of stem cell transplantation in ALD.

Published experience with UCB in ALD

Martin and Carter et al. 2006

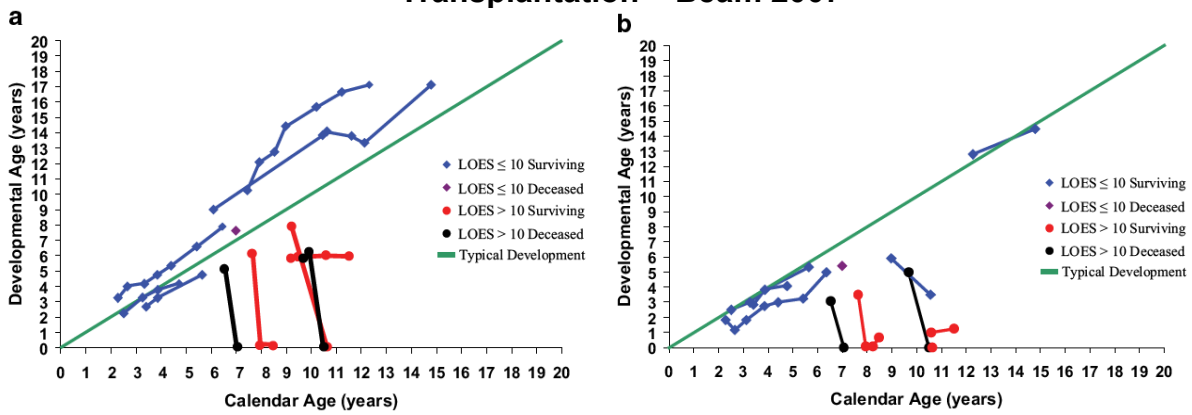
This a report of 69 patients with lysosomal and peroxisomal storage disorders who received UCB transplantation under the COBLT study sponsored by NHLBI. Almost all (67) were transplanted at Duke. The populations included 8 patients with adrenoleukodystrophy. The report presents summaries of engraftment, survival, toxicity, and GVHD, but results are not broken down by disease. For the entire group, survival was 80% at 6 months and 72% at one year. Survival was not statistically significantly associated with age, cell dose, CD34+ dose, performance status, or HLA match number, but it was significantly worse for non-Caucasians and those who received units as part of an expanded access program. The article does not provide efficacy information specifically for ALD patients.

Beam and Poe et al. 2007

This reports on a retrospective analysis of 12 patients with ALD referred to Duke for transplantation. This presumably consists of patients whose data were also included in the Docket submission, so it does not provide additional survival information. Median follow-up was 3.3 years; survival past 6.25 months was 67% (95% CI: 40% – 93%), which is slightly lower than, but consistent with, the experience shown in Figure 17. The report noted that one patient died after starting conditioning and did not receive transplant. The death was attributed to "shock and brain herniation likely secondary to adrenal crisis."

From an analysis aimed at determining whether baseline observations predicted outcome after cord blood transplantation, the authors found that pretreatment MRI-based Loes score correlated with post-transplant cognitive and motor development, but baseline neurophysiologic studies were not predictive. A graphic from the article is reproduced below as Figure 23 (colors referenced in the caption refer to the graphic as originally published):

Figure 23: Cognitive and Gross Motor Development in ALD Following UCB Transplantation – Beam 2007



(a) Cognitive development and pretransplant MRI Loes scores. The green line [long diagonal] represents typical development. Each blue line [diamonds] represents the longitudinal cognitive course of a surviving patient with baseline Loes Scores <10. The red lines [circles] represent the longitudinal cognitive course of surviving patients with Loes Scores >10. The black and purple represent deceased patients.
(b) Gross motor development and pretransplant MRI Loes scores. The green line [long diagonal] represents typical development. Each blue line [diamonds] represents the longitudinal motor course of a surviving patient with baseline Loes scores >10. The red lines [circles] represent the longitudinal motor course of surviving patients with Loes scores <10. The black and purple represent deceased patients. Note that motor scores are in general lower than cognitive scores in (a).
Source: Beam and Poe et al. 2007

The article did not provide control cognitive and gross motor data from an untransplanted ALD population for comparison.

Reviewer's Comments:
This report is on patients transplanted at Duke, but there are some noteworthy differences between the data reported in this article and the Duke dataset. The Duke dataset contains two patients older than 20; they were not included in the article. The article reports that one of the 12 patients died after beginning conditioning and did not get transplanted; that patient does not appear in the Duke dataset. Further, the follow-up times reported in the article exactly match those in the Duke dataset if the Excel "NOW()" function is replaced by the date 8/1/2006. This is evidence that the follow-up times used in the article have the same data quality issue as identified for the Duke dataset (see Dataset Integrity and Quality*, in Section 3.1).*

By the nature of the population studied, this analysis did not address prediction of disease course in patients who were not transplanted, but the finding that MRI is predictive of outcome is generally in accord with a similar finding in untreated patients, as indicated by Figure 21.

Prasad and Mendizabal et al. 2008

This is a report of 159 patients who received UCB transplantation at Duke, including 13 patients with adrenoleukodystrophy. This appears to be comprised of patients whose data were also submitted to the Docket, and therefore does not provide additional evidence regarding survival. The article does not state how the diagnosis of ALD was established and does not identify patients' clinical status at time of transplant. Most results are presented for the study population as a whole. However, the ALD-specific data showed a 69% survival through 2 years and extending to 10 years, based on a median follow-up of 3.1 years. The survival is slightly lower than, but consistent with, the experience shown in Figure 17. The rate of engraftment with high (>90%) donor chimerism was 85%. No comparisons to untreated ALD control data were provided.

Reviewer's Comment:
Evidence from published data regarding the effect of UCB on aspects of ALD other than survival is limited by lack of objective comparisons to controls and susceptibility to possible selection or reporting bias.

6.4 Primary Immunodeficiency Diseases – Severe Combined Immunodeficiency (SCID)

Primary immunodeficiency diseases are a heterogeneous collection of congenital disorders of immune function. Even Severe Combined Immunodeficiency (SCID) is a collection of different entities. Many of the various individual primary immunodeficiency disorders are represented by a very small number of cases in the pooled Docket datasets. The clear predominant subcategory was the SCID syndrome(s).

SCID is caused by mutation in various genes involved in lymphocyte development and function. The incidence is estimated to be between 1 in 50,000 to 500,000 live births. The gene defect is unknown in about 14% of cases. Of the known gene defects, only one causes an X-linked syndrome, but about half of all SCID cases are X-linked.

Children affected with SCID usually present in the first year of life with recurrent infections and failure to thrive. T cell counts are very low, the thymic shadow is small or absent, hypogammaglobulinemia is common, and various tests of immune function are abnormal. Diagnostic criteria are: lymphocyte count < 300/mm^3, less than 20% T cells, and mitogen response < 10% of control. Presence of maternal T cells in the circulation is also diagnostic. If uncorrected, SCID is usually fatal in the first year of life. Omenn syndrome, in which T cells may be present but function is abnormal, is included under the SCID umbrella for purposes of this review.

The only approved specific therapy for SCID is Adagen (PEG-ADA, pegademase bovine), which is effective for the subset of patients in whom SCID is due to adenosine deaminase deficiency. IVIG is an approved therapy for a variety of primary immunodeficiency disorders.

6.4.1 Methods

Efficacy was evaluated by computing estimates for post-transplant survival obtained from pooling the three datasets described in Section 5.1. Results were compared to historical control survival data obtained from the literature. Review of a reasonably well documented case report in the Docket was also contributory.

In the Docket datasets, diagnostic information other than the diagnosis of SCID was not provided; however, the NMDP dataset did identify subtypes of SCID. Eligibility criteria for the series and the criteria for classification of the phenotype are unknown. Information on disease-specific outcomes other than survival that might have been of interest, such as immune function evaluation or infection history, were not provided in the datasets. The Docket included one case report that did provide some additional clinical data other than survival.

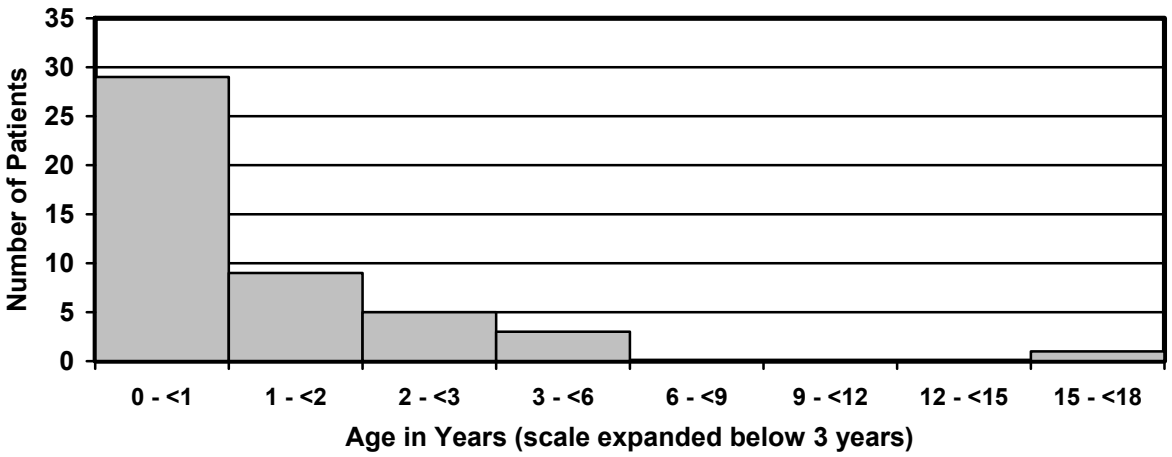
6.4.2 Demographics

The case report is described in a subsequent section. Basic demographic information for the SCID syndrome patients in pooled datasets are shown below, together with basic treatment data. Demographic information other than age was not provided in the NYBC dataset.

Table 13: Demographics and Treatment Data for SCID Patients – Docket Data

Total N	47
Age in Years	
Mean (SD)	1.2 (25)
Median (Range)	0.6 (0 – 17)
Gender	
Male	36% (17)
Female	11% (5)
Unknown	53% (25)
Race	
Caucasian	43% (20)
African/American	2% (1)
Asian	2% (1)
Unknown	53% (25)
Dosing (TNCx10^7/kg prefreeze)	
Median	12.7
10^{th}, 25^{th}, & 75^{th} percentiles	6.5, 8.5, 20.3
Dose < 2.5	0% (0)
HLA Match	
6/6	15% (7)
5/6	36% (17)
4/5	40% (19)
3/6	4% (2)
2/6	2% (1)
Unknown	2% (1)
Data source	
NMDP	47% (22)
NYBC	53% (25)

Figure 24: Age Distribution for SCID Patients – Docket Data



While a breakdown of ages below one year would be desirable, most of the cases came from the NYBC database, which reported age in years only as whole numbers. The presence in the dataset of 9 patients who are 2 years or older is not expected for patients with the usual presentation of SCID. The presence of a 17 year old with SCID in the NYBC dataset is difficult to understand unless it represents a data entry error or a second transplant for a patient initially transplanted in childhood.

6.4.3 Subject Disposition

No protocol was provided for this study, and there is no information available about screening, eligibility criteria, or diagnostic criteria. Of the 47 total SCID patients, 16 are reported to have died. The causes of death are tabulated below:

Table 14: Cause of Death in SCID Patients – Docket Data

	N
Respiratory	8
Infection	3
Misc.*	5

* Pulmonary embolism-1, cardiotoxicity-1, "HemolAnCard"-1, other, unspecified-2

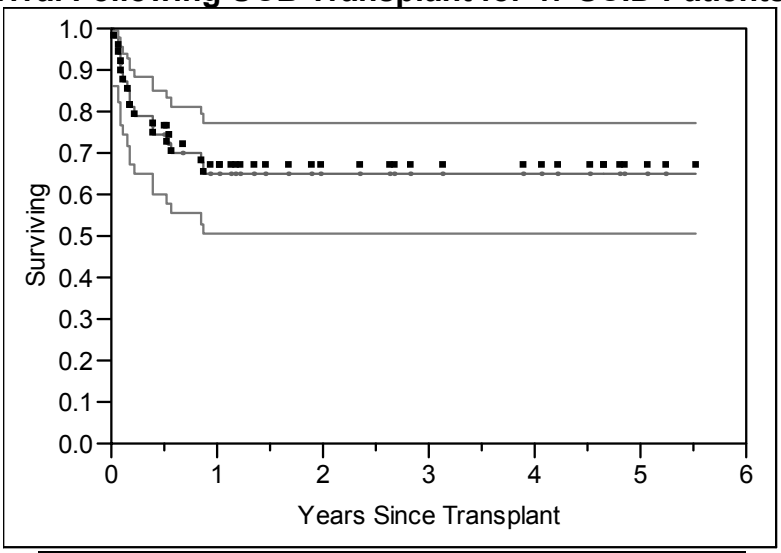
Three patients received a second transplant due to engraftment failure (one of these subsequently died). A fourth patient received a second transplant after 19 months for an unspecified reason.

6.4.4 Analysis of Primary Endpoint(s)

Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown below for the 47 SCID patients from the Docket datasets. There is about 35% mortality by the end of the first year, but mortality is low thereafter. Median follow-up was 1.1 years; the 75th quartile of follow-up was 3.1 years.

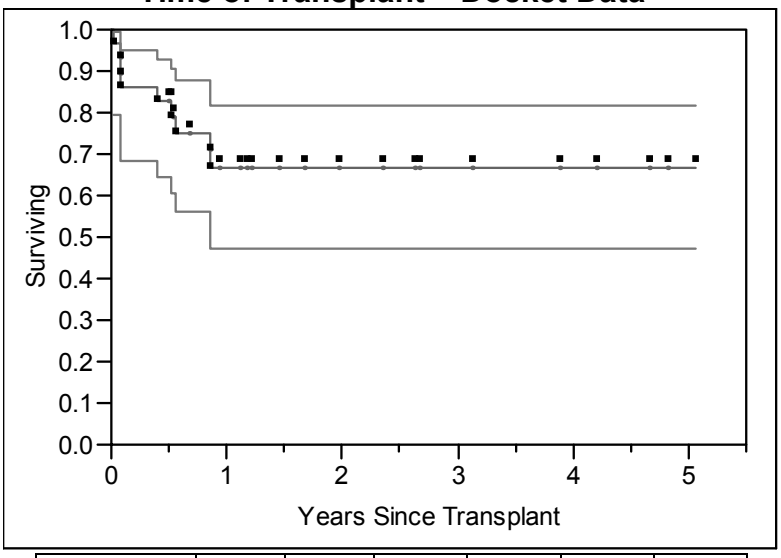
Figure 25: Survival Following UCB Transplant for 47 SCID Patients – Docket Data



Year	0	1	2	3	4	5
Survival	1.00	0.65	0.65	0.65	0.65	0.65
No. at Risk	47	26	16	12	10	3

Since the presence of patients 2 years and older raises questions about the accuracy of the SCID diagnosis for those patients, an analysis of survival was performed for only the 29 patients under 1 year of age. Results were generally similar, as shown in Figure 26:

Figure 26: Survival Following UCB Transplant for 29 SCID Patients < 1 Year Old at Time of Transplant – Docket Data



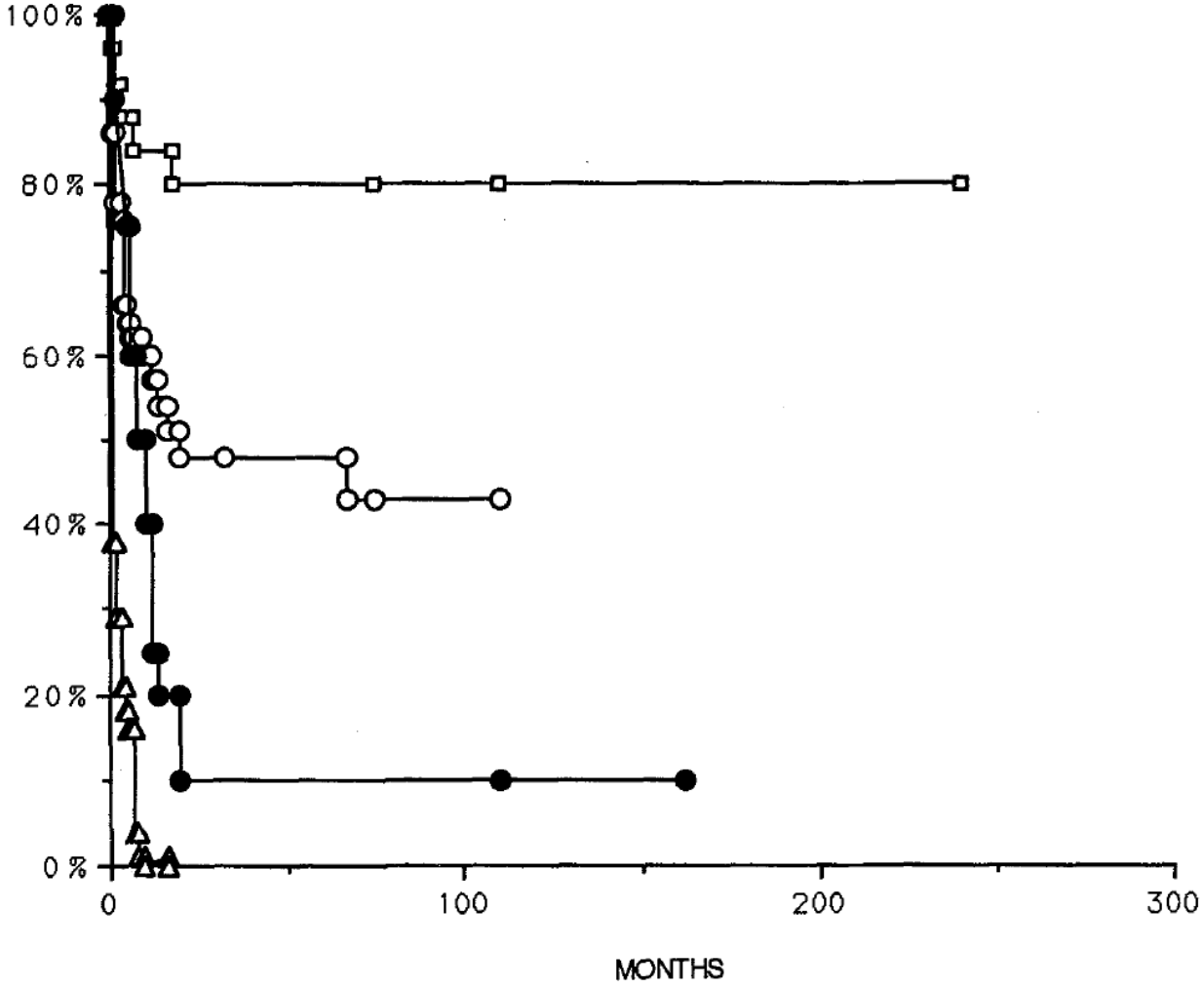
Year	0	1	2	3	4	5
Survival	1.00	0.67	0.67	0.67	0.67	0.67
No. at Risk	29	15	9	6	4	1

Historical Experience

A case series of 434 cases published by Hitzig (Hitzig and Kenny 1978) reported that "All untreated infants died within the first months of life." The article does not identify how may patients were treated or how (although transplants were being performed by that time), but the article does report on 244 autopsies. If one takes 244 as a representation of the untreated cases, then for an observed survival rate of 0 out of 244, the upper 2.5% confidence limit for the survival probability is 0.015, and even if it is allowed that 1 may have survived the upper confidence limit would be 0.023.

A series of 22 patients who did not undergo HSCT was reported by Stephan (Stephan and Vlekova et al. 1993) from a series of 117 cases referred to a Paris hospital between 1970 and 1992. Individual data were not provided in the report, but the graphic (Figure 27) indicates all non-transplanted patients died by about 18 months. Thus, the 2.5% upper confidence limit for the probability of survival past 18 months is 0.154.

Figure 27: Survival in SCID by BMT Type and Without Transplant – Stephan 1993



Survival curves of 117 patients with SCID according to transplantation procedure. Thirty patients received HLA-identical transplants *(clear squares),* with median follow-up of 129 months; 50 patients received T cell-depleted HLA-non-identical transplants *(clear circles),* with median follow-up of 34 months; 10 patients received fetal liver transplants *(dark circles),* with median follow-up of 148 months, and 22 patients did not undergo transplantation *(clear triangles).*
Source: Stephan and Vlekova et al. 1993

Reviewer's Comments:
The lower limit of the confidence interval for survival at 2 years from the Docket data, at about 50%, appears to be well above the survival experience from the historical control. Further, from a sensitivity analysis under the rather conservative assumption that censored events were all actually deaths, the 9 survivors at 2 years, out of 29 UCB treated SCID patients under 1 year of age, differs with nominal p < 0.00001 from the experience of no survivors out of the 266 combined cases reported by Hitzig (using only 244 autopsy cases) and Stephan. The nominal significance would still be p < 0.0013 in the more extreme sensitivity scenario assuming the

historical rate were 7.5%, or assuming that there were only 7 survivors in the UCB transplant cases and that the 2-year survival rate for the historical controls were as high as 5%. The statistical significance is even greater using the entire experience in the 47 patients.

Adagen (pegademase bovine) has been an available therapy since 1990 for patients with SCID due to ADA deficiency. SCID subtypes were only identified in the NMDP dataset, and 2 of those 22 patients were listed as "SCIDAD." For the 20 other patients, estimated survival at 2 years post-transplant was 73% with the lower end of the 95% CI at about 48%, and 9 of the patients were known to have lived to at least age 2 years. Thus, it does not appear the improved survival in SCID after UCB can be explained simply by the availability of Adagen.

Case Report

The case report was provided in Docket document 2006-D-0157-DRAFT-0078. It is a published report (Jaing and Lee et al. 2006) of an infant with SCID who received unrelated UCB transplantation at just over 5 months of age.

The male infant was admitted at 5 months of age with a diagnosis of SCID. He had hypogammaglobulinemia and lymphopenia, with T cell count of 6/mm^3 and B cell count of 291/mm^3. He had a mutation of the IL-2 common γ-chain. His medical history included E. coli UTI at 3 months and oral candidiasis at 4 months. On admission he had P. carinii pneumonia and evidence of disseminated BCG disease (he had been vaccinated at 3 days of age). He received UCB transplant with 2 mismatches at a dose of 3.5 x 10^7 nucleated cells/kg and 3 x 10^5 CD34 cells/kg. Following transplant he had 20-30% donor chimerism, increased lymphocyte counts of 819 T cells/mm^3 and 228 B cells/mm^3, and normal immune responses. He had acute grade I GVHD involving the skin that responded to topical steroids. At 14 months post-transplant, he was reported in "very good clinical condition without medications."

The report of all deaths "within the first months of life" for untreated patients reviewed by Hitzig (Hitzig and Kenny 1978) was mentioned above. While it did not provide specific data, both that experience and that of Stephan (Stephan and Vlekova et al. 1993) appear to be highly incompatible with any patient being in "very good clinical condition without medication" at 14 months of age.

6.4.5 Analysis of Secondary Endpoint(s)

The potential to substantiate claims for clinical benefits other than survival was not evaluated because no disease-specific outcome data were included in the Docket datasets. The case report reviewed above included information on immune status, but that cannot be directly corroborated with the Docket datasets.

6.4.7 Subpopulations

Of the 47 patients with SCID, gender and race data were not recorded for 25 (53%).

Although a univariate proportional hazards model identified a borderline significant relationship between age and survival (p = 0.053), no relationship (p = 0.48) was seen when excluding the patient with age coded as 17 years. In light of the questionable nature of the reported age, that patient was excluded for any subpopulation analyses involving age.

By proportional hazards analysis, none of the variables age (teenager excluded), gender, or race appeared to be related to survival outcome, either in univariate analyses, or in a multivariate analysis (n = 22) incorporating age, gender, race, and dose (p = 0.32 for age, p = 0.38 for gender, p = 0.51 for race, and p = 0.95 for dose in the multivariate analysis).

6.4.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A univariate proportional hazards model found no significant relationship between dose (as prefreeze TNC/kg) and survival (nominal p = 0.33) with an estimated 1.9% decrease in hazard for each increase of 10^7 TNC/kg. The relationship was slightly weaker with adjustment for age (teenager excluded). There was no patient with a dose < 2.5 x 10^7 TNC/kg. An analysis comparing patients with TNC doses above and below the median dose of 12.7 x 10^7 TNC/kg showed a trend toward improved survival for doses above the median, but the difference was not statistically significant (nominal log-rank p = 0.28).

6.4.10 Additional Efficacy Issues/Analyses

Published Reviews and Opinions

In a review of cord blood banking by an AAP Work Group (Work Group on Cord Blood Banking 1999), the summary of indications for allogeneic stem cell transplantation included “immune deficiency (e.g., severe combined immunodeficiency disease)” in the category of “effective.” Those conclusions were reflected in the 2005 IOM report on cord blood (Meyer and Hanna et al., 2005). The AAP review did not provide references to specific data in support of its determination, and the IOM report referenced studies in mice. The Cochrane Collaboration has not reviewed the use of stem cell transplantation in SCID.

A more recent review addressing the use of cord blood in SCID is found in Gennery and Cant 2007. The authors aggregated reports from several small case series and found a 77% survival in 30 SCID patients treated with UCB. The authors regarded the place of UCB in treating primary immunodeficiency disease as being well established.

6.5 Bone Marrow Failure – Fanconi Anemia (FA)

Fanconi anemia (FA) is a mostly autosomal recessive genetic disorder. Multiple genes have been associated with FA. The disease is subtyped into complementation groups depending on the gene involved. Primary clinical features include anemia and eventual bone marrow failure. Patients also have limb and organ malformations and are at increased risk for leukemia and other neoplasms. The common mechanistic feature is defective production of a multiprotein complex that has a role in a pathway involved in DNA repair. Diagnosis is made on the basis of a test for abnormal cellular response to DNA damage. Based on data from an international registry (Auerbach 2009), hematologic abnormalities manifest at a median age of 7 years, and the incidence of bone marrow failure rises over time, reaching 90% by age 40.

There is no approved drug or biologic therapy for Fanconi anemia.

6.5.1 Methods

Efficacy was evaluated by computing estimates for post-transplant survival obtained from pooling the three datasets described in Section 5.1. Results were compared to historical control survival data obtained from the literature. The literature was reviewed for additional reports of experience with unrelated cord blood use in FA.

In the Docket datasets, diagnostic information other than the diagnosis of Fanconi anemia was not provided. Thus, eligibility criteria for the series and the criteria for classification of the phenotype are unknown. There was no explicit representation of a patient's hematologic status at the time of UCB transplantation. Information on disease-specific outcomes that might have been of interest, such as blood counts or bone marrow analysis, was not provided.

6.5.2 Demographics

Basic demographics for the FA patients in pooled datasets are shown below, together with basic treatment data. Demographic information other than age was not provided in the NYBC dataset, from which most of the cases came.

Table 15: Demographics and Treatment Data for Patients with Fanconi Anemia – Docket Data

Total N	39
Age in Years	
Mean (SD)	8.3 (3.2)
Median (Range)	8 (3 – 15)
Gender	
Male	5% (2)
Female	18% (7)
Unknown	77% (30)
Race	
Caucasian	15% (6)
African/African-American	3% (1)
Hispanic	3% (1)
Unknown	79% (31)
Dosing (TNCx10^7/kg prefreeze)	
Median	4.5
10^{th}, 25^{th}, & 75^{th} percentiles	1.3, 2.8, 7.6
Dose < 2.5	23% (9)
HLA Match	
6/6	15% (6)
5/6	31% (12)
4/5	44% (17)
3/6	8% (3)
Unknown	3% (1)
Data source	
NMDP	23% (9)
NYBC	77% (30)

Figure 28: Age Distribution of Fanconi Anemia Patients – Docket Data

6.5.3 Subject Disposition

Of the 39 total patients with Fanconi anemia, 28 are reported to have died. The causes of death are listed in the table below:

Table 16: Causes of Death in Fanconi Anemia Patients – Docket Data

	N
Infection	13
Pulmonary disease	5
Acute GVHD	2
Veno-occlusive disease	2
Multi-organ failure	2
GI hemorrhage	1
Unknown	3

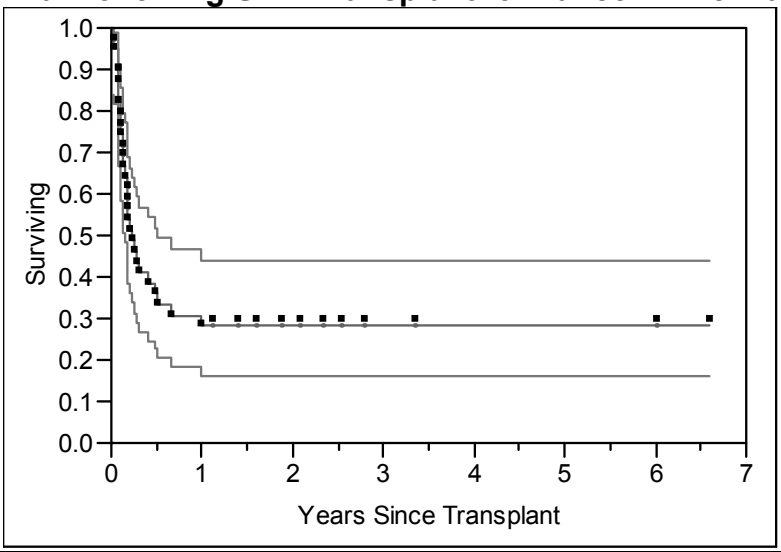
There were 8 patients who received a second transplant. All died within the first year following the initial UCB transplant.

6.5.4 Analysis of Primary Endpoint(s)

Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown in Figure 29 below for the 39 FA patients in the Docket datasets. The estimated mortality is about 64% in the first 6 months and 72% by the end of the first year, so that the probability of survival plateaus at 28% after a year. The numbers at risk at 3 years and beyond is low. Median follow-up was 0.2 years.

Figure 29: Survival Following UCB Transplant for Fanconi Anemia – Docket Data

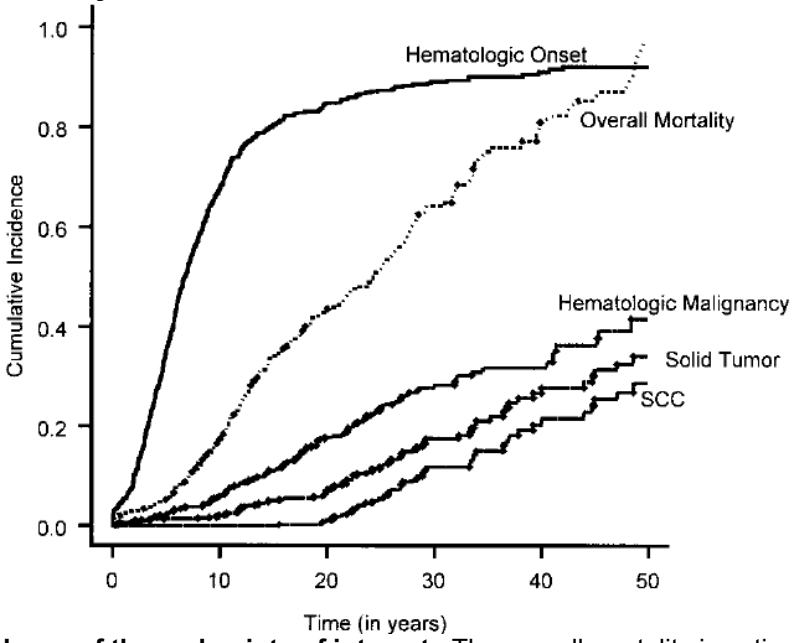


Year	0	0.5	1	2	3	4	5	6
Survival	1.00	0.36	0.28	0.28	0.28	0.28	0.28	0.28
No. at Risk	39	14	11	7	3	2	2	2

Historical Experience

The International Fanconi Anemia Registry (IFAR) was established in 1982 and is the only substantial source of historical data regarding FA. In the most recent analysis of survival data from IFAR, Kutler reported on 754 FA patients followed for a median of 10.6 years (Kutler and Singh et al. 2003). A graphic showing overall mortality is reproduced in Figure 30. The mortality is approximately linear with age, rising at a rate of about 2% per year.

Figure 30: Mortality and Other Outcomes in Fanconi Anemia Patients – IFAR



Cumulative incidence of the end points of interest. The overall mortality is estimated by means of the Kaplan-Meier method. Overall survival rate is 1 – overall mortality rate. The cumulative incidence of all the other end points are calculated by treating death as a competing cause of risk. [SCC = squamous cell carcinoma, Hematologic Onset = plt < $100x10^9$/L, Hgb < 10 g/dL, or ANC < $1x10^9$/L]
Source: Kutler and Singh et al. 2003

The article provided a display of only overall mortality, regardless of bone marrow status or transplant history, but the results of some additional analyses were reported. A subset of 593 patients experienced bone marrow failure (BMF), which was defined in that study as plt < 100 x 10^9/L, Hgb < 10 g/dL, or absolute neutrophil count (ANC) < 1 x 10^9/L. Of this group, 219 received HSCT. However, 4 who had no follow-up after receiving HSCT were not included, leaving 215 HSCT patients with follow-up. Using a Cox regression of the time-dependant covariate for HSCT, the hazard ratio for HSCT was estimated to be 5.0 (95% CI 3.8 – 6.6) in a multivariate model incorporating sex and complementation group (Table 17).

Table 17: Overall Survival Time in the Subgroup of FA Patients with BMF, multivariate results (Cox proportional hazards model)

Variable	No. patients	Hazard ratio (95% CI)	P
Group			
A/G	212	1.0†	NA
C	72	1.7 (1.2-2.6)	.007
Nontyped*	305	1.5 (1.2-2.1)	.004
Sex			
Female	290	1.0†	NA
Male	299	1.3 (1.0-1.7)	.06
HSCT	589	5.0 (3.8-6.6)	< .0001

N/A indicates not applicable
* Complementation group unknown
† Baseline
Source: Kutler and Singh et al. 2003

Reviewer's Comments:
While the IFAR results of Kutler and Singh seem to indicate a greatly increased risk associated with HSCT, their criteria of BMF are less stringent that those used by other authors to define severe aplastic anemia. Since the fraction of patients receiving HSCT was only 37% of the total defined as having BMF, it is quite possible that that the results of the survival analysis reflect the possibility that going on to receive HSCT is a marker for disease progression or worsening prognosis. Even if a therapy has a moderate benefit, its selective administration to the sickest patients could give rise to a paradoxical result of apparent harm in an epidemiologic study such as this. Further, early experience in HSCT for FA showed that these patients do poorly unless they have a reduced-intensity conditioning regimen; some fraction of the patients in this study may not have received the currently recommended regimen. The report does not provide enough additional data to be able to evaluate these possibilities. The findings from Kutler need to be interpreted cautiously, but they do seem to run counter to the notion that the HSCT treatment could be expected to provide a dramatic sustained survival benefit in most patients.

On a visual basis, the 72% one-year mortality observed in the docket datasets well exceeds the mortality in FA over even a decade for the first 30 or 40 years of life as reported from the IFAR experience. However, a much more relevant comparison would be against patients in the IFAR database after they had developed a severity of bone marrow failure that would make them transplant candidates. The available data do not accommodate that analysis. The closest approximation to doing such a comparison is the hazard analysis reported by Kutler, which suggested harm rather than benefit from HSCT, but which is not specific to UCB and which is subject to the difficulties in interpretation as noted above.

6.5.5 Analysis of Secondary Endpoint(s)

The potential to substantiate claims for clinical benefits other than survival was not evaluated because no other disease-specific outcome data were included in the Docket datasets.

6.5.7 Subpopulations

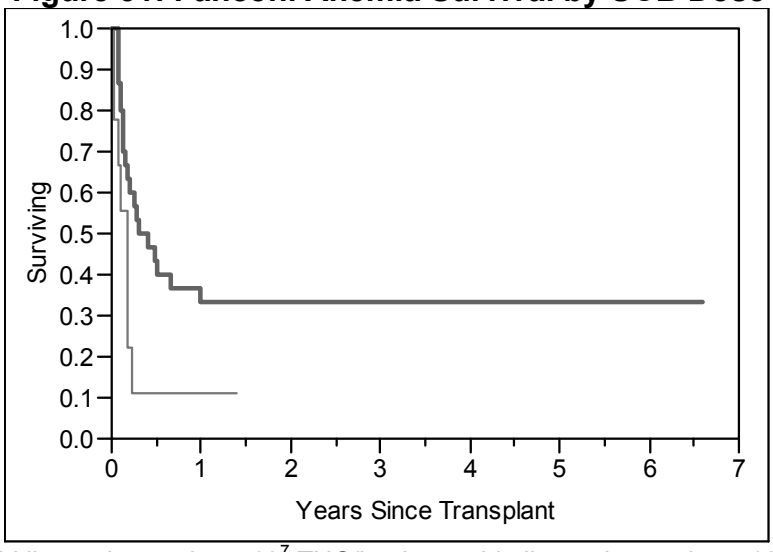
Of the 39 patients with Fanconi anemia, gender was not recorded for 30 (77%) and race was not recorded for 31 (79%).

By proportional hazards analysis, none of the variables age, gender, or race appeared to be related to survival outcome, either in univariate analyses, or with adjustment for dose. In a multivariate analysis incorporating age, gender, and race (n = 9, due to missing data), none of the variables had a significant relationship with survival outcome ($p > 0.40$ for all). (A multivariate analysis that also included dose could not be performed due to numerical instability).

6.5.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A proportional hazards model found a relationship between TNC dose and survival with an estimated 15% ± 6% (SE) decrease in hazard for each increase of 10^7 TNC/kg (nominal $p = 0.013$). There were 9 patients with a dose $< 2.5 \times 10^7$ TNC/kg. An analysis comparing these 9 patients to those with TNC doses ≥ 2.5 showed decreased survival (11% at 3 months) with the lower dose (nominal log-rank $p = 0.036$), but the survival experience with the higher dose was similar to that of the overall group (Figure 31). An analysis comparing patients with TNC doses above and below the median dose of 4.5×10^7 TNC/kg showed a trend toward improved survival for doses above the median, but the difference was not statistically significant (nominal $p = 0.14$)

Figure 31: Fanconi Anemia Survival by UCB Dose



Upper solid line = dose ≥ 2.5 x 10^7 TNC/kg, lower thin line = dose < 2.5 x 10^7 TNC/kg.

6.5.10 Additional Efficacy Issues/Analyses

Published Reviews and Opinions

In a review of cord blood banking by an AAP Work Group (Work Group on Cord Blood Banking 1999), the summary of indications for allogeneic stem cell transplantation included "aplastic anemia and other cytopenias (not environmentally caused)" in the category of "effective." Those conclusions were reflected in the 2005 IOM report on cord blood (Meyer and Hanna et al., 2005). The AAP review did not provide references to specific data in support of that determination. The IOM report cited the primary sources for evidence in Fanconi anemia as several small case series and bone marrow transplant experience: Gluckman and Devergie et al. 1990, Kohli-Kumar and Shahidi et al. 1993, Aker and Varadi et al. 1999, Guardiola and Kurre et al. 2003, and Guardiola and Socie et al. 2004. More recent reviews addressing the use of cord blood in Fanconi anemia are found in Smith and Wagner 2009, which cites evidence in Gluckman and Rocha et al. 2007 and Wagner and Eapen et al. 2007 (although the latter reference specifically excludes consideration of cord blood). Review of the literature identified the following additional primary sources: Motwani and Lawson et al. 2005 and Ruggeri and Peffault de Latour et al. 2008. The Cochrane Collaboration has not conducted a review of the use of stem cell transplantation in Fanconi anemia.

Published experience with UCB for Fanconi anemia

Rubinstein and Carrier et al. 1998 (n=35)
This is a report of 562 patients who received UCB for a wide variety of conditions. While presumably based on the same dataset as the 562 patients submitted to the

Docket, the Docket dataset from NYBC has only 30 patients with Fanconi anemia. The article reports a cumulative event-free survival at 1 year of about 20% for Fanconi anemia but does not report the overall survival for that disease.

Motwani and Lawson et al. 2005 (U-UCB n=4)
This is a report of 7 children in the UK who received stem cell transplantation for FA. This included 4 patients, ages 5 to 10 years, who received fully matched, unrelated UCB. In one patient, the UCB was a second transplant after failure of initial BMT. All four who received UCB had engraftment with full donor chimerism. All were alive at least through 13 months, although one developed Evans syndrome and another developed an autoimmune hemolytic anemia.

Gluckman and Rocha et al. 2007 (U-UCB n=93)
This is a retrospective analysis of unrelated UCB transplantation in 93 patients with Fanconi anemia reported to the Eurocord Registry from 26 countries using a standardized questionnaire. Median age was 8.6 years. At the time of transplant, 87% had aplastic anemia, 9% had myelodysplastic syndrome, and 4% had acute leukemia. The HLA match was full in 13%, 1 mismatch in 38%, and 2 or 3 mismatches in 48%. Reduced-intensity conditioning regimens incorporating fludarabine were used for 61% of patients. Median follow-up was 22 months with a minimum of 3 months; only two patients were lost to follow-up. Overall survival at 1 year and beyond was 40% ± 5% (SE). In a multivariate analysis, the factors that were found to be favorably related to survival were negative CMV serology in the recipient, use of fludarabine in the conditioning regimen, and infused TNC ≥ 4.9×10^7/kg.

Ruggeri and Peffault de Latour et al. 2008 (U-UCB n=8)
Reports on 14 patients who received double cord transplants for bone marrow failure syndromes, including 8 with FA (of whom 2 had secondary acute leukemia). Age range was 7 to 24 years. Within 5 months, 5 of the 8 had died, including one with acute leukemia. The remaining 3 have been followed 10 to 19 months and have full donor chimerism.

Several other reports of UCB use for FA were identified in the literature but are not reviewed here in detail because the series was too small or the UCB was not unrelated: Gluckman and Broxmeyer et al. 1989 (n=1, sibling R-UCB); Gluckman and Devergie et al. 1990 (N=3, sibling R-UCB); Kohli-Kumar and Shahidi et al. 1993 (n=1, sibling R-UCB); Aker and Varadi et al. 1999 (n=1, sibling R-UCB); de Medeiros and Silva et al. 2001 (n=1); Yoshimasu and Tanaka et al. 2001 (n=1); Grewal and Kahn et al. 2004 (n=1, matched sibling R-UCB); Bielorai and Hughes et al. 2004 (n=1, matched sibling R-UCB);

Reviewer's Comment: Published literature in Fanconi anemia generally confirms a similarly high mortality following UCB transplant.

6.6 Bone Marrow Failure – (Acquired) Severe Aplastic Anemia (SAA)

For purposes of this section, severe aplastic anemia (SAA) is taken to connote diseases other than primary anemias. One definition of SAA was given by Camitta (Camitta and Thomas et al. 1976) and appears to be widely (but not universally) adopted:

> To qualify as severely aplastic, patients had to have at least two of the following three peripheral blood values: (1) granulocytes <500/cu mm (2) platelets <20,000/cu mm and (3) reticulocytes < 1% (corrected for hematocrit). In addition the marrow had to be either markedly hypoplastic (<25% of normal cellularity) or moderately hypoplastic (25%-50% of normal cellularity with < 30% of remaining cells being hematopoietic) as estimated from biopsies.

Other proposed definitions are closely similar but differ in using criteria for absolute reticulocyte count (Camitta and Thomas et al. 1979; Myers and Davies 2009) or in the marrow cellularity criteria (Howard and Naidu et al. 2004). SAA is a serious condition with a poor prognosis. Bleeding or infections can be the life-threatening complications, depending on the particular cytopenias. Prognosis may depend on the severity of the disease. Overviews of SAA often cite a general mortality of 20% by 1 year.

Atgam (lymphocyte immune globulin) is an immunosuppressive therapy (IST) approved in 1981 as treatment for patients with SAA who are unsuitable for bone marrow transplantation. Other immunosuppressive therapies (antithymocyte globulin and cyclosporine), while not FDA-approved for that purpose, are also used to treat SAA.

6.6.1 Methods

Efficacy was evaluated by computing estimates for post-transplant survival obtained from pooling the three datasets described in Section 5.1. Results were compared to historical control survival data obtained from the literature. The literature was reviewed for additional reports of experience with unrelated cord blood use in SAA.

In the Docket datasets, diagnostic information other than the diagnosis of SAA was not provided. Thus, eligibility and diagnostic criteria for the series are unknown. There was no explicit representation of a patient's hematologic status at the time of UCB transplantation. Information on disease-specific outcomes that might have been of interest, such as blood counts, bone marrow analysis, infections, or bleeding events was not provided.

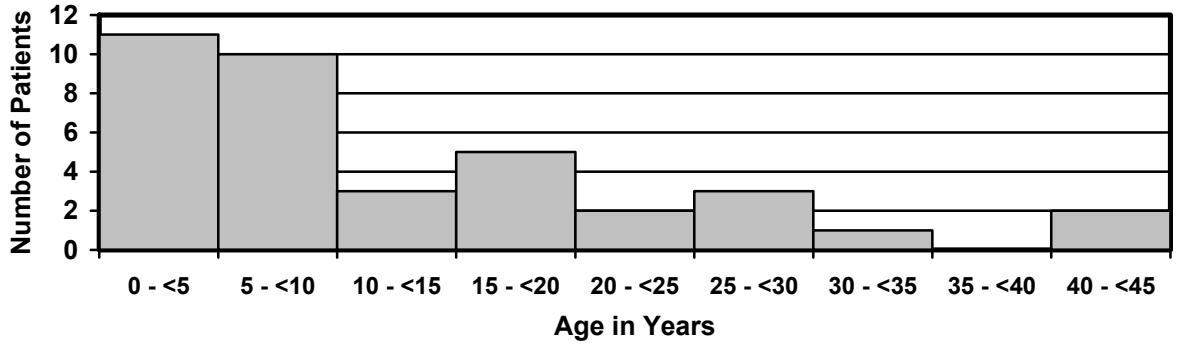
6.6.2 Demographics

Basic demographics for all the severe aplastic anemia (SAA) patients in pooled datasets are shown in Table 18 below, together with basic treatment data. Demographic information other than age was not provided in the NYBC dataset.

Table 18: Demographics and Treatment Data for Patients with SAA – Docket Data

Total N	37
Age in Years	
Mean (SD)	12 (11)
Median (Range)	7 (0 – 44)
Gender	
Male	27% (10)
Female	19% (7)
Unknown	54% (20)
Race	
Caucasian	32% (12)
African/African-American	8% (3)
Asian	5% (2)
Unknown	54% (20)
Dosing (TNCx10^7/kg prefreeze)	
Median	3.8
10^{th}, 25^{th}, & 75^{th} percentiles	1.8, 2.8, 5.5
Dose < 2.5	22% (8)
HLA Match	
6/6	3% (1)
5/6	43% (16)
4/5	43% (16)
3/6	5% (2)
2/6	3% (1)
Unknown	3% (1)
Data source	
NMDP	46% (17)
NYBC	54% (20)

Figure 32: Age Distribution of Severe Aplastic Anemia Patients – Docket Data



6.6.3 Subject Disposition

Of the 37 total patients with severe aplastic anemia, 24 are reported to have died. The causes of death were:

Table 19: Causes of Death in Severe Aplastic Anemia Patients

	N
Infection/Sepsis	8
Respiratory	5
Hemorrhage	3
GVHD	2
Multi-organ failure	2
Misc.*	4

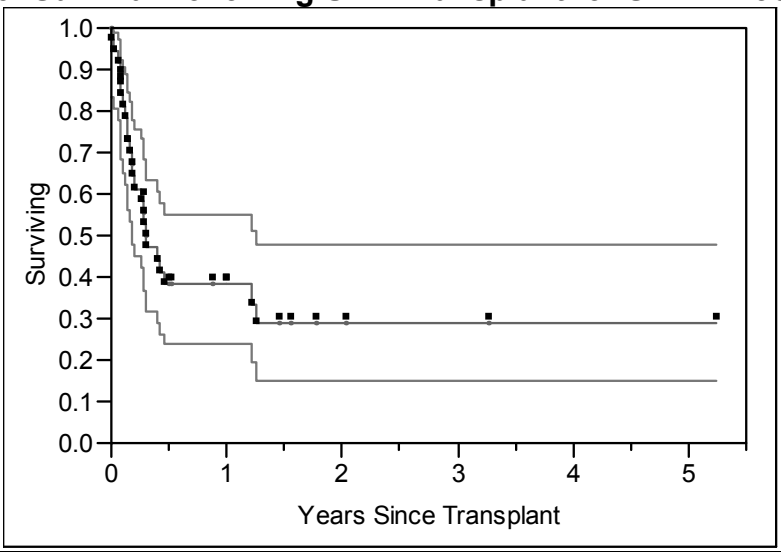
* Graft failure-1, "RECUR/RESDL LEUK"-1, other, unspecified-1, unknown-1.

6.6.4 Analysis of Primary Endpoint(s)

Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown in Figure 33 below for the 37 patients with SAA from the pooled docket datasets. The mortality is about 62% in the first 6 months. The probability of survival plateaus at 29% after 15 months, with the lower end of the confidence interval at 16%. Median follow-up was 0.3 years.

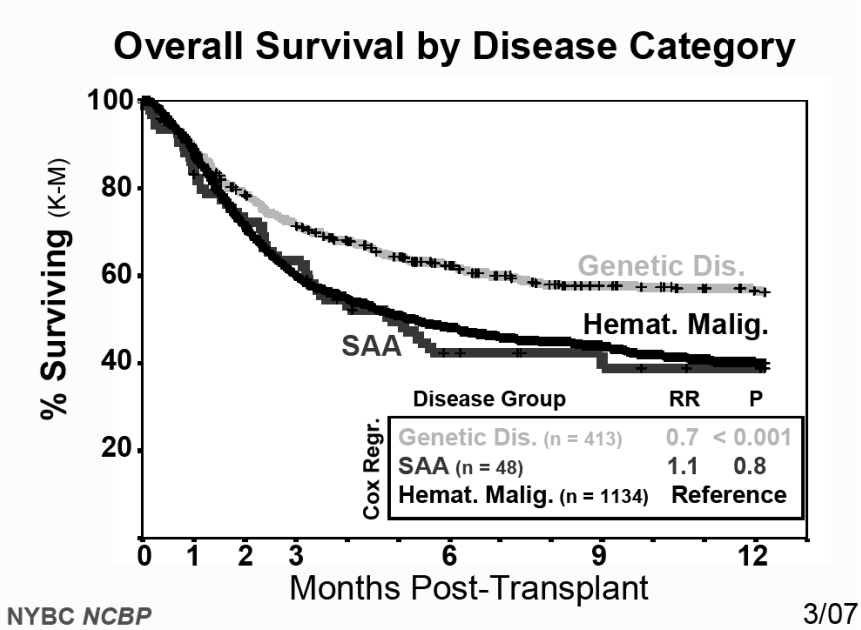
Figure 33: Survival Following UCB Transplant for SAA – Docket Data



Year	0	0.5	1	2	3	4	5	6
Survival	1.00	0.38	0.38	0.29	0.29	0.29	0.29	0.29
No. at Risk	37	13	8	3	2	1	1	1

A summary analysis of SAA that was submitted as one of the Docket documents is shown in Figure 34. The population used for the analysis presumably overlaps with patients represented in the dataset submitted to the Docket by NYBC (listed as item 2 under Section 5.1, above), but the NYBC dataset had only 20 cases with a diagnosis coded as "SAA," whereas the summary analysis included 48. The results of the summary analysis show slightly less than 40% survival after 1 year, which is higher than the 29% survival probability estimated from the analysis of the Docket pooled datasets shown in Figure 33.

Figure 34: Survival following SAA (& Other Conditions) following UCB – Summary Results Reported by NYBC



Source: (Docket document FDA-2006-D-0157-DRAFT-0064, -0065)

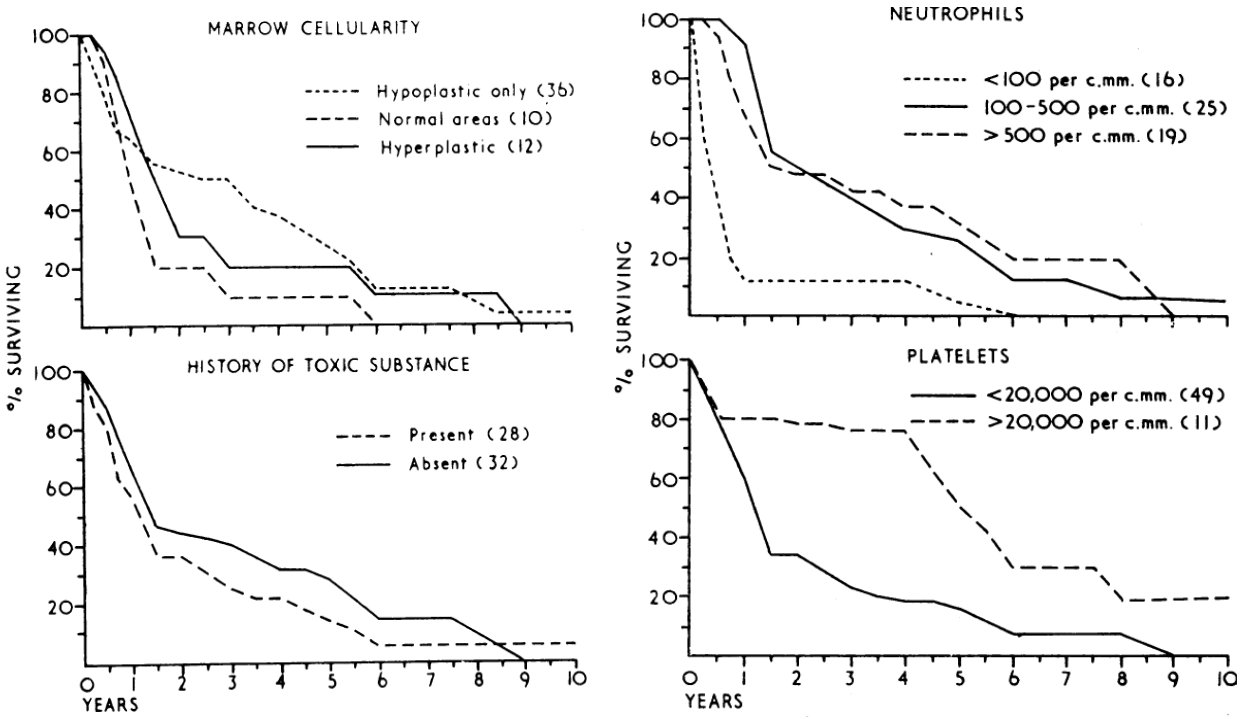
Historical Experience

In contrast to the conditions considered previously, there is a relative abundance of potential sources of historical survival data in SAA. There is, as well, variability in the reported survival experience. The earlier reports come close to providing data that can be regarded as reflecting natural history. Reports of large series published in the past decade have consisted of patients who have received immunosuppressive therapy (IST). While less like natural history, these historical data may still be relevant either for providing a germane control group in IST failures or for consideration in a risk/benefit assessment.

A series of 60 patients with acquired aplastic anemia was reported by Lewis in 1965 along with an analysis to identify prognostic factors. The exact diagnostic criteria were

not described. Given the date of the series, none is presumed to have received HSCT. A majority received steroid or anabolic hormones and intermittent transfusions.

Figure 35: Survival in 60 Patients with Acquired Aplastic Anemia – Lewis 1965

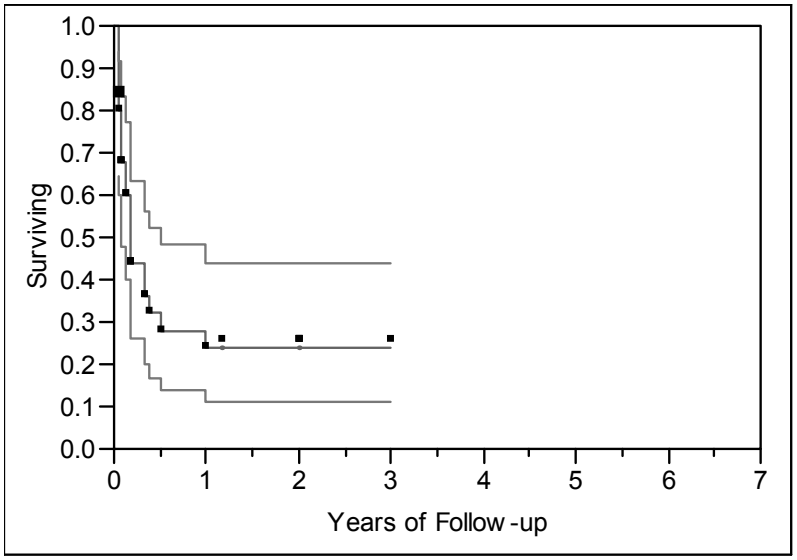


Source: Lewis 1965

The report illustrated how prognosis can vary depending on cell counts. Overall survival appeared to be 55% to 65% at 1 year and 35% to 45% at 2 years.

In 1972 Davis reported on a series of 25 patients with acquired aplastic anemia (Davis and Rubin 1972). Data were tabulated, but survival analysis was not presented. The report states that "Six patients received allogeneic bone marrow infusions without sustained benefit." Transcribing from the tabulated data, this Reviewer was able to present the outcomes for the 19 untransplanted patients as a survival analysis, which is presented in Figure 36. The survival at 1 year is estimated to be approximately 24%.

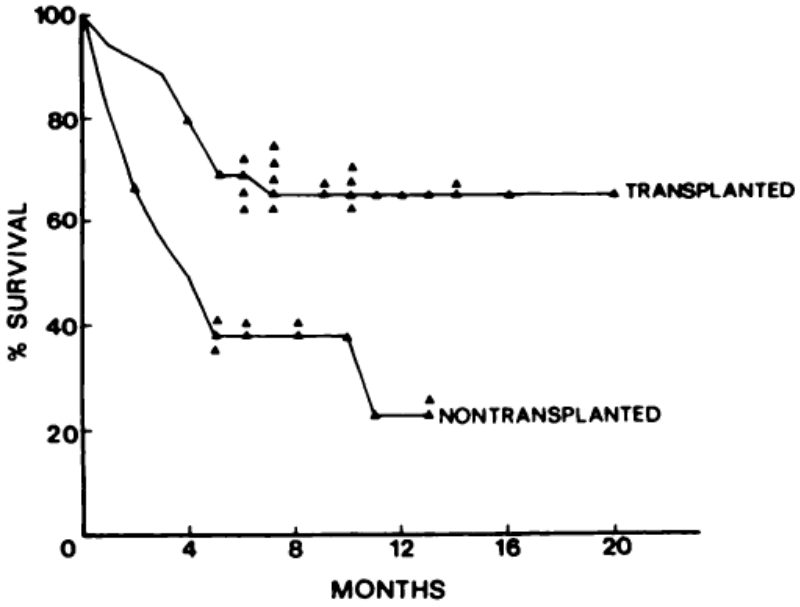
Figure 36: Survival of 19 Untransplanted Patients with Aplastic Anemia – Davis 1972



Source: Reviewer's graph of published tabulated data in Davis and Rubin 1972

Camitta presented a prospective study of 67 patients with SAA randomized to BMT according to the availability of a matched sibling (Camitta and Thomas et al. 1976). In the study, there were 31 patients who were not transplanted. The 1-year survival in the latter group was just over 20%, and survival was statistically significantly better in the transplanted group.

Figure 37: Life Table Plot of the Effect of Sibling BMT on Survival in SAA – Camitta 1976

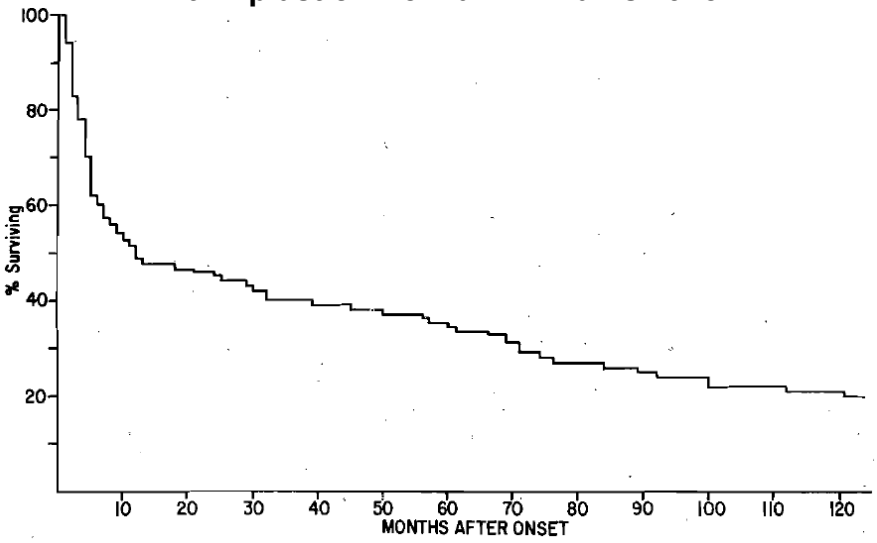


Life table plot of the effect of treatment on survival in severe aplastic anemia. Triangles indicate duration of follow-up of current survivors.

Source: Camitta and Thomas et al. 1976

In a study of 101 patients with aplastic anemia seen in Utah between 1944 and 1972 (Williams and Lynch et al. 1978) the 1-year survival was about 50%. The use of HSCT was not described.

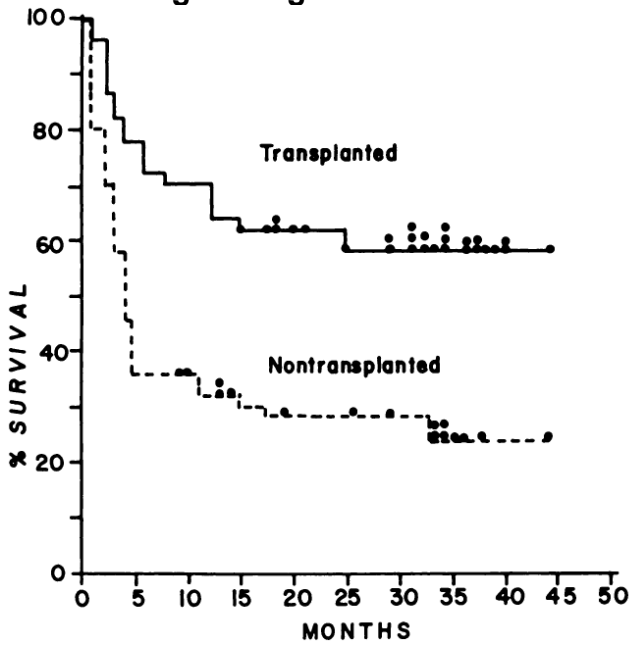
Figure 38: Survival after the Onset of Symptoms in 101 Patients with Aplastic Anemia – Williams 1978



Source: Williams and Lynch et al. 1978

In what appears to be an extension of the study reported in 1976, Camitta reported on a larger series of patients prospectively “randomized” to BMT based on availability of a matched sibling (Camitta and Thomas et al. 1979). The analysis appears to show a substantial improvement in survival for the 43 transplanted patients compared to 63 untransplanted patients. In that series, the untransplanted 1-year survival appeared to be slightly greater than 30% (Figure 39), which was within the range of the previous historical results.

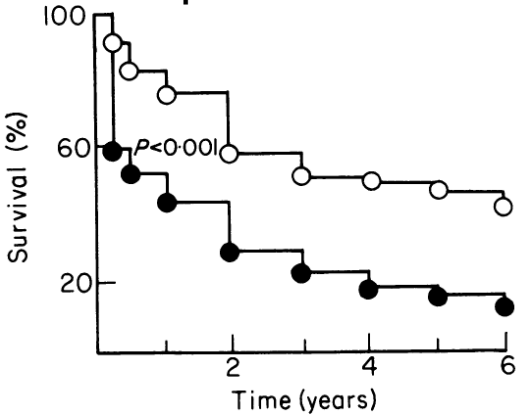
Figure 39: Survival Following Sibling BMT or No BMT in SAA – Camitta 1979



Source: Camitta and Thomas et al. 1979

A series of patients in England with SAA, excluding FA, was reported by Mir; none was treated with HSCT (Mir and Geary 1980). Exact diagnostic criteria were not stated. In the subset of 55 patients with the more severe disease, as judged by cell counts and speed of onset, the 1-year survival was close to 50%.

Figure 40: Survival in Aplastic Anemia Patients – Mir 1980



Patients were allocated in the 2 groups on the basis of the speed of onset of illness and the initial hemoglobin and platelet values. Patients in the smaller group of 55 [filled circles] had a rapid onset, lower hemoglobin and platelet values at diagnosis and an acute course.
Source: Mir and Geary 1980

In 1989 Halperin (Halperin and Grisaru et al. 1989) reported on a series of 34 children with acquired SAA (diagnosed by standard criteria) treated at Toronto, of whom 20 did not receive HSCT but had either immunosuppression or supportive care (consisting of transfusions and antimicrobial agents; these were patients diagnosed prior to availability of antithymocyte globulin). The 8 who had only supportive care had estimated survival through 2 years of about 25%.

Figure 41: Survival in Children with SAA – Halperin 1989

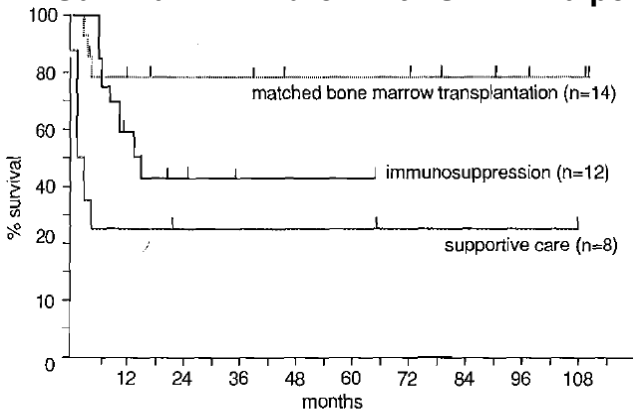


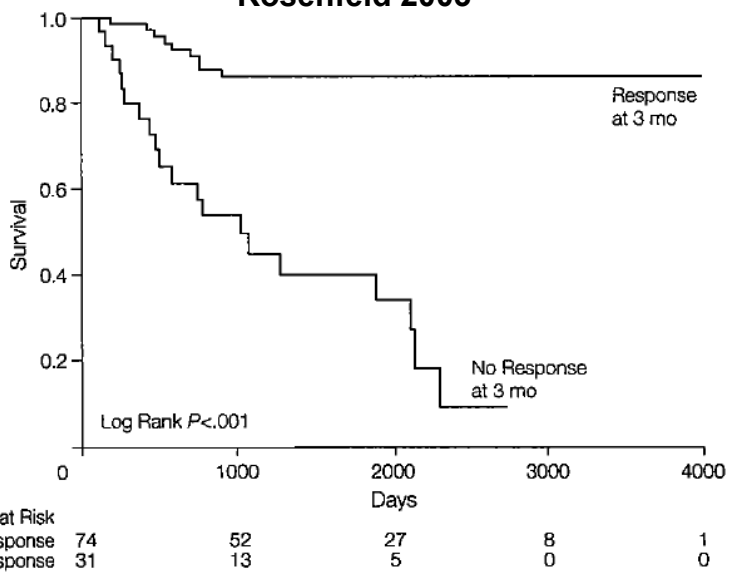
FIG. 1. Survival curves for children with severe acquired aplastic anemia treated with allogeneic histocompatible bone marrow transplantation, immunosuppression with antithymocyte globulin and/or high-dose corticosteroids, or supportive care. Ticks indicate latest follow-up examination of each patient.

The available natural history data for aplastic anemia were reviewed by Heimpel (Heimpel 2000), who reported median survival ranging from 10 months, in a series of

101 cases seen from 1944 to 1973 (Williams and Lynch et al. 1978), to 20 months in his series of 70 patients through 1974. In the subset of his patients meeting criteria for severe, median survival was only 10 months. His review of more recent series found median survival of 20 to 60 months. A significant fraction of remissions in acquired SAA were reported when patients were treated with antithymocyte globulin (Sanchez-Medal and Gomez-Leal et al. 1969).

Rosenfeld and Follmann et al. 2003 reported on 122 patients who received immunosuppressive therapy (IST) in the form of antithymocyte globulin and cyclosporine in a study at NIH. At 1 year, 58% responded, and the 7-year overall survival was 55%. In the subgroup that did not respond to IST by 3 months, the 5-year survival was 40%, compared to 86% in the IST responders (Figure 42).

Figure 42: Survival in SAA in Patients Not Responding to Antithymocyte Globulin – Rosenfeld 2003



Overall survival of 122 patients with severe aplastic anemia treated with antithymocyte globulin and cyclosporine; median follow-up was 7.2 years. Recovery defined by blood count no longer satisfying severity criteria.
[There was 13% mortality prior to the 3-month evaluation. Four non-responders have matched, unrelated BMT; all died. Three responders had matched, related BMT; one survived.]
Source: Rosenfeld and Follmann et al. 2003

In 2009 Scheinberg (Scheinberg and Wu et al. 2009) reported the results of a prospective, randomized trial of standard immunosuppressive regimen (antithymocyte globulin plus cyclosporine) with or without the addition of sirolimus for 77 patients older than 2 years meeting the criteria for SAA (using marrow cellularity < 30%). The study excluded those with Fanconi anemia, prior immunosuppressive therapy, HIV seropositivity, underlying clonal disorder, or other significant comorbidity. The 3-year survival was 90% or better in each group (Figure 43).

Figure 43: Survival in Immunosuppressive Trial for SAA – Scheinberg 2009

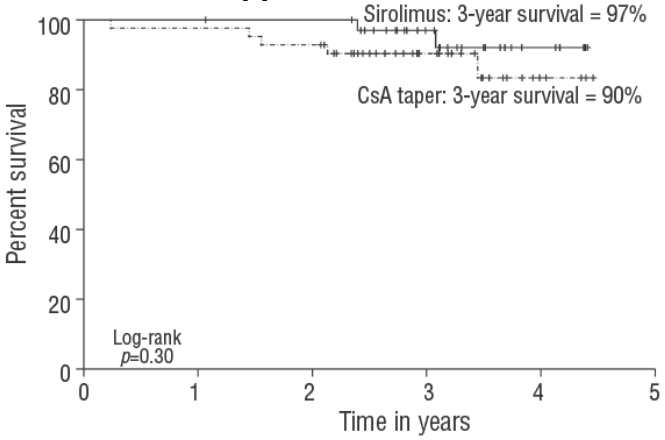
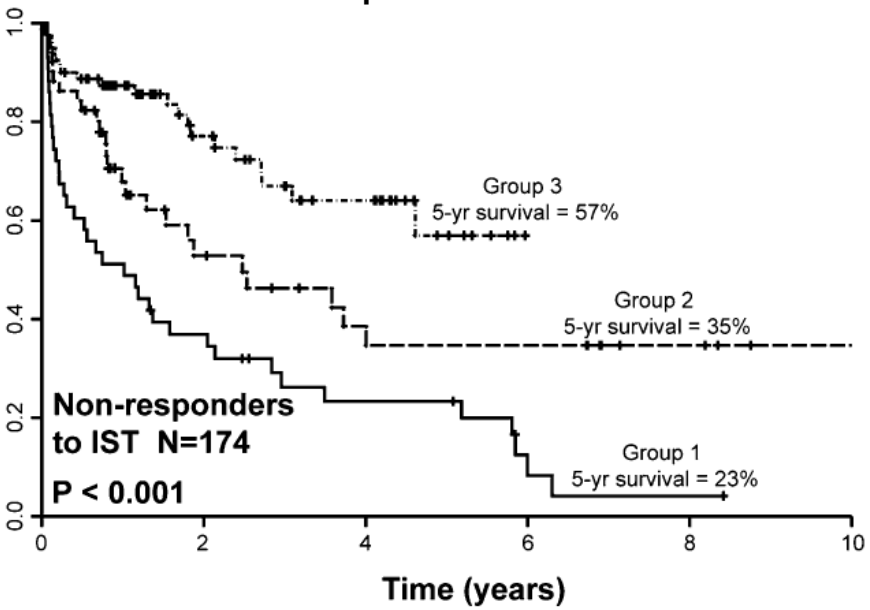


Figure 3. Overall survival for patients in the h-ATG/CsA/sirolimus (solid line) and h-ATG/CsA taper arm (dotted line). Patients who underwent hematopoietic stem cell transplantation were censored at the time of transplantation.

Source: Scheinberg and Wu et al. 2009

Most recently, Valdez (Valdez and Scheinberg et al. 2011) reported on changes over the preceding 20 years in survival for patients who were not responsive to immunosuppressive therapy, and presented survival curves censored by HSCT (Figure 44). In the most recent cohort (Group 3, 2002 – 2008), the 5-year survival was 57%.

Figure 44: Survival in IST Non-Responders in Past Two Decades – Valdez 2011



Survival probability for patients not responding to immunosuppressive therapy. Group 1 = 1989–1996, Group 2 = 1996–2002, Group 3 = 2002–2008. Survival is censored at time of hematopoietic stem cell transplant.
Source: Valdez and Scheinberg et al. 2011

Reviewer's Comments:
The experience with severe aplastic anemia in the datasets provided in the Docket do not demonstrate post-transplant survival that improves meaningfully upon the experience of untransplanted patients as found in the literature.

The survival experience for SAA in the docket datasets (38% survival at 1 year, 29% at 2 years) or from the summary data submitted to the docket (40% at 1 year) appears to fall in the lower part of the range of outcomes seen in the earlier historical data. Although the analysis reported by Camitta (Figure 39) suggest effectiveness of BMT in improving survival, the docket experience for UCB more closely resembled the No BMT group from that report. The docket survival experience also appears inferior to that reported for SAA patients who have not responded to IST.

6.6.5 Analysis of Secondary Endpoint(s)

The potential to substantiate claims for clinical benefits other than survival was not evaluated because no other disease-specific outcome data were included in the Docket datasets.

6.6.7 Subpopulations

Of the 37 patients with SAA, gender and race data were not recorded for 20 (54%).

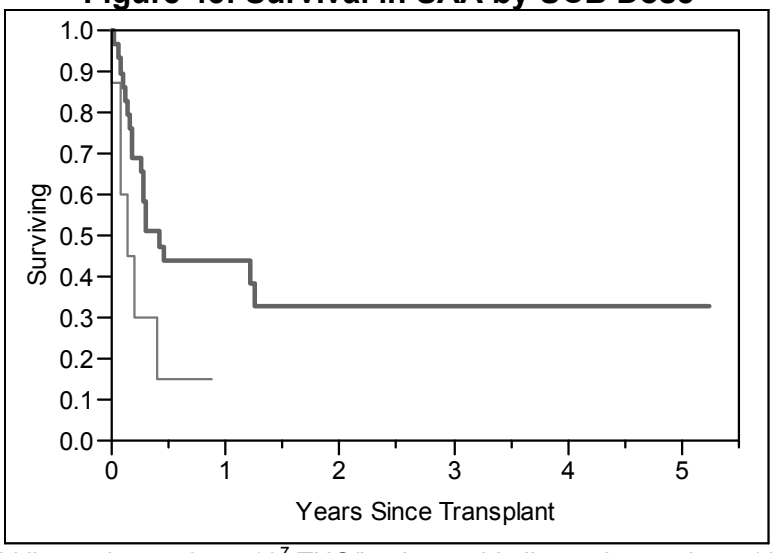
By proportional hazards analysis, neither gender nor race appeared to be related to survival outcome, either in univariate analysis or when adjusted for dose. In a univariate analysis, age appeared to increase the hazard by 3.5% ± 1.6% (SE) per year of age (nominal p = 0.044), but the relationship diminished substantially when adjusted for dose (hazard coefficient of 2.1% per year of age, p = 0.30). (See also discussion in Section 6.6.8 below.)

In a multivariate analysis (n = 17) incorporating age, gender, race, and dose, none of the variables was statistically significantly related to survival outcome (p = 0.78 for age, p = 0.21 for gender, p = 0.91 for race, and p = 0.15 for dose in the multivariate analysis).

6.6.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A proportional hazards model using the docket datasets found a significant relationship between TNC dose and survival, with an estimated 15% ± 8% (SE) decrease in hazard for each increase of 10^7 cells/kg (nominal p = 0.021). There were 8 patients with a dose < 2.5 x 10^7 TNC/kg. An analysis comparing these 8 patients to those with TNC doses ≥ 2.5 x 10^7 TNC/kg showed a trend toward decreased survival (15% at 5 months) with the lower dose (nominal log-rank p = 0.0620), but the survival experience with the higher dose was similar to that of the overall group (Figure 45). An analysis comparing patients with TNC doses above and below the median dose of 3.8 x 10^7 TNC/kg found no statistically significant difference and showed similar survival curves for both groups through the first year (after which numbers at risk were too small for meaningful comparison).

Figure 45: Survival in SAA by UCB Dose



Upper solid line = dose ≥ 2.5 x 10^7 TNC/kg, lower thin line = dose < 2.5 x 10^7 TNC/kg.

Age and dose were inversely related. In a proportional hazards model incorporating both age and dose, there was a relationship to survival outcomes overall (nominal p = 0.40), but neither variable was significantly related to survival outcome after adjustment for the other (p = 0.12 for dose, p = 0.30 for age). In that model, the estimated effect of dose was a reduction in hazard of 11% ± 8% (SE) per 10^7 TNC/kg. Although the relationship to survival outcomes is statistically slightly stronger for dose than for age, observational data such as these cannot identify the causative factor(s), if any, underlying the apparent relationships.

6.6.10 Additional Efficacy Issues/Analyses

Published Reviews and Opinions

In a review of cord blood banking by an AAP Work Group (Work Group on Cord Blood Banking 1999), the summary of indications for allogeneic stem cell transplantation included "aplastic anemia and other cytopenias (not environmentally caused)" in the category of "effective," and those conclusions were reflected in the 2005 IOM report on cord blood (Meyer and Hanna et al., 2005). The AAP review did not provide references to specific data in support of that determination. However, this category of diseases appears to exclude acquired aplastic anemia, and SAA is not otherwise addressed. The Cochrane Collaboration has not reviewed the use of stem cell transplantation in aplastic anemia; however, a report on that topic is in the protocol stage.

Published experience with UCB in SAA

Search of the literature identified the following additional experience with UCB in SAA:

Rubinstein and Carrier et al. 1998 (n=21)
This is a report of 562 patients who received UCB for a wide variety of conditions. While presumably based on the same dataset as the 562 patients submitted to the Docket, the Docket dataset from NYBC analyzed above has only 20 patients with Fanconi anemia. The article reports a cumulative event-free survival at 1 year of about 20% after UCB transplant for SAA but does not report overall survival.

Mao and Wang et al. 2004 (n=6)
This appears to be a report of the first six patients subsequently reported in Mao and Zhu et al. 2005, described below.

Mao and Zhu et al. 2005 (n=9)
This is a report of 9 adults in China transplanted with UCB for SAA. Average age was 25 years. All had failed one course of immunosuppressive therapy. Conditioning regimen used cyclophosphamide and antithymocyte globulin. Dose ranged from 1.9 to 4.4 x 10^7 per unit MNC/kg post-thaw [MNC not defined]; 6 patients received two units.

In patients who received two units, only one of the two engrafted. At a median follow-up of 32 months, 7 patients (78%) were alive.

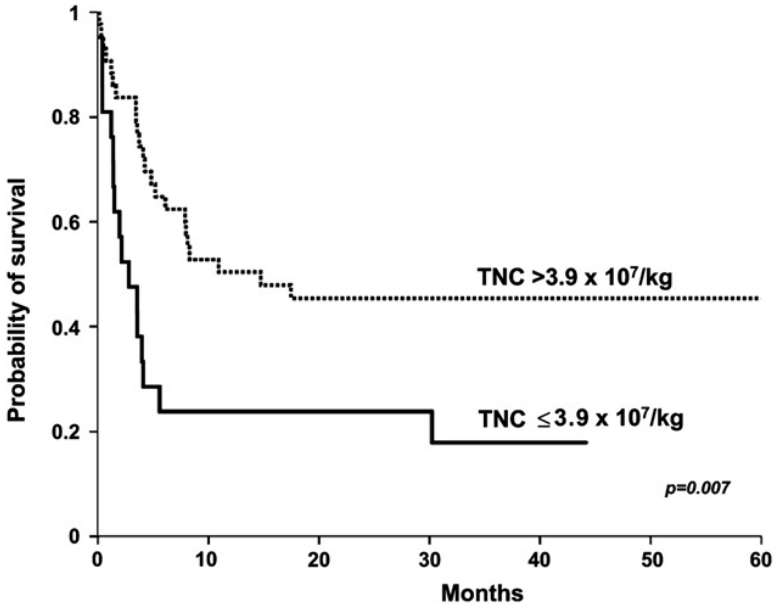
Chan and McDonald et al. 2008 (n=9)
This is a report of 9 children treated with UCB for SAA in Texas. Median age was 9 years. All had failed at least on course of immunosuppressive therapy. Three did not engraft with the first transplant, but two of those were engrafted after a second transplant. With a median follow-up of 34 months, 7 patients (78%) remained alive.

Yoshimi and Kojima et al. 2008 (n=31)
This is a report of 31 patients in Japan with SAA who received UCB as their initial stem cell transplant. Median age was 27 years (range 0.9 – 72). There were 25 who had previous immunosuppressive therapy. A variety of conditioning regimens were used. At a median follow-up of 34 months, 13 were alive, with an estimated 2-year overall survival of 41% (95% CI: 24% – 58%).

Jaing and Huang et al. 2011 (n=5)
This was a retrospective review of 5 children aged 3.8 to 16 treated with unrelated UCB for relapsed or refractory SAA after failing one or more courses of IST. Median time since diagnosis was 16 months. Conditioning used fludarabine, cyclophosphamide, and antithymocyte globulin. The TNC dose was at least 3.7×10^7 for four patients. All patients were alive and transfusion independent at a median follow-up of 25 months (range 7 to 34), but one subsequently received sibling UCB transplant and one had autologous recovery.

Peffault de Latour and Purtill et al. 2011 (n=71)
This is a retrospective analysis of 71 patients with SAA reported to Eurocord from 32 centers. The age range was 2 to 68 years with a median of 13 years; 61% were under 18. Of the 71, 13% had a diagnosis of paroxysmal nocturnal hematuria. Conditioning regimen was reduced intensity in 68%, with 46% being fludarabine-based. Double cord transplantation was given to 19%. For the single-cord transplants, HLA match was 6/6 for 10%, 5/6 for 33%, 4/6 for 51%, and 3/6 for 6%. Median follow-up was 35 months with a minimum of 8 months. The 3-year overall survival was 38% ± 6% (SE). In a multivariate analysis, only prefreeze TNC dose > 3.9×10^7/kg was associated with improved survival (Figure 46). (The dose cut point was selected after analysis of the data.)

Figure 46: Survival in SAA Following UCB Transplantation from Eurocord Registry – Peffault de Latour 2011



Estimated 3-year OS according to TNC dose

Source: Peffault de Latour and Purtill et al. 2011

The discussion in the article notes:

> The results of well-designed prospective trials, like one currently underway in France, which incorporate the requirement of a large cell dose and hopefully demonstrate better OS [overall survival], are needed before including UCBT [unrelated cord blood transplantation] in the treatment strategy for SAA can be recommended." (Peffault de Latour and Purtill et al. 2011)

Yamamoto and Kato et al. 2011 (n=12)

This is a report of 12 consecutive adult patients in Japan treated with UCB for SAA, of which 6 were very severe and 2 were fulminant. All but the fulminant cases had failed to respond to immunosuppressive therapy. All patients received a reduced-intensity conditioning regimen. Two of the very severe cases died; the remaining patients are alive at a median of 36 months. The estimated 3-year overall survival is 83%.

Several other reports of UCB use for SAA were identified in the literature but are not reviewed here in detail because the series was too small or the UCB was not unrelated: Shaw and Haut et al. 1999 (n=3); Fruchtman and Hurlet et al. 2004 (n=1, autologous UCB); Ohga and Ichino et al. 2006 (n=1); Tajika and Mizuki et al. 2007 (n=2); Kosaka and Yagasaki et al. 2008 (n=2 among a much larger group receiving BMT); Stepensky and Revel-Vilk et al. 2008 (n=1, related UCB + BMT); Lee and Kang et al. 2009 (n=1); Kang and Lee et al. 2010 (n=1).

6.7 Beta Thalassemia

Beta thalassemia is a congenital disorder of hemoglobin production due to a mutation affecting beta-globin synthesis. In the severe form, beta thalassemia major, patients present with severe anemia in the first year of life. They are dependent on regular blood transfusions for survival, typically 1 to 3 units every 3 to 5 weeks. Iron overload is a complication of treatment. Although approved chelation therapy is available, compliance is difficult, and heart, liver, and endocrine damage from iron overload are common complications. Patients often die in the middle decades.

For patients being considered for bone marrow transplantation, prognosis following transplant is associated with the Pesaro classification, which is a scoring system based on hepatomegaly, liver fibrosis, and regularity of chelation therapy (Lucarelli and Galimberti et al. 1990). Class 1 represents the best prognosis, and Class 3 is the worst.

6.7.1 Methods

Efficacy was evaluated by computing estimates for post-transplant survival obtained from pooling the three datasets described in Section 5.1. Results were compared to historical control survival data obtained from the literature. The literature was reviewed for additional reports of experience with unrelated cord blood use in beta thalassemia. Review of reasonably well documented case reports in the Docket was also contributory.

In the Docket datasets, diagnostic information other than the diagnosis of beta thalassemia was not provided. Thus, eligibility criteria for the series and clinical status at time of transplant are unknown. Information on disease-specific outcomes other than survival that might have been of interest, such as transfusion requirements or hemoglobin profile, were not provided in the datasets. The Docket included case reports that provided data useful for evaluating efficacy regarding endpoints other than survival.

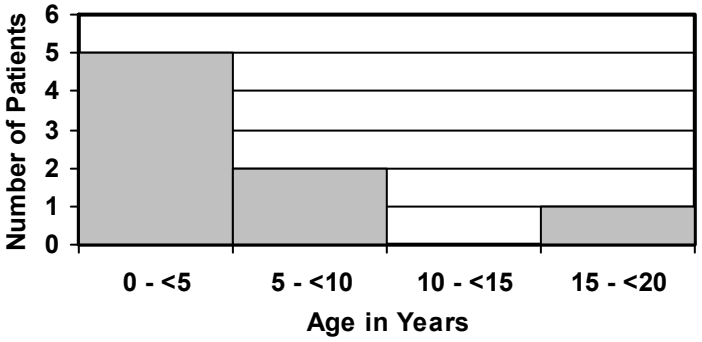
6.7.2 Demographics

The case series is described in a subsequent section. Basic demographics for the patients with beta thalassemia in pooled datasets are shown in Table 20 below, together with basic treatment data. Demographic information other than age was not provided in the NYBC dataset.

Table 20: Demographics and Treatment Data for Patients with Beta Thalassemia – Docket Data

Total N	8
Gender	
Male	13% (1)
Female	63% (5)
Unknown	25% (2)
Age in Years	
Mean (SD)	6.2 (5.9)
Median (Range)	4.2 (2.0 – 20.0)
Race	
Caucasian	50% (4)
Asian	25% (2)
Unknown	25% (2)
Dosing (TNCx10^7/kg prefreeze)	
Median	6.4
10^{th}, 25^{th}, and 75^{th} percentiles	2.5, 5.1, 10.4
Dose < 2.5	0% (0)
HLA Match	
6/6	13% (1)
5/6	75% (6)
4/5	13% (1)
Data source	
NMDP	75% (6)
NYBC	25% (2)

Figure 47: Age Distribution for Patients with Beta Thalassemia – Docket Data



(Ages were: 2.0, 2.0, 3.7, 4.2, 4.2, 5.6, 8, and 20)

6.7.3 Subject Disposition

No protocol was provided for this study, and there is no information available about screening, eligibility criteria, or diagnostic criteria. Of the 8 total patients with beta

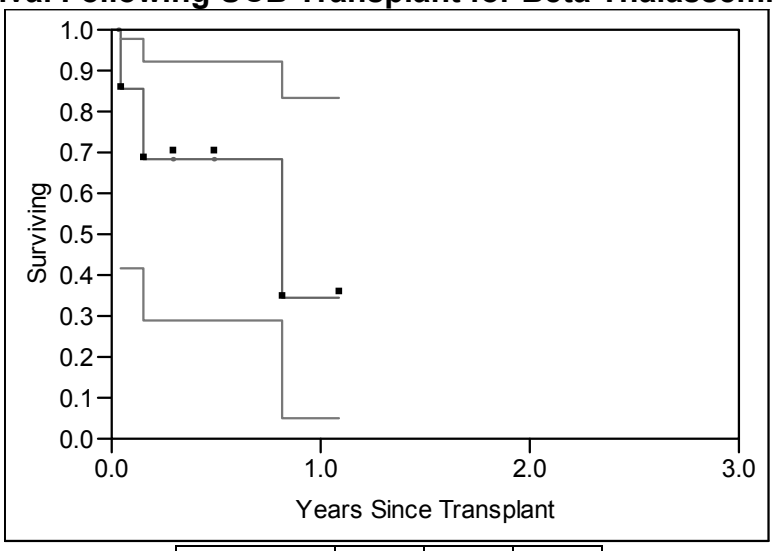
thalassemia, 3 are reported to have died: two from respiratory disease, and one from multi-organ failure.

6.7.4 Analysis of Primary Endpoint(s)

Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown below for the 8 patients with beta thalassemia in the Docket datasets. As estimated from the Kaplan-Meier curve, the mortality at 1 year is 66%, and the corresponding estimate of survival at 1 year is 34%. The median follow-up was 0.2 years.

Figure 48: Survival Following UCB Transplant for Beta Thalassemia – Docket Data

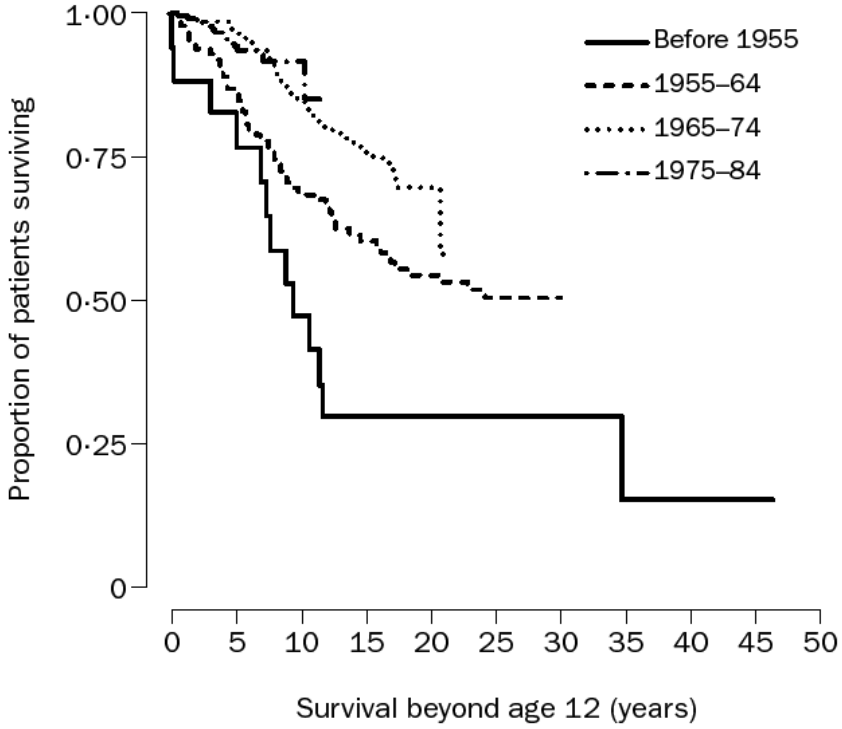


Year	0	0.5	1
Survival	1.00	0.69	0.34
No. at Risk	8	2	1

Historical Experience

In 2000, Modell evaluated the survival beyond age 12 years in patients with beta thalassemia major according to birth cohort using data from the UK Thalassemia Register (Modell and Khan et al. 2000). Modell also noted that about 50% of patients die by the age of 35 years. For the cohort born in the decade starting in 1975, it appears that around 90% of 12-year-olds survived to adulthood (Figure 49).

Figure 49: Survival Beyond Age 12 in Beta Thalassemia by Birth Year Cohort in the UK – Modell 2000



Survival beyond 12 years of age by 10-year birth cohort

Source: Modell and Khan et al. 2000

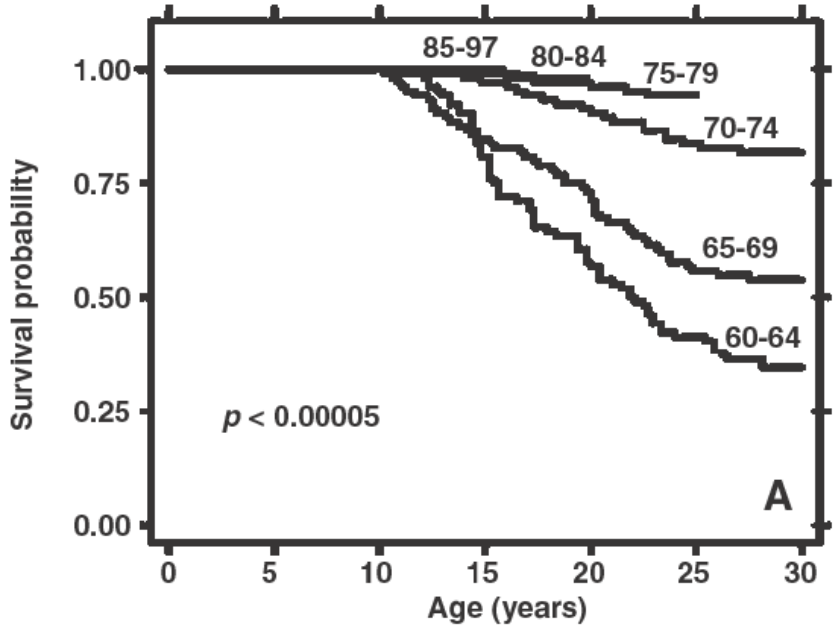
Similar analyses by Borgna-Pignatti also found a pattern of improving survival over time (Borgna-Pignatti and Rugolotto et al. 1998; Borgna-Pignatti and Rugolotto et al. 2004).

Table 21: Survival by Birth Cohort at Different Ages of Patents with Transfusion-Dependent Thalassemia – Borgna-Pignatti 1998

Age (years)	1970–1974	1975–1979	1980–1984
10	98% (96–99)	98% (96–99)	99% (95–100)
15	95% (92–97)	97% (94–98)	98% (93–100)
20	89% (85–92)	96% (93–98)	
25	82% (77–86)		

Source: Borgna-Pignatti and Rugolotto et al. 1998

Figure 50: Survival in Beta Thalassemia Without Transplantation by Birth Year Cohort – Borgna-Pignatti 2004



Source: Borgna-Pignatti and Rugolotto et al. 2004

From Figure 50, it appears that the most recent birth cohorts have a better than 95% probability of reaching age 20 years.

HSCT Experience Not in the Docket

Lucarelli observed about a 60% multi-year survival using BMT for beta thalassemia in adults (Lucarelli and Clift et al. 1999), but much higher survival rates with BMT in adolescents (Lucarelli and Gaziev 2008).

Figure 51: Survival following Sibling BMT in Adults with Beta Thalassemia – Lucarelli 1999

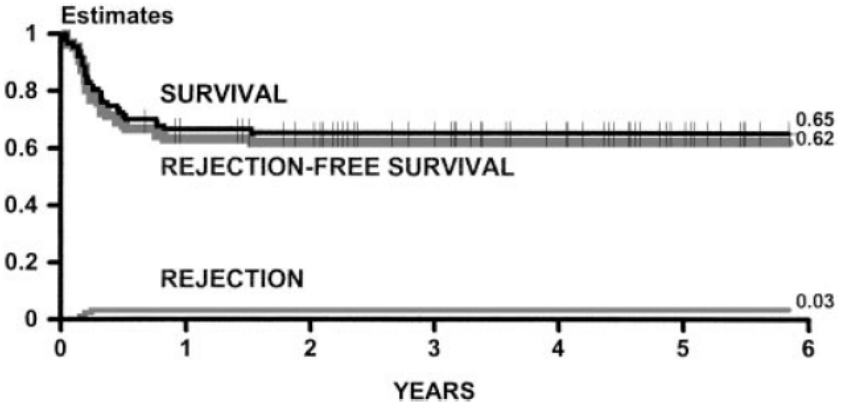


Fig 2. Kaplan-Meier estimates of survival and rejection-free survival and cumulative incidence estimates of rejection for 87 adult patients transplanted between May 1991 and September 1996. This experience is updated as of December 1997.

Source: Lucarelli and Clift et al. 1999

Figure 52: Survival Following Allogeneic BMT in Beta Thalassemia in Adolescents – Lucarelli 2008

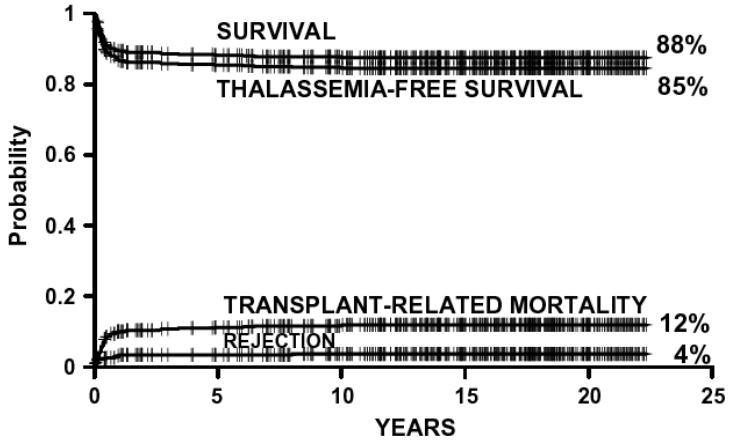


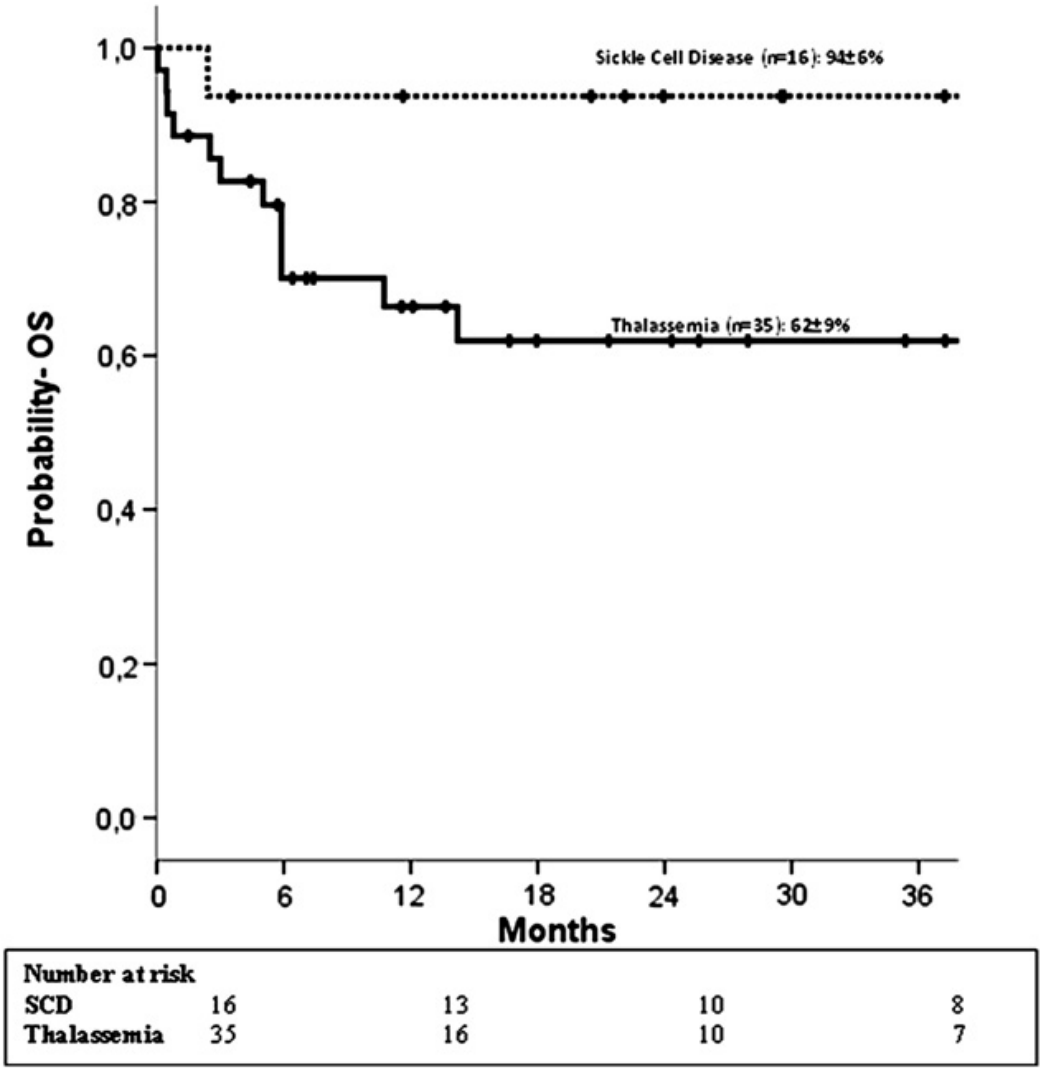
Figure 1 Estimates of survival, thalassemia-free survival, non-rejection mortality and rejection for 515 class 1 and class 2 patients younger than 17 years who were treated with busulfan 14 mg/kg, cyclophosphamide 200 mg/kg and ± thiotepa 10 mg/kg.

Source: Lucarelli and Gaziev 2008

In experience reported by Locatelli (Locatelli and Rocha et al. 2003), of 33 patients treated for thalassemia using UCB transplantation from an HLA-matched sibling (three or fewer had an HLA-A mismatch), there were no deaths in a median follow-up of 24 months, but 7 had graft failure.

In contrast, recent experience using UCB transplantation reported by Ruggeri (Ruggeri and Eapen et al. 2011) found a lower proportion of post-transplant survival in beta thalassemia; the experience was not too different from the small experience in the Docket data.

Figure 53: Estimated Overall Survival Following UCB Transplantation for Beta Thalassemia (and Sickle Cell Disease) – Ruggeri 2011



Source: Ruggeri and Eapen et al. 2011

Case reports

Case report information was provided in publications and related information in Docket documents 2006-D-0157-DRAFT-0079, -0080, and -0081.

Jaing reported on a series of five consecutive patients who received UCB for beta thalassemia major (Jaing and Hung et al. 2005a). The first case of the five was also reported separately in greater detail (Jaing and Hung et al. 2005b). The median age was 3.7 years with a range of 2.3 to 11.4 years. The oldest patient continued chelation therapy into the early post-transplantation period. The median follow-up following UCB transplant was 303 days, range 152 to 454 days. All patients achieved 100% donor chimerism and transfusion independence following transplant.

Reviewer's Comments:
While it is not explicitly documented per se, this Reviewer can accept the premise that near correction of the hemoglobinopathy and elimination of transfusion dependence in beta thalassemia major does not occur spontaneously. Evidence that UCB can have that effect comes from the case reports in the literature that were submitted to the Docket. The datasets in the Docket provide a limited experience (n=8) for estimating the mortality of UCB Transplantation, but that experience raises questions about risk-benefit assessment and the comparability or the risk with other hematopoietic stem cell therapy for this disease. The 66% one-year mortality appears to be unacceptably high given the expected usually excellent short- to intermediate-term prognosis for pediatric patients with beta thalassemia major.

6.7.5 Analysis of Secondary Endpoint(s)

The potential to substantiate claims for clinical benefits other than survival was not evaluated in the Docket datasets, because no disease-specific outcome data were included.

6.7.7 Subpopulations

The population in the Docket datasets (n = 8, with 3 deaths) was too small to permit meaningful subpopulation analyses.

6.7.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A proportional hazards model found no significant relationship between TNC dose and survival (nominal p = 0.71) with an estimated 4.0% *increase* in hazard for each increase of 10^7 cells/kg. There was no patient with a dose < 2.5 x 10^7 TNC/kg. The number of patients was too small to permit meaningful subset analysis of groups with dose above and below the median dose.

6.7.10 Additional Efficacy Issues/Analyses

Published Reviews and Opinions

In a review of cord blood banking by an AAP Work Group (Work Group on Cord Blood Banking 1999), the summary of indications for allogeneic stem cell transplantation included thalassemia in the category of "effective, controversial in unrelated subjects," and those conclusions were reflected in the 2005 IOM report on cord blood (Meyer and Hanna et al., 2005). However, the AAP review did not provide references to specific data in support of that determination. The Cochrane Collaboration has not reviewed the use of stem cell transplantation in beta thalassemia, although a report on that topic is in the protocol stage. However, on the related topic of stem cell transplantation for sickle cell disease, the Cochrane Collaboration concluded:

> Reports on the use of hematopoietic stem cell transplantation improving survival and preventing symptoms and complications associated with sickle cell disease are currently limited to observational and other less robust studies. No randomized controlled trial assessing the benefit or risk of hematopoietic stem cell transplantations in children was found. Thus, this systematic review identifies the need for a multicentre randomized controlled trial assessing the benefits and possible risks of hematopoietic stem cell transplantations comparing sickle status and severity of disease in children. (Oringanje and Nemecek et al. 2010)

In support of the use of stem cell transplantation for thalassemia, the IOM report cited primary sources of Issaragrisil and Visuthisakchai et al. 1995, Goussetis and Peristeri et al. 2000, and Locatelli and Rocha et al. 2003, of which only the last contains substantial data. More recent reviews addressing the use the use of cord blood in hemoglobinopathies are found in Lucarelli and Gaziev 2008, Smith and Wagner 2009, Boncimino and Bertaina et al. 2010, Kanathezhath and Walters 2010, and Gaziev and Lucarelli 2011. Boncimino's review noted that unpublished results from the Eurocord experience suggested transplant with unrelated cord blood was "significantly inferior" to results with sibling cord blood. References cited in the various reviews in support of the effectiveness of cord blood in thalassemia are: Locatelli and Rocha et al. 2003, Jaing and Hung et al. 2005a (one of the Docket submissions discussed above), Jaing and Yang et al. 2007, a 2008 abstract by Jaing (that appears similar to the subsequent publication Jaing and Hung et al. 2011), and Jaing and Chen et al. 2010. Search of the literature identified additional primary reports of outcomes from experience with UCB in beta thalassemia: Lau and Ma et al. 1998; Jaing and Hung et al. 2005b; Jaing and Tan et al. 2008; Jaing and Hung et al. 2005b; Lisini and Zecca et al. 2008; Jaing and Hung et al. 2011; Laughlin and Kurtzberg et al. 2011; Ruggeri and Eapen et al. 2011. The evidence from these publications is described below:

Published experience with UCB in beta thalassemia

Lau and Ma et al. 1998 (R-UCB n=2)
This is a report of two girls with beta thalassemia major in Hong Kong who received *related* (HLA-matched sibling) UCB transplants and became transfusion independent. The report is of interest because it included quantitative results of serial hemoglobin typing that showed HbF and HbA_2 both eventually falling below 5%.

Suvatte and Tanphaichitr et al. 1998 (R-UCB n=6)
This is a report of 69 children in Thailand who received stem cell transplantation, including 35 patients with thalassemia (beta thalassemia major or double heterozygotes with an additional β chain variant), of whom 6 received *related* (HLA-matched sibling) cord blood. Among the 35, 77% were reported to be cured, and the probability of survival was 86%. Of the 6 who received sibling UCB, two died from infection within a year of transplant.

Locatelli and Rocha et al. 2003 (R-UCB n=33)
This reports on a retrospective analysis of 44 patients from 22 centers worldwide who received *related* (HLA-identical sibling) UCB transplant for hemoglobinopathies, including 33 cases of beta thalassemia. Median follow-up was 24 months, and none was lost to follow-up. Of the beta-thalassemic patients, 61% were Pesaro class 1; the rest were class 2. Transfusion history was not reported. No deaths were reported; however, 7 (21%) of the thalassemia patients failed to engraft with the initial transplantation; four had subsequent BMT from the same donor, and three of these are reported “alive without disease” 3 or more years after transplant. The failure rate was higher in class 2 patients. Three of the thalassemia patients who engrafted had stable mixed chimerism (< 95% donor cells) with donor fractions between 80% and 90%. All three were reported as “alive without disease” with 1 to 2 years of follow-up. Transfusion dependence status is not described, and there were no results of hemoglobin studies. The authors noted that use of methotrexate in the GVHD prophylaxis regimen reduced the likelihood of engraftment, as did use of a conditioning regimen that did not include thiotepa.

Jaing and Hung et al. 2005a, Jaing and Hung et al. 2005b (U-UCB n=5)
Case reports of 5 patients with beta thalassemia transplanted in Taiwan with unrelated cord blood. These are the articles that were submitted to the Docket and that are reviewed in Section 6.7.4 above.

Jaing and Yang et al. 2007 (U-UCB n=5)
This is a report of 5 patients in Taiwan with beta thalassemia, ages 11 through 13, treated with double-unit unrelated cord blood transplants. One patient appears to be the same as the oldest patient previously reported in Jaing and Hung et al. 2005a. Median follow-up was 18.5 months. One patient died of pulmonary hemorrhage, 1 had autologous recovery, and 3 achieved transfusion independence. All but the patient who

had graft failure showed 100% single donor chimerism. Hemoglobin studies are not reported.

Jaing and Tan et al. 2008 (abstract, U-UCB n=51)
This is a brief abstract report on experience with 51 patients who received unrelated cord blood for beta thalassemia. Author affiliations are California and southeast Asia. Most of the patients received unwashed and plasma-depleted units. The abstract reports that 7 (14%) died, but also states that 38 (75%) were alive with a median follow-up of 296 days. The authors report that use of plasma-depleted units was favorably associated with transplant-related mortality, overall survival, and disease-free survival.

Kabbara and Locatelli et al. 2008 (abstract, UCB n=42)
This is a brief abstract report of a series of 388 patients with hemoglobinopathies who received HSCT, including 42 patients with thalassemia major who received cord blood (relatedness not specified). They reported the 5-year disease-free survival rate in thalassemia was 83% for UCB vs. 87% for BMT.

Lisini and Zecca et al. 2008 (R-UCB n=27)
This was a retrospective review of 106 patients given HSCT for beta thalassemia in Italy. The patients received related BMT (n=42), unrelated BMT (n=37) or *related* UCB (n=27). Median follow-up was 40 to 51 months, depending on the group; the minimum for any patient was 15 months. All transplants were identical HLA matches. For the related UCB patients, thiotepa was included in the conditioning regimen, and methotrexate was not used for GVHD prophylaxis. The overall survival was 95% and overall thalassemia-free survival (alive and transfusion independent) was 85%, but there were no deaths or graft failures in the related UCB group. The unrelated BMT group tended to have the worst outcomes regarding GVHD, engraftment, and survival. In the related UCB group, 48% achieved full donor chimerism. The remainder had mixed chimerism after discontinuation of immunosuppressants that was stable through 1 year of follow-up, and all are reported to be “disease-free.” All patients in any group who had full donor chimerism or stable mixed chimerism maintained hemoglobin in the range 9.3 to 14.7 g/dL.

Jaing and Chen et al. 2010 (cf. Jaing and Hung et al. 2011)
This article reports on 45 patients treated in Taiwan with unrelated UCB for nonmalignant conditions, including 32 patients with transfusion-dependent thalassemia. The patients with thalassemia appear to be a subset of those described in the thalassemia-specific publication (Jaing and Hung et al. 2011) reviewed below.

Jaing and Hung et al. 2011 (U-UCB n=35)
This is a report of a prospective study of 35 patients with transfusion-dependent thalassemia who received unrelated UCB in Taiwan. Most had beta thalassemia major, but 4 were double heterozygotes with an additional β chain variant. Median age was 5.5 years. No patient had a splenectomy. Pesaro class was not reported in this publication, but in subsequent symposium proceedings (Laughlin and Kurtzberg et al.

2011), it was reported that 63% of patients were Pesaro class 1. All had conditioning regimens that involved busulfan, cyclophosphamide, and antithymocyte globulin. Cyclosporine and methylprednisolone were used for GVHD prophylaxis. HLA matching was full for 15%, one mismatch for 31%, two mismatched for 52%, and 3 mismatched for 2%. Mean dose was 7.8 x 10^7 TNC/kg; 26% of patients received double units initially. Four deaths were reported. With a median follow-up of 36 months, the estimated overall 5-year survival was 88% ± 7% (SE), and the estimated 5-year thalassemia-free percentage after first transplant was 74% ± 7%. Including second transplants, 30 (86%) were alive and transfusion independent. Hemoglobin studies were not reported.

Laughlin and Kurtzberg et al. 2011 (cf. Jaing and Hung et al. 2011)
These symposium proceedings include a description of a session report by T. H. Jaing that appears to be the same population reported in Jaing and Hung et al. 2011, but it is of note that this report provides the additional information that 63% of patients were Pesaro class 1.

Ruggeri and Eapen et al. 2011 (U-UCB n=35)
This is an analysis of cases of unrelated UCB used for sickle cell disease and thalassemia as reported to Eurocord, the National Cord Blood Program, the New York Blood Center, and the Center for International Blood and Marrow Transplant Registry between 1996 and 2009. Duplicate reports were removed. The review included 35 unique reports of patients with thalassemia. Median age was 4 years. Pesaro class was unknown for the majority of patients. All but 3 received a conditioning regimen that included antithymocyte globulin. HLA matching was full for 14%, one mismatch for 40%, two mismatches for 43%, and 3 mismatches for 3%. There were 12 deaths, 7 in patients that had engraftment. Median follow-up of survivors was 21 months. At 15 months and beyond the estimated overall survival was 62% ± 9% (SE), and disease-free survival was 21% ± 7%. Survival and disease-free survival proportions were about 30% higher in patients with sickle cell disease than in patients with thalassemia. [Despite coincident number (35) with the report of Jaing and Hung et al. 2011, it appears that the different reporting agency, median age, HLA matching, and outcomes all point to this not being the same population.]

The results led the authors to make the following statement in their discussion:

> Taken together, the transplantation strategies using unrelated CB [cord blood] as the stem cell source is suboptimal for patients with hemoglobinopathy. Graft failure remains a major limitation to success, and the continuing use of CB for this disease must be discouraged outside of well-designed novel clinical trials. (Ruggeri and Eapen et al. 2011)

Additional reports of single cases or small case series were identified but not subject to detailed review due to their small size: Issaragrisil and Visuthisakchai et al. 1995; (n=1, sibling UCB); Wagner and Kernan et al. 1995 (n=2, sibling UCB); Chik and Shing et al.

1996 (n=1, sibling UCB); Gluckman and Rocha et al. 1997 (related and unrelated UCB; 5 thalassemia patients as part of much larger group, but thalassemia-specific results not provided); Goussetis and Peristeri et al. 2000 (n=3, BMT plus sibling UCB); and Hall and Martin et al. 2004 (n=1).

9 Appendices

9.1 Literature Review/References

9.1.1 Literature Searches

Literature searches were conducted in an effort to identify historical experience that could be used as control experience for comparing results of the UCB transplant experience from the Docket datasets. The general search strategies that were used are presented below.

Hurler Syndrome

The following PubMed searches were used:
mucopolysaccharidosis i [MeSH Terms] AND natural history n=9
mucopolysaccharidosis i [MeSH Terms] AND clinical trial [Publication Type] n=31
(The broader search for "clinical trial" was used, because a search using "…AND controlled clinical trial [Publication Type]" produced only 1 citation.)

Krabbe Disease

The following PubMed searches were used:
leukodystrophy, globoid cell [MeSH Terms] AND natural history n=5
leukodystrophy, globoid cell [MeSH Terms] AND clinical trial [Publication Type] n=4
(The broader search for "clinical trial" was used, because a search using "…AND controlled clinical trial [Publication Type]" produced no citations.)

X-linked Adrenoleukodystrophy

The following PubMed searches were used:
adrenoleukodystrophy [MeSH Terms] AND natural history n=11
leukodystrophy, globoid cell [MeSH Terms] AND clinical trial [Publication Type] n=32
(The broader search for "clinical trial" was used, because a search using "…AND controlled clinical trial [Publication Type]" produced only 5 citations.}

Primary Immunodeficiency

The following PubMed searches were used:
(immunologic deficiency syndromes [MeSH Terms] NOT hiv infections [MeSH Terms]) AND natural history n=112
(immunologic deficiency syndromes [MeSH Terms] NOT hiv infections [MeSH Terms]) AND controlled clinical trial [Publication Type] n=66

(The narrower search for *controlled* clinical trials was used, because a search using "…AND clinical trial [Publication Type]" produced 568 citations.
Although it is possible to restrict searches using "congenital" as a subheading, a search using "…AND congenital[sh] AND natural history" produced no citations, and a search using "…AND congenital [sh] AND clinical trial [Publication Type]" produced only 1 citation.)

Bone Marrow Failure

The following PubMed searches were used:
anemia, aplastic [MeSH Terms] AND natural history n=31
anemia, aplastic [MeSH Terms] AND controlled clinical trial [Publication Type] n=35
(The narrower search for "controlled clinical trial" was used, because a search using "…AND clinical trial [Publication Type]" produced 427 citations.)

Beta Thalassemia

The following PubMed searches were used:
beta thalassemia [MeSH Terms] AND natural history n=23
beta thalassemia [MeSH Terms] AND controlled clinical trial [Publication Type] n=48
(The narrower search for *controlled* clinical trials was used, because a search using "…AND clinical trial [Publication Type]" produced 303 citations.)

Additional Sources

Several documents submitted to the Docket provided references to publications; these were scanned for relevant titles suggesting natural history, clinical trial data, or related analyses. For example, document 2006-D-0157-DRAFT-0047 (repeated in -0050 and -0082) by Dr. Kurtzberg included a bibliography, and document 2006-D- 0157-DRAFT-0064 (repeated in -0065) from NYBC included citations along with comments on indications.

For Hurler syndrome, Krabbe disease, X-linked adrenoleukodystrophy, and beta thalassemia, the disease overviews in Online Mendelian Inheritance in Man (OMIM) were used to identify an additional list of references to review in an attempt to identify relevant natural history data or controlled studies for those conditions.

Less systematic PubMed searches were also used in an attempt to expand the identification of pertinent publications. For example, if the search for a reference in PubMed produced related articles from the search or generated a PubMed suggestion list, promising leads were also pursued. In all cases, the citations listed in the publications from the other search methods were scanned to identify any additional publications that could be contributory.

Use of Online Publications

Publications that were only available online (such as publications from CIBMTR.org that were not available as journal articles) were not relied upon as sources of data for this review. However, online information was referred to for general information (e.g., Cochrane review, OMIM, UpToDate) and as potential leads to identify relevant published information.

9.1.2 References

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CLINICAL REVIEW

Application Type	BLA
Division / Office	DCEPT/OCTGT
Reviewer Name(s) Team Leader	Maura O'Leary, M.D. Bindu George, M.D.
Review Completion Date	November 8, 2011
Established Name	Hematopoietic progenitor cells-cord
Therapeutic Class	Allogeneic cord blood hematopoietic progenitor cell therapy
Formulation(s)	Cell suspension for infusion
Indication(s) Intended Population(s)	Hematological Malignancies Adult and Pediatric

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Table of Abbreviations

AC	Advisory Committee
ALL	Acute Lymphocytic Leukemia
Allo-HCT	Allogeneic Hematopoietic Stem Cell Transplant
AL	Acute Leukemia
AML	Acute Myelogenous Leukemia
AP	Accelerated Phase
APML	Acute Promyelocytic Leukemia
Auto-HCT	Autologous Hematopoietic Stem Cell Transplant
BC	Blast Crisis
BLA	Biologics Licensing Application
BM	Bone Marrow
BMT	Bone Marrow Transplant
BRMAC	Biological Response Modifiers Advisory Committee
CCG	Childrens Cancer Group
CFR	Code of Federal Regulations
CIBMTR	Center for International Blood and Marrow Transplant Research
CML	Chronic Myelogenous Leukemia
COBLT	Cord Blood Transplantation Study
COG	Childrens Oncology Group
CP	Chronic Phase
CR	Complete Remission
CR1	First Complete Remission
CR2	Second Complete Remission
CTGTAC	Cellular, Tissue and Gene Therapies Advisory Committee
EFS	Event-Free Survival
DSI	Division of Scientific Investigations
FR	Favorable-risk
FDA	Food and Drug Administration
FR	Federal Register
GCP	Good Clinical Practice
GCSF	Granulocyte Colony Stimulating Factor
GvHD	Graft versus Host Disease
GVT	Graft versus Tumor
HCT	Hematopoietic Stem Cell Transplantation
HCT/P	Human Cell & Tissue Products
HD	Hodgkin Disease
HDCT	High-Dose Chemotherapy
HLA	Human Leukocyte Antigens
HPC-C	Hematopoietic progenitor cells – cord (umbilical cord blood)
HR	High-risk
IBMTR	International Bone Marrow Transplant Registry
IND	Investigational New Drug Application

IR	Intermediate-Risk
ITT	Intent to Treat
JMML	Juvenile Myelomonocytic Leukemia
Kg	Kilogram
K-M	Kaplan-Meier
LFS	Leukemia-Free Survival
LR	Low-risk
MDS	Myelodysplastic Syndrome
MRC	Medical Research Council
MRD	Matched Related Donor
MSD	Matched Sibling Donor
MUD	Matched Unrelated Donor
NC	Nucleated Cells
NCBP	National Cord Blood Program
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NMDP	National Marrow Donor Program
NYBC	New York Blood Center
OS	Overall Survival
PBSC	Peripheral Blood Stem Cell
Ph+ALL	Philadelphia chromosome-positive Acute Lymphocytic Leukemia
PIF	Primary Induction Failure
POG	Pediatric Oncology Group
RFS	Relapse-Free Survival
RIC	Reduced Intensity Conditioning
RR	Relapse Rate
SDTM	Standard Data Tabulation Model
SR	Standard-Risk
T-UBMT	T cell-depleted Unrelated Bone Marrow Transplant
TKI	Tyrosine Kinase Inhibitors
TNC	Total Nucleated Cells
TRM	Transplant-Related Mortality
UBMT	Unrelated Donor Bone Marrow Transplant
UCB	Umbilical Cord Blood

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This review is limited to an assessment of the efficacy of Umbilical Cord Blood (UCB) as a stem cell source for allogeneic hematopoietic stem cell transplantation (allo-HCT) for hematological malignancies. There is sufficient evidence of efficacy to support marketing approval of UCB for the treatment of hematological malignancies.

However, a recommendation regarding a regulatory action on a specific biologics licensing application (BLA) for UCB to treat hematological malignancies should consider not only the conclusions from this review, but also the conclusions from Dr. Przepiorka's review of safety of UCB, and a review of the specific BLA. Therefore, this review does not make any recommendations on regulatory action.

See Section 6, Efficacy Summary, Hematological Malignancies for further discussion of the efficacy evidence.

1.2 Risk Benefit Assessment

Since this review is limited to efficacy and does not consider safety, a risk benefit assessment is not possible.

2 Introduction and Regulatory Background

This review is intended to be considered with the reviews by Drs. Hyde and Przepiorka and each applicant's specific BLA submission when recommending a regulatory action for the marketing approval of UCB.

2.1 Product Information

Please refer to Dr. Hyde's review of the efficacy of non-malignant UCB-HCT.

In general, HPC-C is a minimally manipulated placental/cord blood product (UCB) containing live human cord blood cells for unrelated allogeneic use. The cord blood is collected for banking from newborns with maternal consent. It is cryopreserved for storage and shipping.

2.2 Currently Available Treatments for Hematological Malignancies

Table 1: Available Treatments for Hematological Malignancies

FDA-Approved Therapies	Other Available Treatments
Chemotherapy, Immunotherapy Targeted Biologic Agents	HCT with matched, mismatched related and unrelated donors HCT with matched, mismatched related and unrelated donors (+/- GCSF stimulation)

2.3 Availability of Proposed Active Ingredient in the United States

Umbilical Cord Blood has been used as a source of hematopoietic stem cells for allo-HCT for over 20 years in the United States. The FDA issued a Guidance in 2009 on the use of UCB: *Guidance for Industry: Minimally Manipulated Unrelated Allogeneic Placental-Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications*; October 20, 2009 (74 FR 53753). As of October 20, 2011, per the Guidance, distribution of UCB in the United States will require an IND or BLA.

2.4 Summary of Pre-Submission Regulatory Activity Related to Submission

Please refer to Dr. Hyde's efficacy review of non-malignant indications for UCB.

2.5 Other Relevant Background Information

2.5.1 Product Comparability

After review of the published literature, the October 2009 Guidance stated that HPC-Cs (or UCB) were found to have sufficient evidence of effectiveness for the indication of HCT in hematological malignancies.

However, related-donor bone marrow, unrelated-donor bone marrow, and peripheral blood stem cells have recognized differences from each other and from UCB regarding likelihood of engraftment, rates of engraftment, and incidence of various complications.

2.5.2 Combination Therapy Issues

For patients who received UCB transplantation for the treatment of hematological malignancies, a preparative regimen is used to reduce the disease burden. This regimen also provides a permissive environment for engraftment of the donor hematopoietic stem cells. Thus, the preparative regimen may be a contributory factor in the effectiveness of any allo-HCT in the treatment of hematological malignancies. This review acknowledges that differences in preparative regimens may influence outcomes. The scope of this review does not include evaluation of differences in outcomes resulting from these differences in preparative regimens.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

3.1.1 Organization

This review relies on published literature instead of submitted data. Thus no comments are made on the quality of the organization of the data submitted to the docket.

3.1.2 Deficiencies

Reports in the published literature are not designed to support a BLA review. Consequently, the information in the published literature has deficiencies that limit this review. Those deficiencies include the following:

- Individual subject data are lacking. Characteristics of the individual subjects and specific aspects of the disease (e.g., disease stage; number of treatments needed to induce remission) were lacking. Independent clinical assessment by the reviewer to ensure that subjects met entry criteria was not possible.

- The published studies used to compare UCB to other donor sources were retrospective in nature and are subject to selection bias.

- These publications did not provide sufficient information to verify whether the control cohorts for alternate donor sources were matched to the UCB cohorts. There was insufficient information to confirm whether the cohorts in these registry studies were matched for prognostic factors.

- The p-values cited in this document were obtained from the individual citations. Many of the studies cited were retrospective and the meaningfulness of a p-value in this context is unclear. In addition, the FDA did not have access to the raw data; therefore, the FDA was unable to reproduce and confirm the results of the statistical tests.

- The types of preparative regimens, GvHD prophylaxis, and GvHD treatment affect peri-transplant outcomes, which in turn affect long-term outcomes. The details of the preparative regimens, GvHD prophylaxis, and GvHD treatment were not available in some of the studies reviewed. Thus, the confounding effects on long-term outcomes due to the difference in preparative regimens between matched cohorts could not be assessed.

Section 5.2 presents review strategies that were applied to improve reliability of the published literature.

3.2 Compliance with Good Clinical Practices

Compliance with Good Clinical Practices cannot be adequately assessed from the review of published literature.

3.3 Financial Disclosures

Financial disclosures were not available for the literature reviewed. Therefore, this review does not consider whether financial conflicts of interest might have influenced the results in the published literature.

5 Sources of Clinical Data

The data submitted to the docket was primarily to evaluate engraftment and peri-transplant morbidity. This data was inadequate to meet the primary objective of this review which was to evaluate the long-term outcomes. Thus a formal review of docket data was not performed for the review.

5.1 Tables of Studies/Clinical Trials

This review is not based on specific studies conducted under an IND, but based on review of extensive scientific literature for allo-HCT as a therapeutic modality for the treatment of hematological malignancies. Once allo-HCT is established as a treatment modality for a hematological malignancy, then the review documents the available literature on the use of UCB as the stem cell source for the allo-HCT. In ALL, AML and CML there is extensive scientific literature on the use of allo-HCT for the treatment of these hematologic malignancies. These studies are described in Section 6 under disease types.

5.2 Review Strategy

5.2.1 Regulatory Standards for Review of Effectiveness for UCB for Long-term Outcomes in Hematological Malignancies

Per the FDA Guidance to Industry: *Providing Clinical Evidence of Effectiveness for Human Drugs and Biologics*, proof of effectiveness would consist of clinical investigations as defined in the provision for "adequate and well-controlled studies" for new drugs (21 CFR 314.126), unless waived as not applicable to the biological product or essential to the validity of the study when an alternative method is adequate to substantiate effectiveness (21 CFR 601.25 (d) (2)). UCB now considered for licensure is unique in that the class of HPC-Cs are HCT/Ps

that have been utilized in medical practice as alternative sources of hemato-poietic stem cells for the last twenty years.

The data submitted to the docket consists of outcomes reported retrospectively to the blood banks from multiple treatment sites to the cord blood banks. The nature of this reporting was voluntary. As a result, the reports of long-term outcomes to the blood banks database are incomplete. The strength of the literature review is large studies that provide overall survival and leukemia-free survival (LFS) in patients from large national and international transplantation databases. Thus evaluation of effectiveness to support approval of UCB for long-term outcomes is based mainly on review of the published literature.

5.2.2 Review Strategy to Improve Reliance on Published Literature

To provide sufficient reliability to this review based on published literature, data from randomized studies comparing allo-HCT to chemotherapy were reviewed to establish that allo-HCT was an appropriate treatment option. Registry or single institution retrospective studies comparing UCB to alternate stem cell sources were then reviewed. The endpoints of interest are overall survival (OS) and disease-free survival (DFS) or leukemia-free survival (LFS).The role of allo-HCT is an evolving field. Risk categorization in current practice has changed from the categorization used in previous publications. It is therefore important to consider a review of literature which is consistent with current practice. Where multiple studies were available, the reviews that are included contain large sample sizes. This review includes the most recent updates to studies where the accounting of enrolled subjects was optimal. The availability of data in acute leukemias and chronic myelogenous leukemia (CML) was considered sufficient and reliable to evaluate for effectiveness in these disease sub-types.

In other disease sub-types, the sample size was relatively small. The data is considered insufficient to determine efficacy based on long-term outcomes. The review of the literature suggests that it is not feasible to conduct randomized studies to evaluate long-term outcomes in these diseases. Thus, for these diseases the review relied on the detailed outcomes from hematopoietic reconstitution from a single uncontrolled prospective study of unrelated UCB transplantation. This study was the COBLT Study (Cord Blood Transplantation Study) (Kurtzberg J, Prasad VK et al, 2008). This review strategy was consistent with the review procedures for evidence of effectiveness as suggested in the above guidance, since hematopoietic reconstitution is considered the general purpose of UCB transplantation for acute leukemias, CML, and other hematological malignancies where allo-HCT is indicated.

5.2.3 General Organization of the Efficacy Review and Modifications to the Review Template

All discussion of clinical studies is located in subsections of Section 6.

The discussion of efficacy of UCB for hematological malignancies is in three major sections for AML, ALL, and CML and other hematological malignancies. Within the ALL and AML major sections, the discussion for pediatric and adult diseases is included under separate categories.

A separate section (6.8) of the review examines the relationship of efficacy outcomes to cell dose and HLA disparity.

Evaluation of efficacy in older subjects, where data is limited, is reviewed under section 6.9.1.

Sections 7 and 8 of the review template relate to safety and are omitted because the Docket safety data are addressed in a separate safety review by Dr. Przepiorka. Sections 9.2 and 9.3 of the review template are omitted because the review is not for a specific BLA.

5.2.4 General Approach to the Review of Efficacy of UCB

Use of UCB in the past twenty years has been driven by the need to find an alternate donor source for allo-HCT. In practice, the approach to using UCB in both adults and pediatric patients has been as a source of allo-HCT when related or unrelated donor sources were unavailable. This practice limits the feasibility of conducting studies that provide control groups that use related and unrelated donor sources as comparator groups. Thus the evaluation of efficacy of UCB is based on retrospective studies from registries that compare UCB transplantation against related and unrelated donor transplantation. The first step of the efficacy review was evaluation of the benefit of allo-HCT for each of the acute leukemias and CML. Randomized studies comparing the long-term outcomes in allo-HCT with chemotherapy and/or auto-HCT were selected for this purpose. Subsequently, the efficacy of UCB transplantation was compared to related and/or unrelated donor in retrospective studies. Thus, the review of efficacy for the acute leukemias and CML is based on a two-part approach: 1) review of efficacy of allo-HCT; 2) review of efficacy of UCB compared to other allo-HCT donor sources.

5.3 Discussion of Individual Studies/Clinical Trials

See the discussions for each hematologic malignancy (ALL, AML, CML, other) in the subsections of Section 6.

5.4 Methods

See section 9.1 for literature search methods.

6 Review of Efficacy

6.1 Summary of Reviewer Conclusions Regarding Effectiveness

This clinical efficacy review of the literature for UCB as a stem cell source for allo-HCT concludes that:

- LFS and/or OS outcomes are comparable for UCB to alternate donor sources in acute leukemias (ALL, AML) and CML.
- Evidence of effectiveness for these LFS and/or OS outcomes does not exist for the other hematological malignancies.
- In general, the purpose of UCB-HCT is hematopoietic reconstitution. The COBLT study (Kurtzberg J, Prasad VK et al, 2008) provides sufficient evidence for UCB transplantation for hematopoietic reconstitution in other hematological malignancies.
- There is no conclusive data to support specific recommendations regarding cell dose and HLA disparity based on long-term outcomes.
- The use of UCB-HCT for treatment of hematological malignancies in older subjects who receive reduced-intensity conditioning regimens provides long-term outcomes comparable to UCB-HCT in younger subjects.

6.2 Nature and Scope of Efficacy Review for Hematological Malignancies

This efficacy review focuses on the scientific literature regarding the role of allo-HCT in the treatment of hematological malignancies with emphasis on the efficacy of UCB. In hematological malignancies, where allo-HCT is considered an acceptable treatment option, this review will address the pediatric and adult populations separately. Related transplantation, unrelated transplantation, and

umbilical cord blood transplantation (UCB) are reviewed. The review considers the risks and comparability of these different donor sources of hematopoietic stem cell transplant in the treatment of hematological malignancies. Where the availability of scientific literature was substantial, the scope of the review is limited to literature with relevant updates with a preference for studies that were multi-national and included large sample sizes.

6.3 General Background: Hematological Malignancies

Hematological malignancies are a diverse group of neoplasms. Table 2 below provides the disease types, incidence, median age at diagnosis, distribution by sex, and 5-year survival rates based on the SEER database (*Howlander and Noone et al., 2011).

Table 2: Hematological Malignancies (SEER database 2004-2008)*

Disease	% of hematological malignancies	Incidence per 100,000	Median Age	M:F	5-yr Survival Rates (%)	Comments
AML	8.7%	3.5	67	M>F	22.6	AML & ALL constitute approximately 13% of all hematological malignancies.
ALL	4.2%	1.7	13	M>F	64.4	
CLL	10.4%	4.2	72	M>F	78	
CML	4%	1.6	65	M>F	57.2	
Acute Monocytic Leukemias	0.7%	0.3	61	M=F	24.0	
Other Leukemias	1.7%	0.7	75	M>F	26	
NHL	49.1%	19.8	66	M>F	67.3	Lymphomas constitute approximately 56% of all hematological malignancies.
Hodgkin Disease	7%	2.8	38	M>F	83.9	
Myeloma	14.1%	5.7	69	M>F	39.7	

AML = Acute myelogenous leukemia
ALL = Acute lymphocytic leukemia
CLL = Chronic lymphocytic leukemia
CML = Chronic myelogenous leukemia
NHL = Non-Hodgkin lymphoma

Prognosis is variable and dependent on the specific disease, stage, cytogenetic factors, response to treatment, and stem cell transplant options. If left untreated,

hematologic malignancies are fatal (Applebaum and Forman et al., 2008). Available treatments include chemotherapy, targeted therapies, and autologous and/or allogeneic stem cell transplant (allo-HCT).

6.4 Allogeneic Stem Cell Transplantation in Hematological Malignancies

Allogeneic hematopoietic stem cell transplant (allo-HCT) has evolved from being a source of rescue following high-dose chemotherapy to a treatment used to eradicate hematological malignancies based on the graft vs. tumor (GVT) effect. The initial adoption of allo-HCT as standard clinical practice in the treatment of acute leukemias was based primarily on published literature with limited controlled comparisons of bone marrow transplantation (BMT) to conventional chemotherapy in the most common hematological malignancies.

Improvements over time to reduce the co-morbidities of transplant have included the use of non-myeloablative or reduced intensity regimens, treatment and mitigation of severe graft vs. host disease (GvHD) through a better understanding of HLA matching, and improvements in post-grafting immunosuppressive regimens and supportive care, all of which have decreased transplant-related mortality (TRM). As the clinical experience with allo-HCT evolved and with improvements in TRM, the role of allo-HCT in clinical practice was generalized from acute leukemias to other hematological malignancies.

Lymphomas constitute approximately 56% of all hematological malignancies. However, the role of allo-HCT in lymphoma is limited, due in part to the availability of other curative therapies, the availability of sibling donors, the role of autologous HCT and the toxicities associated with the conditioning regimens. Currently, acute leukemias, predominantly AML and ALL, constitute the most common hematological malignancies in which allo-HCT is used as a treatment option. New effective therapies for the treatment of specific hematological malignancies diseases (CML, MDS) provide prolonged remissions and expanded treatment options for patients. In CML, the tyrosine kinase inhibitors (TKIs), and in MDS, lenalidomide, have changed the treatment paradigm. Allo-HCT in these diseases is now reserved for patients who fail these therapies. There is limited scientific literature for the use of UCB in these disease types, especially where the role of allo-HCT is reserved for advanced disease. However, use of allo-HCT in earlier phases of these diseases was an accepted standard practice prior to the availability of these new effective therapies.

Improvements in TRM and donor selection have resulted in the increasing use of allo-HCT in the treatment of hematological malignancies. The inventory of suitable stem cell sources remains limited despite the availability of bone marrow, peripheral blood and UCB as stem cell sources.

Allo-HCT is presently considered for individual patients on a risk-based approach. This risk-based approach considers the stage and prognostic factors associated with the specific disease, available curative options, availability of related and unrelated HLA-matched donors, the conditioning regimen, and the source of the allo-HCT.

6.5 Indication: Acute Lymphocytic Leukemia (ALL)

6.5.1 Pediatric ALL: Background

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy of childhood and represents about twenty-five percent of all childhood malignancies (Margolin JF, Rabin K et al, 2011). The peak incidence is between ages 2-8 years with a gradual decline until late adulthood (over 60) when the incidence again begins to increase (Howlader N, Noone AM, 2011). The choice of consolidation therapy for childhood ALL is dependent on two important evaluations performed at diagnosis and after assessment of response to initial induction therapy. Patients with primary induction failure have a poor prognosis. The overall 5-year event-free survival (EFS) for childhood ALL is 75-85 percent and can be predicted by the risk status at diagnosis and response to induction therapy (Margolin JF, Rabin K et al, 2011).

6.5.2 General approach to treatment: Pediatric ALL

General approach to allo-HCT in Pediatric ALL

Cure rates of approximately 75-85% are achieved with chemotherapy alone in Pediatric ALL, suggesting that patients in CR1 are likely to have favorable long-term outcomes without consolidation treatments like allo-HCT. The role of allo-HCT is primarily in second remission (CR2) after early relapse (less than 36 months from diagnosis) or very high-risk ALL. Very high-risk ALL is defined as:

- hypo-diploid (<44 chromosomes) in CR1
- patients who fail to respond to initial induction therapy (PIF) as indicated by poor marrow response (M2, M3 at end of induction)
- and/or the presence of minimal residual disease (Mehta PA, Davies SM, 2008; Schultz KR, Bowman WP et al, 2009, Schrappe M, Reiter A et al 2000).

With the identification and validation of new risk factors, targeted therapies and detection of early relapse, the determination of when to recommend allo-HCT is changing for pediatric ALL. The definition of "very high-risk ALL in CR1" has

changed in the past decade. For example, Philadelphia chromosome (Ph+) ALL in CR1 is no longer considered as an indication for allo-HCT in CR1. Presently, allo-HCT is not recommended as a consolidation therapy for Ph+ ALL patients (Schultz KR, Bowman WP et al, 2009, Pui CH, Carroll WL et al 2011). In this review, the discussion of the role of allo-HCT in high-risk and very high-risk disease in CR1 is limited due in part to the newer approaches to therapy and in part to the small proportion of patients that constitute this group.

Review Strategy for Efficacy of UCB-HCT as a Treatment in Pediatric ALL

As stated in Section 5.2, this review takes a two-step approach to evaluating efficacy of UCB in pediatric ALL was to first evaluate the benefit of allo-HCT in this disease and subsequently evaluate the benefit of UCB as an alternate donor source of allo-HCT.

- Three randomized studies were selected to evaluate the benefit of allo-HCT in pediatric ALL as compared to chemotherapy and/or auto-HCT. Two of these studies (Barrett et al and Eapen et al, 2006) evaluated the benefit of allo-HCT for subjects in CR2. The third study by Oudot et al evaluated the benefit of allo-HCT in subjects with Primary Induction Failure (PIF).

- Retrospective registry studies by Rocha et al and Eapen et al were selected to assess the long-term benefit of UCB transplantation as compared to other donor sources of allo-HCT in acute leukemias. These studies only provided for limited evaluation outcomes separately for pediatric ALL and AML. However, at least half of the enrolled population was diagnosed with pediatric ALL, providing for evaluation of the benefit of UCB in a large sample size in this disease.

6.5.3 Comparison of Matched Sibling Allo-HCT Donor (MSD) to Chemo-therapy in Pediatric ALL in CR2

Barrett 1994 (Barrett AJ, Horowitz MM et al, 1994)

Objective:
The objective of this study was to compare the LFS for matched sibling donor transplant (MSD) to chemotherapy in children with ALL in CR2 from data in two registry studies.

Study design:

Retrospective registry analysis from IBMTR and POG studies evaluating LFS outcomes in subjects who received an MSD allo-HCT compared to subjects who received chemotherapy from 1983-1991.
376 subjects from the International Bone Marrow Transplant Registry (IBMTR) were selected and compared to 540 subjects from the Pediatric Oncology Group (POG) group to identify variables associated with treatment failure in both groups. Subjects received transplant from 1983-1991. A subset of 255 matched pairs were selected from both registries and analyzed for treatment effect for LFS at 5 years.

Figure 1: Probability of LFS in the Matched Pair Cohort
(Barrett AJ, Horowitz MM et al, 1994)

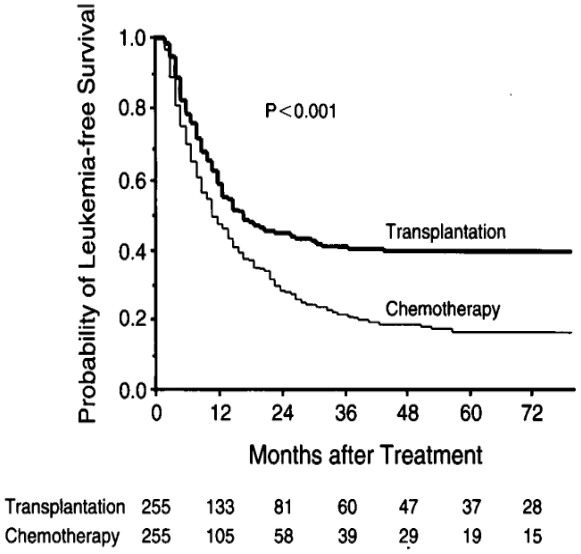


Table 3: Estimated LFS for Allo-HCT vs. Chemotherapy in Pediatric ALL
(Barrett AJ, Horowitz MM et al, 1994)

LFS at 5 years	Allo-HCT	Chemotherapy	p-value
Matched pair cohort (n=510)	40%	17%	<0.001
Unmatched pair cohort (n=916)	36%	16%	<0.001

Study Conclusions:

- There were less relapses and an increased LFS in pediatric patients with ALL in CR2 who received a MSD allo-HCT. This benefit was for patients who experienced their first relapse before or after 36 months.

Reviewer Comments and Conclusions:

- There was a greater likelihood of LFS for subjects receiving HLA donor MSD HCT at five years compared to chemotherapy. This affirms the benefit of allo-HCT for pediatric ALL in CR2.

Eapen 2006 (Eapen M, Raetz E et al 2006)
Objective:
The objective of this study was to evaluate treatment options for pediatric subjects less than 18 years with relapsed B precursor ALL. Efficacy outcomes of interest for the purpose of this review were treatment failure and overall mortality.

Design:
Patients who received chemotherapy were selected from the Pediatric Oncology Clinical Trials (POG) registry, and patients receiving transplant were selected from the Center for International Bone Marrow Transplant Research (CIBMTR) registry. The patients were drawn from the years 1991-1997. All patients had at least bone marrow relapse with or without extramedullary relapse and were in second CR. Allo-HCT recipients had a HLA MSD.
One hundred and eighty-eight chemotherapy recipients and 186 MSD HCT recipients were identified and reviewed. Within the HCT group, 82% of subjects received Total Body Irradiation (TBI) in the conditioning regimen. Time from primary induction to relapse is a known prognostic factor for pediatric ALL. This study evaluated the effect of the treatment type on long-term outcomes. Subjects with pediatric ALL in CR2 who experienced relapse within 36 months of initial CR1 are considered to have early relapse. Subjects with relapses at or beyond 36 months are considered to have late relapse.

Results:
The 8-year overall survival for children in early relapse was 32% and 44% after chemotherapy alone or transplantation with radiation (TBI), respectively. In late first-relapse patients, the overall survival at 8-years for these same groups was 66% and 63%.

Table 4: Treatment Failure and OS of Chemotherapy vs. MSD BM-HCT in Pediatric B-precursor ALL
(Eapen M, Raetz E et al, 2006)

Outcome	Treatment	Early relapse (<36 mo)			Late relapse (≥36 mo)		
		N1/N2	RR (95% CI)	p-value	N1/N2	RR (95% CI)	p-value
Treatment Failure	Chemotherapy	85/110	1.00	<0.001	32/78	1.00	<0.001
	TBI regimen HCT	50/92	0.55 (0.39-0.79)	<0.001	24/61	1.10 (0.66-1.84)	0.70
	Non-TBI regimen HCT	17/19	1.56 (0.92-2.48)	0.06	9/14	3.11 (1.72-5.62)	<0.001
Overall mortality	Chemotherapy	77/110	1.00	<0.001	26/78	1.00	<0.001
	TBI regimen HCT	48/92	0.58 (0.41-0.83)	0.003	22/61	1.10 (0.66-1.84)	0.49
	Non-TBI regimen HCT	15/19	1.51 (0.94-2.43)	0.09	9/14	3.11 (1.72-5.62)	<0.001

N1: number of events
N2: number evaluable

Study Conclusions:

- For patients with pediatric ALL in CR2, the timing of first relapse and the type of conditioning regimen are important in determining the role of MSD Allo-HCT.
- Patients with early relapse who received a TBI-containing conditioning regimen followed by MSD allo-HCT appeared to have improved LFS and OS as compared to patients receiving chemotherapy alone or MSD allo-HCT preparative regimens without TBI.
- For those subjects with late relapse, the LFS and OS outcomes were similar with transplant containing TBI as against chemotherapy, while subjects receiving a MSD allo-HCT without TBI fared worse.

Reviewer Comments and Conclusions:

- The sources of patients for the Barrett and Eapen studies were similar but did not overlap in the years from which the subjects were chosen.

- This study differs from the Barrett study in that it identifies a specific group of subjects in CR2 (early relapse) who are likely to benefit from MSD transplants.

- This study also highlights the possible potential effects of HCT conditioning regimens on outcomes. However, conclusions about the effect of a conditioning regimen must be interpreted with caution since the sample size for the non-TBI containing arm was small. Non-randomized allocation of subjects to transplantation with selection being at the discretion of the transplant center could potentially have produced a selection bias that may have influenced the outcomes.

6.5.4 Comparison of Matched Related Allo-HCT in Patients with Primary Induction Failure (PIF) in CR1 (Oudot C, Auclerc M et al, 2008)

Patients with PIF are often refractory to salvage therapy with no likelihood of survival. In those patients with PIF who achieve a CR with salvage induction treatment, post-remission therapies are important to decrease the risk of relapse.

Objective:
The objective of this study was to compare outcomes for MSD allo-HCT to outcomes for auto-HCT or chemotherapy in subjects with PIF.

Results:
One thousand three hundred and ninety five children with newly diagnosed ALL were enrolled in the FRALLE 93 study conducted in France and Belgium. Ten of 53 patients in PIF failed to reach CR1 with salvage therapy. Overall survival in those 10 patients was 0%. Forty-three patients responded to salvage treatment and achieved CR1. DFS at 5 years in the group that received MSD allo-HCT was 50% (five of ten patients). DFS at 5-years after auto-HCT was 50% (four of eight patients) while the DFS rates in the chemotherapy group was 25% (three of twelve) at less than 5 years (≥ 53 months).

Study Conclusions:

- Five-year OS for patients with PIF was poor when compared to patients who responded to initial therapy (30% vs. 85%).

- Allo-HCT and auto-HCT for PIF in ALL provided the best treatment options after salvage therapy.

Reviewer Comments and Conclusions:

- Even with the small sample size, the study supports the use of allo-HCT in pediatric subjects with ALL with PIF who are able to achieve CR1.
- The imbalance in prognostic factors may have affected the outcomes.

6.5.5 Summary Comments and Conclusions from the Review of the Literature for the Role of Allo-HCT in the Treatment of Pediatric ALL

- In pediatric ALL, MSD allo-HCT is an effective treatment option for patients in CR2 and in CR1 after salvage therapy for PIF.
- The risk factors associated with identifying very high-risk (HR) patients with pediatric ALL have changed in the past decade. The comparative studies supporting the use of allo-HCT in very HR pediatric ALL were conducted at a time prior to the current practice of selection for very HR patients. This change in the treatment paradigm poses a challenge in assessing the appropriateness of allo-HCT in very HR pediatric ALL in CR1 depending on risk factor.

6.5.6 Efficacy of UCB in Comparison with Other Allo-HCT Donor Sources in Pediatric ALL

Studies that have evaluated the efficacy of UCB-HCT in pediatric acute leukemias (ALL, AML) are summarized in a review by Brunstein CG, Weisdorf DJ, 2009. These studies are not a comparison of UCB to other allogeneic donor sources and will not be included in this efficacy review.

General Approach to Evaluation of UCB in Treatment of Pediatric ALL

The purpose of this portion of the efficacy review is to compare the efficacy of UCB to other allogeneic donor sources for the treatment of pediatric ALL. The selection of the stage of pediatric ALL in this review is guided by the current standard practice of use of allo-HCT in this disease. The impact of selection based on a threshold cell dose on the variability of the results is probably minimal. This is due to the fact that pediatric UCB transplants are likely to meet the cell dose thresholds because of the size of the patients. Thus it appears

prudent to include registry studies from the 1990's in the discussion of the role of pediatric leukemia (ALL and AML) as well as analyses from more recent data.

The single institution analysis by Barker compares long-term outcomes between UCB and unrelated or related matched BM donor sources in pediatric subjects with a variety of pediatric diseases for which allo-HCT is generally used (Barker JN, Davies SM et al, 2001). This study is not included in the review of efficacy comparing different allogeneic donor sources on outcomes due to small sample size and lack of disease-specific outcome data.

Two studies have been included in the efficacy review of UCB as a donor source in pediatric ALL. These are retrospective registry analyses from Europe and the United States. The Rocha study (Rocha V, Cornish J et al, 2001) compared two broad categories of UCB against matched and mismatched unrelated HCT. The Eapen study (Eapen M, Rubinstein P et al, 2007) compared sub-categories of UCB and unrelated HCT donor sources and attempted to evaluate the impact of cell dose on outcomes.

Comparative analysis of Allogeneic Bone Marrow Donor Sources on Long-term Outcomes in Pediatric ALL

Rocha 2001 (Rocha V, Cornish J et al, 2001)

Objective:
Rocha et al published a retrospective registry study predominantly from the Eurocord transplantation registry. The objective of this study was to compare outcomes of unrelated donor transplants using either Umbilical Cord Blood (UCB) or Unrelated Bone Marrow (UBM) as donor source in pediatric subjects under 16 years of age for HCT in the Acute Leukemias (AL).

Study design:
UBM-HCT was grouped further into T cell depleted (T-UBM HCT) and un-manipulated UBM-HCT. In both UBM groups, the source of the BM was unrelated to the recipient. Subjects were treated between 1994 and 1998. Efficacy outcomes evaluated were Event-Free Survival (EFS) and Overall Survival (OS).

Results:
Pediatric patients with ALL and AML were included in this study. In patients with ALL, 195 received an Unmanipulated UBM-HCT, 145 received a T – UBM- HCT and 65 received a UCB-HCT.

Table 5: Efficacy Outcomes of UCB-HCT vs. BM-HCT for Pediatric Acute Leukemia
(Rocha V, Cornish J et al, 2001)

Outcomes for AL at 2 yrs	UCB-HCT (n=99)	Unmanipulated UBM-HCT(n=262)	T-UBM-HCT (n=180)
Relapse	38%	39%	47%
EFS	31%	43%	37%
OS	35%	49%	41%

Study Conclusions:

- Neutrophil recovery and platelet recovery were associated with cell dose for UCB-HCT. A cell dose of 3.7 x 10e7 TNC/kg was associated with increased probability of engraftment.
- In patients who received a UCB-HCT, relapse was associated with younger patients, AML, and advanced stage of disease at time of HCT.
- UCB-HCT had less cGvHD than the unmanipulated UBM-HCT.
- The main differences in outcomes occurred in the first 100 days post-HCT. In the UCB-HCT group; this was reflected in delayed engraftment, failed engraftment, and an increase in TRM.

Reviewer Comments and Conclusions:

- Long-term outcomes of EFS and OS are comparable between UCB-HCT and UBM-HCT. In patients without a suitable UBM-HCT donor, UCB-HCT provides an alternative donor source.
- This is not a randomized study. Differences in prognostic factors, treatment regimens and selection bias could have impacted outcomes. Outcomes for ALL were not reported separately. However, more than half of these subjects with AL were of the ALL sub-type.

Eapen 2007 (Eapen M, Rubinstein P et al, 2007)

Objective:
The objective of this study was to compare 5-year LFS outcomes of UCB-HCT to allele matched unrelated BM HCT in children less than 16 years old with AL. The source of subjects is the Center for International Blood and

Marrow Transplant Research (CIBMTR) and the National Cord Blood Program (NCBP) of the New York Blood Center (NYBC).

Design:
The study selected pediatric subjects with either AML or ALL. Subjects received a single unit of cord blood. HLA mismatches up to two HLA loci were permitted. Time of transplant ranged from 1995-2003.

Results:
Five hundred and three children who received a UCB-HCT were compared with 282 BM-HCT recipients. Of the subjects receiving UCB, 201 mismatched at one antigen level and 267 at two antigen levels. For the BM-HCT recipients, 44 subjects are mismatched at one allele level, and 122 subjects are mismatched at two allele levels. Approximately 60% of the patients were ALL, of whom 55% were transplanted in CR2. Cell dose in the UCB group ranged from 2.2-6.9 x 10^7 TNC/kg. LFS outcomes were similar in all groups.

Table 6: Estimated 5-year LFS Outcomes of UCB-HCT vs. BM-HCT in Pediatric Acute Leukemia (Eapen M, Rubinstein P et al, 2007)

Registry source/ Author/ Age range	Stem cell source based on HLA disparity (n)	Disease (n)	LFS probability (%)	Outcome summary
CIBMTR (Pediatric) Eapen 2007[1] Age 0-16 yrs	M UCB (35)	AML (16) ALL (19)	5-yr LFS: 60%	No statistically significant differences for LFS were noted between matched, low or high cell dose mismatched UCB, mismatched BM compared to matched BM
	MM UCB-1L (44)	AML (8) ALL (36)	5-yr LFS: 36%	
	MM UCB-1H (157)	AML (69) ALL (88)	5-yr LFS: 45%	
	MM UCB-2 (267)	AML (101) ALL (166)	5-yr LFS: 33%	
	M UBM (116)	AML (36) ALL (80)	5-yr LFS: 37%	
	MM UBM (166)	AML (60) ALL(106)	5-yr LFS: 38%	

M UCB = Matched UCB
MM UCB-1L = Mismatched UCB at 1/6 HLA loci with low cell dose (low cell dose was ≤ $3x10^7$ TNC/kg
MM UCB-1H = Mismatched UCB at 1/6 HLA loci with high cell dose (high cell dose was > $3x10^7$ TNC/kg
MM UCB-2 = Mismatched UCB at 2/6 HLA loci with any cell dose for Eapen 2007
M UBM = Unrelated BM Matched at 8/8 HLA Loci
MM UBM = Matched at 6/8 and 7/8

Study Conclusions:

- HLA matched or 1-2-antigen mismatched UCB is a suitable stem cell source for pediatric acute leukemia.

- The patients with HLA-matched UCB-HCT had the best 5-year LFS (60%) but the numbers were small. For the remaining donor sources the 5-year LFS was similar.

- Cell dose and HLA match affected the rate of TRM in UCB-HCT.

- GvHD rates both acute and chronic were similar for matched and mismatched UCB-HCT and allele matched BM-HCT.

Reviewer Comments and Conclusions:

- The results of this study suggest that LFS outcomes for mismatched BM-HCT, matched BM-HCT and mismatched UCB-HCT were similar.

6.5.7 Summary Comments and Conclusions from the Review of the Literature for the Role of Allo-HCT and UCB-HCT in the Treatment of Pediatric ALL

- In pediatric ALL, MSD allo-HCT is an effective treatment option for patients in CR2 and in CR1 after salvage therapy for PIF.

- The risk factors associated with identifying very high-risk (HR) patients with pediatric ALL have changed in the past decade. The comparative studies supporting the use of allo-HCT in very HR pediatric ALL were conducted at a time prior to the current practice of selection for very HR patients. This change in the treatment paradigm poses a challenge in assessing the appropriateness of allo-HCT in very HR pediatric ALL in CR1 depending on risk factor.

- The two registry retrospective analyses of long-term outcomes suggest that UCB-HCT may be comparable to other unrelated allogeneic donor sources. The degree of HLA matching for UCB donors does not seem to impact outcomes in pediatric ALL if the number of mismatches is restricted to no more than two HLA loci.

6.5.8 Adult ALL: Background

In adults, ALL represents 20 percent of all leukemias seen in persons over 20 years of age (Margolin JF, Rabin K et al, 2011 and carries a five-year mortality

rate of 65 percent (Margolin JF, Rabin K et al, 2011). Treatment for adult ALL is also based on risk categorization (Bassan R, Hoelzer D, 2011; Forman SJ, 2008).

6.5.9 General Approach to Treatment: Adult ALL

As with pediatric ALL, risk factors at the time of diagnosis impact the type of treatment that may be needed to achieve the greatest benefit to the patient. In adult ALL, the overall survival with best available therapy is in the range of 25-35% (Thiebaut A, Vernant JP et al, 2000).

General Approach to Allo-HCT in Adult ALL

Adult high-risk patients in CR1 after induction therapy are candidates for hematologic stem cell transplantation from various graft sources. The joint study by the Medical Research Council (MRC) and the Eastern Cooperative Oncology Group (ECOG) found that MSD allo-HCT is beneficial in CR1 for standard risk ALL. (Goldstone AH, Richards SM et al, 2008). This study also concluded that in the absence of sibling donor sources, chemotherapy or auto-BMT was preferable to Allo-HCT in standard risk ALL. The majority of adult patients with ALL are considered high-risk due to the advanced median age at diagnosis (Bassan R, Hoelzer D, 2011). Therefore, the applicability of the study by Goldstone 2008 is limited and the study has not been considered in detail in this review. Studies that evaluated benefit in high-risk adult ALL were selected for review and will discussed below.

Review Strategy for Efficacy of UCB-HCT in Adult ALL

As stated in Section 5.2, this review takes a two-step approach to evaluating efficacy of UCB in adult ALL was to first evaluate the benefit of allo-HCT in this disease and subsequently evaluate the benefit of UCB as an alternate donor source of allo-HCT.

- The assessment of the efficacy of allo-HCT is based on two randomized studies selected to evaluate the benefit of allo-HCT in the treatment of adult ALL with high-risk disease. These studies (Sebban et al and Hunualt et al, 1994) compared allo-HCT against auto-HCT and/or chemotherapy. These studies were selected because they were prospective randomized studies based on the donor vs. no donor analysis (ITT).

- The efficacy of UCB compared to other allo-HCT sources was based on four retrospective registry or single institution studies in adult leukemia. Two of these studies (Tomblyn 2009 and Atsuta 2009) evaluated the benefit specifically in adult ALL while the other two studies by Laughlin 2004 and Rocha 2004 evaluated outcomes in Acute Leukemia in general in which

approximately half the total number of subjects had ALL. The large sample sizes from the registry studies and the use of matched cohorts for controls were major advantages of these two studies.

6.5.10 Evidence Based Approach to Use of Allo-HCT in Adult ALL

Non-randomized retrospective studies comparing outcomes of MSD allo-HCT to chemotherapy have been published (Horowitz MM, Messerer D et al, 1991 and Oh H, Gale RP et al 1998). These studies have not been included in this review because the studies were retrospective. Studies by Sebban (Sebban C, Lepage E et al, 1994) and Hunault (Hunault M, Harousseau JL et al, 2004) are randomized prospective studies that evaluated the benefit of Allo-HCT in high-risk adult ALL. These studies are discussed below.

6.5.11 Comparison of Allo-BM-HCT against Chemotherapy or Auto-BM-HCT (Sebban C, Lepage E et al, 1994)

Objective:
The objective of the LALA87 study, a French prospective study, was to evaluate auto-HCT or chemotherapy vs. MSD allo-HCT as optimal post-remission therapy in adults with ALL in CR1 or subsequent CR.

Study design:
Enrollment period was between 1986 and 1991. Subjects between 15-40 years of age in CR after either induction therapy CR1 or salvage therapy were allowed to participate. Subjects with HLA MSDs were assigned to the BM-HCT group and subjects without an MSD were assigned to the control group. Subjects in the control group were randomized after consolidation treatment to receive chemotherapy or auto-HCT. Conditioning regimens were the same for auto-HCT and allo-HCT. Based on available literature, high-risk ALL was defined as:

- Presence of Philadelphia chromosome (Ph+)
- Undifferentiated or Null leukemia
- Other leukemias with one or more adverse features of either age >35 years, WBC count >30x10^9, or time to CR>4 weeks.

Results:
One hundred and sixteen subjects were assigned to the BM-HCT group and 141 to the control group. Subjects were well balanced in both arms for the high-risk factors except for the presence of Ph+ALL. The control group had more subjects with Ph+ALL (13% vs. 6%) than the BM-HCT group. Ninety-two subjects (81%) in the BM-HCT group were transplanted in CR1; 33 of

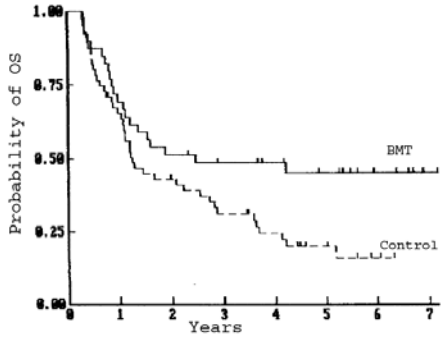
these subjects had high-risk ALL. In the control group, only 83% were randomized to either maintenance chemotherapy or auto-HCT. Of those randomized to auto-HCT only 69% received the allocated treatment. The primary cause for the failure to treat with auto-HCT was early relapse. The median duration of follow-up was 62 months.

Table 7: OS and DFS in BM-HCT vs. Control (Auto-HCT/Chemotherapy)
(Sebban C, Lepage E et al, 1994)

Allocation	n	Median Survival (mo) (95% CI)	p-value (OS)	Median DFS (mo) (95% CI)	p-value (DFS)
BM HCT	116	51 (30-NR)	0.08	24 (15-NR)	0.1
Control	141	30 (21-43)		22 (13-29)	
HR-ALL	96	19 (13-34)	<0.001	12 (9-23)	<0.001
Standard risk	161	57 (34-NR)		29 (21-NR)	
HR-ALL (BM HCT)	41	30 (13-NR)	0.03	21 (11-NR)	0.01
HR-ALL(Control)	55	15 (13-31)		9 (6-20)	
SR-ALL (BM HCT)	75	NR (32-NR)	0.7	27 (16-NR)	0.9
SR-ALL (Control)	86	56 (28-NR)		30 (21-NR)	

n = Sample size based on treatment Allocation
CI = Confidence interval
DFS = Disease-Free Survival
NR = Not reached
HR = High-risk
SR = Standard Risk ALL

Figure 2: Probability of OS in High-risk Leukemia Subjects for BM-HCT vs. Auto-HCT/Chemotherapy
(Sebban C, Lepage E et al, 1994)



Study Conclusions:

- Allo-HCT did not improve survival in patients with standard-risk ALL.
- Allo-HCT did provide a significant improvement in median DFS (p=0.01) and OS (p=0.03)

Reviewer Comments and Conclusions:

- When the results are analyzed as BM-HCT (MSD) vs. chemotherapy, there is no statistically significant advantage to BM allo-HCT (MSD).
- The study suggests that the OS and DFS benefit for MSD allo-HCT is limited to high-risk ALL. Outcomes were similar for standard-risk ALL.
- Since age >35 years is considered an independent high-risk factor in subjects with ALL other than the Ph+, undifferentiated and null type ALL, most adult subjects with ALL are likely to be considered as high-risk ALL. This study was not designed to assess age as a risk factor in OS with allo-HCT.
- This study had a small percentage of older (>35) age patients (HCT: 16%; control: 18%), so the conclusions from this study are primarily for HR factors other than age.

6.5.12 Comparison of MSD Allo-HCT Against High Dose Chemotherapy and Auto-HCT in Adult ALL (Hunualt M, Harousseau JL, et al, 2004)

Objective:
The objective of the study by Hunault et al. is to examine the role of MSD allo-HCT in both older and younger adults with high-risk ALL and to compare long-term outcomes to those of auto-HCT after high-dose chemotherapy.

Study design:
This was a randomized prospective trial conducted between 1994 and 1998. High-risk features were similar to the Sebban study, but differed in the inclusion of additional poor-risk cytogenetic abnormalities (t(4:11) or t(1:19) and did not include null or undifferentiated ALL sub-types. Subjects who entered CR1 after first induction or salvage induction were eligible. All subjects received the same induction (Berlin-Frankfurt-Muenster-BFM) and consolidation regimens. Subjects who were 50 years or younger without a 6/6 matched sibling donor were assigned to receive auto-HCT after high-dose conditioning treatment (HDT). Subjects in the auto-HCT arm underwent a

second randomization to maintenance interferon-α or no further therapy after hematopoietic recovery.

Results:
Median follow-up was 5.1 years. Pre-treatment characteristics were well balanced in both groups. The number of subjects alive in CR1 at the end of induction was 156. Thirty-nine of forty-one subjects in the allo-HCT group and 91 of 115 subjects in the auto-HCT group received per-protocol treatment. Four subjects in the auto-HCT group received a matched unrelated allo-HCT. The most common reason for not receiving the assigned treatment was early relapse.

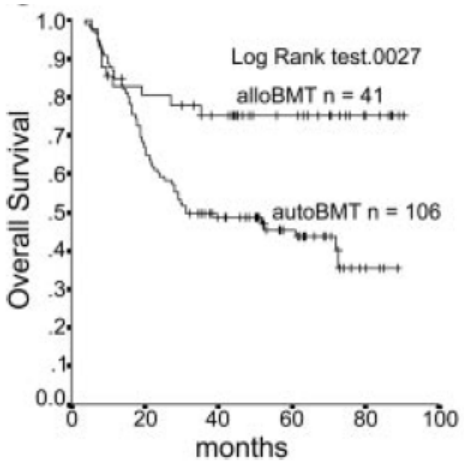
Table 8: OS and DFS Outcomes for Allo-HCT and Auto-HCT in Adult ALL
(Hunualt M, Harousseau JL, et al, 2004)

Outcomes	Allo-HCT (n=41) (months)	Auto-HCT (n=106*) (months)	p-value
DFS	NR	20.9	0.0027
OS	NR	31.2	0.0004

NR=Not Reached

*Of the 115 subjects assigned to Auto-HCT, 106 subjects were used for ITT analysis to provide an age-matched cohort to the Allo-HCT arm. Exclusion of subjects > 50 years old for Allo-HCT is an accepted practice due to the risks associated with Allo-HCT in patients with advanced age.

Figure 5: OS in the Allo-HCT and Auto-HCT in the ITT groups
(Hunualt M, Harousseau JL, et al, 2004)



Study Conclusions:

- Allo-HCT (MSD) provided better outcomes than auto-HCT for adult ALL subjects in CR1.

Reviewer Comments and Conclusions:

- The two prospective studies by Sebban et al and Hunualt et al suggest that MSD Allo-HCT is beneficial in adult ALL in CR1 with high-risk features.

- Direct comparisons of the Sebban study and Hunualt study are difficult to assess since individual patient data regarding prognostic factors and other eligibility criteria are not available.

- The mortality risk for the subjects in the control arm of the Sebban study was higher even though the age group was younger than in the Hunualt study.

6.5.13 Comparison of the Impact of Graft Source for HCT on Outcomes in Adult ALL

Prospective comparative studies of UCB-HCT to other donor sources for allo-HCT have not been done. Selection of studies for comparison of long-term outcomes of HCT with UCB was based on sample sizes from either registries or large single institutions. Analysis of registry studies helps to assess the effectiveness of UCB-HCT as compared to unrelated bone marrow (BM) or peripheral blood stem cells (PBSC) in allo-HCT. They also provide large sample sizes to look for crucial differences in the incidence of relapse, TRM and GvHD. Single-institution studies had a consistent approach to the management of transplant-related complications, conditioning regimens and GvHD prophylaxis between subjects. These factors affect peri-transplant related mortality, which in turn affects long-term outcomes. Reducing the variability in these factors is expected to reduce their impact on differences in long-term outcomes.

The data evaluating outcomes by specific donor sources in adults with ALL is limited. The single-institution study by Tomblyn et al compares outcomes for various graft sources in both adult and pediatric ALL. Registry studies by Rocha (Rocha V, Labopin M et al, 2004), Laughlin (Laughlin MJ, Eapen M et al, 2004), Atsuta (Atsuta Y, Suzuki R et al, 2009) and Eapen (Eapen M, Rocha V et al, 2010) report outcomes for acute leukemia (ALL and AML) by various donor sources in adults. Limited disease-specific outcome data for ALL and AML are presented. These four studies are discussed below to provide supportive data for the use of UCB as compared to other Allo-HCT

stem cell sources in ALL. Since both ALL and AML are included in the registry studies, this portion of the efficacy review is also applicable to the review of the impact of donor sources on outcomes in adult subjects with AML.

Tomblyn 2009 (Tomblyn MB, Arora M et al, 2009)

Objective:

The objective of this study was to evaluate 5-year outcomes based on OS, LFS and relapse rates in high-risk or recurrent ALL comparing various graft sources: autologous donor, related donor (RD), unrelated donor (URD) and umbilical cord blood donor (UCB).

Design:

This is a single institution study from the University of Minnesota. This study retrospectively reviews their experience with patients with ALL from 1980-2005 who received myeloablative allo-HCT from multiple graft sources. Ninety percent of the subjects received a cyclophosphamide/TBI-based HCT preparative regimen. A subset analysis was performed that included a cohort of subjects (n=242) undergoing allo-HCT restricted to CR1 and CR2 receiving transplants between 1990-2005 and aimed at evaluating contemporary practices of allo-HCT in the treatment of ALL.

Results:

The median age was 13 yrs, with range from 6-55 yrs. The total sample size was 623 subjects. Of the 69 subjects receiving UCB transplants, 21 received double-cord units. The overall study results included outcomes for both the autologous and allogeneic groups. In brief, OS was poorest for autologous or mismatched URD sources of stem cells. The analysis of outcomes for patients with ALL suggested that LFS was similar for matched donor, well matched or partially matched URD, and UCB. Disease status at time of allo-HCT was associated with decreased OS if the patients were CR2 or greater (58% of the patients). Late events after two years were rare. TRM was highest in the recipients of mismatched unrelated donor transplant.

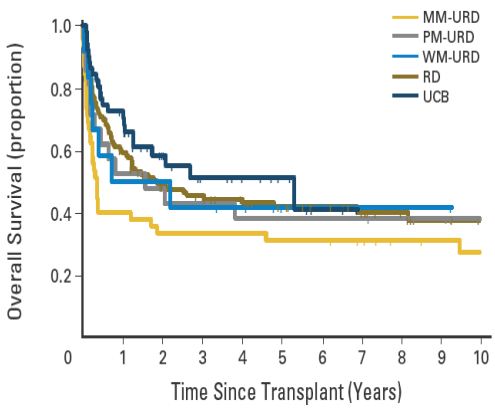
Table 9: Five-year OS and LFS in ALL in CR1 and CR2 by Allogeneic Donor Source (Tomblyn MB, Arora M et al, 2009)

Graft source (n=242)	RD (95% CI) (n=113)	WMURD (95% CI) (n=12)	PM-URD (95% CI) (n=21)	MM-URD (95% CI) (n=45)	UCB (95% CI) (n=51)
OS at 5 yrs	42% (33-51%) (RR=1.0)	42% (14-70%) (p=0.75) (RR=1.1)	38% (18-58%) (p=0.24) (RR=1.5)	31% (17-45%) (p=0.01) (RR=1.7)	51% (46-66%) (p=0.66) (RR=1.1)
LFS at 5 yrs	40% (31-48%) (RR=1.0)	42% (14-40%) (RR=1.1)	(RR=1.5)	27% (14-40%) (RR=1.7)	49% (34-64%) (RR=1.0)

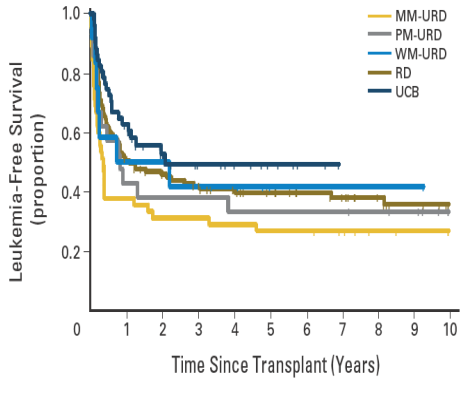
RD: Related Donor PM-URD: Partially matched URD RR: Relative risk
URD: Unrelated Donor MM-URD: Mismatched URD
WM-URD: Well matched URD UCB: Umbilical Cord Blood
LFS: Leukemia Free Survival (patients alive without relapse)

Figure 3: **Five-year OS and LFS in ALL in CR1 and CR2 by Allogeneic Donor Source**

(Tomblyn MB, Arora M et al, 2009)



Overall Survival



Leukemia-Free Survival

Study Conclusions:

- The study provides evidence that durable LFS at 5 years can be achieved with allo-HCT for patients with ALL.
- Five-year OS results were similar for MM URD, WM URD, PM URD, RD and UCB donor sources. These may be considered equivalent options for patients with ALL.
- Analysis of outcomes by year of transplant suggests significant improvement in outcomes, possibly due to improvements in supportive care, recognition of critical factors in HLA matching and availability of UCB units as an alternative to poorly matched unrelated donors.
- The authors observed improvements in OS, LFS and TRM. They attributed this to improved supportive care, improved HLA matching and UCB as an alternative to URD with poor HLA match characteristics.

Reviewer Comments and Conclusions:

- Patients with ALL lacking a sibling donor can receive UCB or a well-matched URD and have acceptable long-term LFS.
- This study supports expanding the donor pool for adults with ALL in CR1 to UCB.

- Of the 69 patients in this study that received UCB, 21 received double units.

- The study results do not provide the median cell dose and the degree of mismatch for the UCB recipients. Since the median age was 13 years of age, the impact of cell dose in the adult population cannot be assessed. The selection of UCB units in current practice uses a higher median TNC/kg cell dose and lesser degree of HLA mismatch as compared to the selection of UCB in this study.

- There is limited information on the impact of prognostic factors such as age and cell dose on outcome.

Rocha 2004 (Rocha V, Labopin M et al, 2004)

Objective:
The objective of this retrospective registry study was to compare outcomes for unrelated UCB-HCT and unrelated HLA matched B- HCT in a series of 682 adults (15-55 years old) with acute leukemia (ALL and AML).

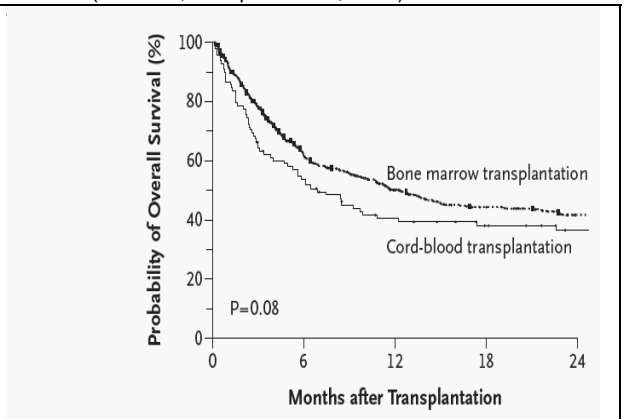
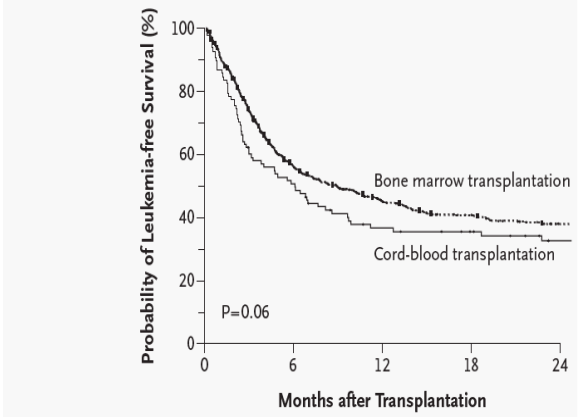
Study design:
Data was obtained from Eurocord and European Blood and Bone Marrow Transplant Group recipients who either received a single cord blood unit mismatched in up to 3 of 6 loci or HLA matched bone marrow from an unrelated donor between 1998 and 2002.

Results:
98 recipients of UCB-HCT and 584 recipients of BM-HCT were evaluable. Forty-nine percent of subjects with ALL were in CR1 and 47% were in CR2. Ninety percent of the recipients of UCB-HCT were matched at 1-2 HLA loci. The median TNC was $2.3x10^7$/kg.

Table 10: Two-year LFS Probability for Unrelated UCB-HCT and BM-HCT in Adults with ALL (Rocha V, Labopin M et al, 2004)

Disease	Unrelated UCB-HCT(n=53) Probability (95% CI)	Unrelated BM-HCT (n=267) Probability (95% CI)	p-value
ALL (overall)	34% (27-41)	33% (30-36)	0.21
ALL in CR1	43% (33-53)	49% (45-53)	0.31
ALL in CR2	44% (32-56)	47% (43-50)	0.64
Advanced ALL	23% (17-29)	19% (16-22)	0.92

Figure 4: Outcomes for Unrelated UCB-HCT and Unrelated BM-HCT in Adults with Acute Leukemia (Rocha V, Labopin M et al, 2004)

Overall survival in AML and ALL	 No. at Risk Bone marrow transplantation 584 324 224 178 148 Cord-blood transplantation 98 51 35 28 21
Leukemia-Free Survival in AML and ALL	 No. at Risk Bone marrow transplantation 584 293 202 165 138 Cord-blood transplantation 98 49 32 27 19

Study Conclusions:

- For acute leukemias, OS and LFS are similar for both unrelated UCB-HCT and unrelated BM-HCT.
- There was no difference in the 2-year cumulative incidence of relapse between UCB-HCT (44%) and BM-HCT (38%) recipients.
- The differences in the probability of 2-year LFS between recipients of UCB-HCT and unrelated matched BM-HCT for ALL in CR1 and CR2 were not statistically significant.

Reviewer Comments and Conclusions:

- The 2 year LFS for the BM-HCT group (predominantly ALL in CR1) in the Sebban study appears to be comparable to the 2-year LFS in the CR1 group for Rocha et al.

- This study supports the use of UCB as a donor source for allo-HCT in patients without an HLA-matched donor.

Laughlin 2004 (Laughlin MJ, Eapen M et al, 2004)

Objective:

The objective of this retrospective registry study was to compare outcomes of unrelated BM-HCT and unrelated UCB-HCT in patients with AL, CML or MDS. The data source was the IBMTR.

Study design:

The sources of the subjects were the IBMTR and the NYBC. One hundred and fifty single-unit UCB recipients were matched for 5/6 (34) or 4/6 (116) alleles. Four hundred and fifty UBM-HCT recipients were selected with one or no mismatches. Transplantations were performed from 1996-2001 in adult patients (16 – 60 years old). Engraftment, LFS and OS were evaluated.

Results:

The majority of the subjects were less than 40 years of age. Approximately 50% of subjects in the UBM-HCT arm and 69% of subjects in the UCB-HCT arm had acute leukemia (ALL and AML). The median cell dose for UCB was $2.2x10^7$ TNC/kg. In this analysis an effect of median cell dose on outcomes was not found. Median follow-up period for UBM-HCT and UCB-HCT were 48 and 40 months respectively. The differences in relapse rates were not statistically significant.

Table 11: LFS and OS in Acute Leukemia for UCB-HCT and UBM-HCT
(Laughlin M, Eapen M et al, 2004)

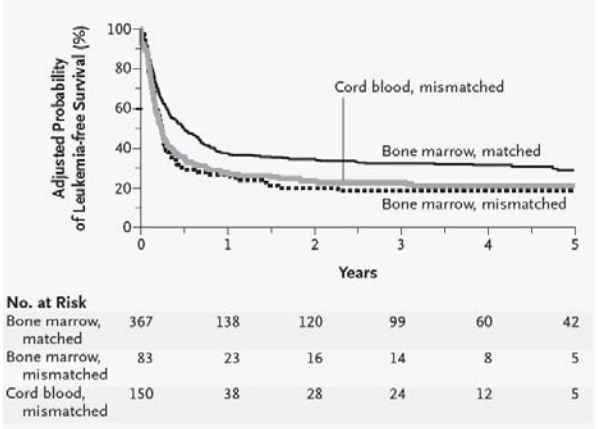
Survival	0-2MM UCB-HCT (n= 150)	MM-UBM-HCT (n=83)	M-UBM-HCT (n=357)	Comments
3 yr LFS	23%	19%	33%	3-yr LFS and OS outcomes favored of the M-UBM-HCT group compared to either the UCB-HCT or MM-UBM-HCT. No differences were seen between MM-UBM-HCT and UCB-HCT.
3 yr OS	26%	20%	35%	

0-2 MM UCB: Mismatched at 0, 1 or 2 HLA loci
M-UBMT: Matched unrelated BM donor
MM-UBMT: Mismatched BM at one HLA locus

Figure 5: LFS and OS in Acute Leukemia for Unrelated Matched BM-HCT, Mismatched BM-HCT and UCB-HCT

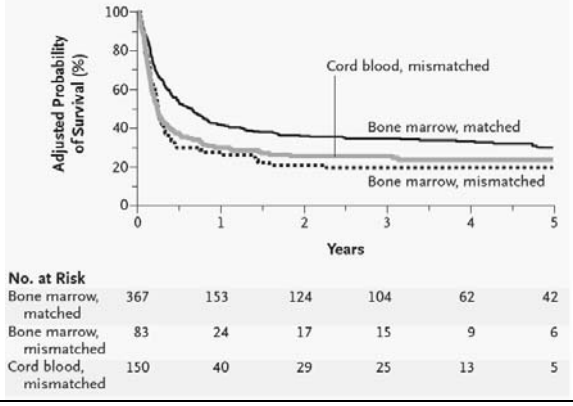
(Laughlin M, Eapen M et al, 2004)

Leukemia-Free Survival



No. at Risk						
Bone marrow, matched	367	138	120	99	60	42
Bone marrow, mismatched	83	23	16	14	8	5
Cord blood, mismatched	150	38	28	24	12	5

Overall Survival



No. at Risk						
Bone marrow, matched	367	153	124	104	62	42
Bone marrow, mismatched	83	24	17	15	9	6
Cord blood, mismatched	150	40	29	25	13	5

Study Conclusions:

- HLA mismatched UCB can be a source of hematopoietic stem cells if no matched donor is available.

- LFS and OS for matched unrelated allo-HCT were significantly better for matched unrelated BM-HCT as compared to UCB-HCT. However the outcomes were similar between HLA-mismatched unrelated BM-HCT and UCB-HCT (one and two loci).

- Patients who received UCB had a higher rate of cGvHD than unrelated matched BM recipients.

- Cell dose did not change the incidence of mortality and treatment failure for UCB recipients. Dose was < $3.0x10^7$ TNC/kg in 80% of the patients.

Reviewer Comments and Conclusions:

- UCB is an acceptable alternative donor source to unrelated mismatched BM for adults with AL, CML or MDS.

Atsuta 2009 (Atsuta Y, Suzuki R et al, 2009)

Objective:
The objective of this retrospective registry study was to compare unrelated UCB-HCT to unrelated matched bone marrow transplantation (MUD BM-HCT) in adults with acute leukemia from two Japanese registries.

Study design:
Patients received either a single UCB unit with 0-2 HLA mismatches or allele matched BM from unrelated donors. Patients who were registered from 2000-2005 were analyzed. Subjects were 16 years or older. Overall survival and LFS were the outcomes of interest.

Results:
The 114 UCB and 222 BM recipients were well balanced for disease status. There were more patients with poor prognostic cytogenetic risk factors for ALL in the UCB group. In the UCB group, 77% of the subjects had 2 HLA mismatched donor transplants. The preparative regimen included cyclophosphamide and total body irradiation. GvHD prophylaxis was methotrexate plus either cyclosporine or Tacrolimus; cyclosporine plus an additional agent or Tacrolimus plus an additional agent.

Table 12: Two-year OS and LFS in Adult ALL for UCB vs. Matched Unrelated Allo-HCT (MUD) (Atsuta Y, Suzuki R et al, 2009)

Outcome	UCB-HCT	BMT-HCT	p-value
2-year LFS	46%	44%	P=0.41
2-year OS	52%	53%	P=0.99

Study Conclusions:

- UCB matched or mismatched for 0-2 loci is an alternative donor source for patients without matched or mismatched BM donor.
- All patients received single units of UCB, the preparative regimens were similar and GvHD prophylaxis was similar even though this was a registry study.
- Patients with AML had lower 2-year OS and LFS than BM recipients, this was not the case for ALL patients.

Reviewer Comments and Conclusions:

- The study provides evidence that OS and LFS are similar in ALL between UCB-HCT and MUD BM-HCT. Therefore UCB is an acceptable alternative donor source for ALL patients who do not have a MUD source as an option.
- These findings are consistent with the findings from the Laughlin study. Comparison to MSD is not available.
- The Japanese donor pool is different from the IBMTR registry in that the Japanese population has a higher genetic homogeneity. Therefore, the Japanese donor pool has the possibility of decreased TRM and GvHD from any unrelated donor source including unrelated UCB.

Eapen 2010 (Eapen M, Rocha V et al, 2010)

This study provides an updated review of registry data on outcomes in acute leukemias (ALL, AML), based on graft selection from UCB, BM, or PBSC unrelated donor sources.

Objective:

The objective of this retrospective study was to evaluate whether changes in the graft selection process had improved the outcomes for UCB when compared to matched and partially matched unrelated BM or PBSC donor sources.

Study design:

CIBMTR and National Cord Blood Program (NCBP) registry data from 2002-2006 were evaluated in patients who were 16 years or older. In this study, matching at HLA-C loci was included in the selection of matched unrelated BM and PBSC. HLA mismatches were restricted to up to 2 loci. The cell dose threshold of $2.5x10^7$ TNC/kg was an eligibility requirement for the analysis. These changes to the graft selection process and minimum threshold for cell dose were expected to reduce the TRM and improve long-term outcomes.

PBSC were included in the analysis group due to the changing practice with regard to donor source.

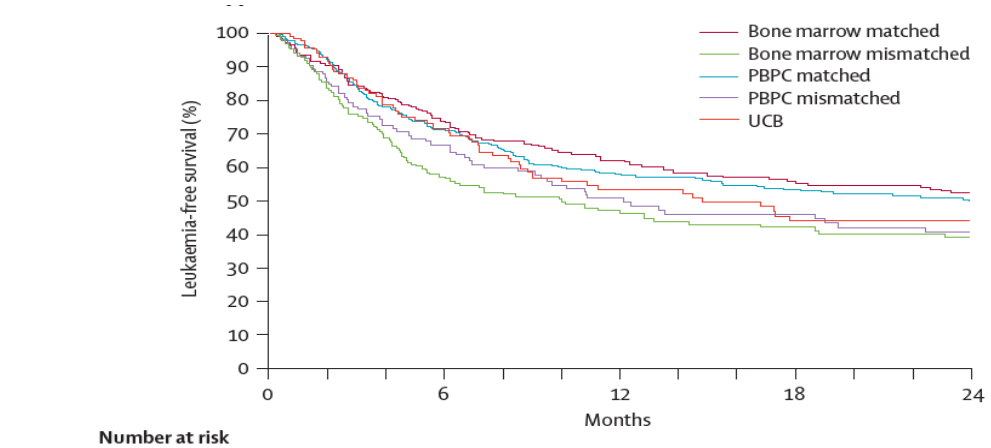
Results:

There were 888 subjects who received PBSC, 472 who received BM, and 165 who received UCB. The study was not designed to evaluate differences in outcomes between BM and PBSC group. The proportion of subjects with ALL (approximately 42%) in both the PBSC and BM groups were similar; however the UCB group had a higher proportion of subjects with ALL (54%). The proportion of subjects in CR1 or CR2 was comparable in all groups. There were no statistically significant difference in LFS and OS between UCB compared to fully or partially matched unrelated BM or PBSC. There were no differences in LFS or OS for the overall group if subjects were in CR as opposed to active disease at the time of transplantation.

Table 13: Two-year LFS for UCB-HCT and Matched and Mismatched Unrelated BM-HCT (Eapen M, Rocha V et al, 2010)

Outcome	UCB-HCT	M-UBM-HCT		MM-UBM-HCT	
		PBSC	BM	PBSC	BM
2-year LFS	44%	50%	52%	39%	41%

Figure 6: LFS Probabilities by Donor Source and HLA Match for Patients with Acute Leukemia in Remission
(Eapen M, Rocha V et al, 2010)



Number at risk					
8/8 matched bone marrow	246	177	139	99	82
7/8 matched bone marrow	106	69	46	35	31
8/8 matched PBPC	452	316	220	143	112
7/8 matched PBPC	166	89	66	45	36
4/6–6/6 matched UCB	123	77	47	30	24

Study Conclusions:

- An effect of cell dose on LFS and OS outcomes was not seen. There was insufficient sample size to analyze the effect of HLA mismatch on outcomes within the UCB group.

Reviewer Comments and Conclusions:

- This study suggests that UCB is comparable in efficacy to both fully matched and partially matched unrelated BM and PBSC for allo-HCT. The comparability of UCB to fully matched unrelated donor allo-HCT differs from the results of the Laughlin 2004 study (Laughlin MJ, Eapen M et al, 2004) where fully matched allo-HCT was superior to unrelated UCB-HCT mismatched at 1 or 2 alleles.

- The overall LFS rate at 2 years in Eapen 2010 appears to be better for all groups than in the Laughlin study. The Eapen 2010 study patients were treated more recently, with improved patient selection, conditioning regimens and GvHD prophylaxis.
- The Rocha 2004 study (Rocha V, Labopin M et al, 2004) did not include mismatched-UBM-HCT, but the overall LFS outcomes are comparable between this Eapen 2010 study and the Rocha 2004 study.

- Since the Rocha 2004 and Laughlin 2004 studies evaluated similar periods of transplantation, the disparity between their overall results cannot be explained by graft selection practices. It is also unclear whether the improvements in LFS for mismatched-UBM-HCT seen in the Eapen 2010 study relative to the Laughlin 2004 study were related to HLA-C locus matching or other advances in standard of care for allo-HCT patients.

6.5.14 Summary Comments and Conclusions for the Role of Allo-HCT and UCB as Donor Sources in Adult ALL

- The studies outlined above:
    - The Sebban (Sebban C, Lepage E et al, 1994) and Hunault (Hunault M, Harousseau JL et al, 2004) studies conclude that compared to conventional chemotherapy, allo-HCT from MSD provides an OS benefit in high-risk ALL in adults in all age groups.

- The Tomblyn study (Tomblyn MB, Arora M et al, 2009) is more pertinent to pediatric subjects with ALL, but the study also included adults with ALL. This study suggests that UCB may be comparable to MSD, fully and partially matched unrelated donor and mismatched donors with regard to OS outcomes.

- The Laughlin study (Laughlin MJ, Eapen M et al, 2004) suggests that matched unrelated donor transplant has superior outcomes compared to UCB or mismatched unrelated donor transplant in Acute Leukemias (AL).

- The Rocha (Rocha V, Labopin M et al, 2004) and Atsuta (Atsuta Y, Suzuki R et al, 2009) studies conclude that LFS and OS outcomes between UCB-HCT and fully matched unrelated HCT were similar for AL.

- The Eapen study (Eapen M, Rocha V et al, 2010) suggests that LFS in UCB-HCT is comparable to both fully matched and partially matched unrelated donor sources for AL

- Based on the above published studies, the reviewer conclusions are:

  - UCB may be a suitable substitute for matched or partially matched donors in the adult ALL population.

  - There is insufficient evidence to conclude that UCB is an acceptable alternative donor source if a MSD donor is available in adult ALL.

  - Thus, UCB may be an acceptable treatment option for adult ALL patients for whom a mismatched unrelated donor is the only other available option after risk vs. benefit assessments are made for the individual patient.

  - UCB may be an acceptable alternative if no other related or unrelated donor source of hematopoietic stem cells is available.

6.6 Indication: Acute Myelogenous Leukemia (AML)

6.6.1 Pediatric AML: Background

AML represents about 15-20 percent of all childhood leukemia. The peak incidence is in the first year of life and then decreases until age 4 and then remains constant throughout childhood and adolescence (Howlader N, Noone AM, 2011). In general, treatment is risk-stratified with 90% of patients achieving initial remission. Sixty percent of patients maintain long-term remission with aggressive consolidation therapy that is risk-based (Niewerth D, Creutzig U et al, 2010). Pediatric patients with AML who have Acute Promyelocytic Leukemia (APML), Down Syndrome, or favorable risk as determined by cytogenetics and response to induction therapy are not considered allo-HCT candidates in CR1.

This efficacy review in pediatric AML will focus on CR1 and CR2. Comparability of UCB to other sources of allogeneic stem cells in subjects with pediatric AML will also be assessed.

6.6.2 General Approach to the Treatment of Pediatric AML

In the last three decades, allo-HCT has been considered for consolidation therapy for pediatric and adult patients with AML. Allo-HCT is the consolidation treatment of choice post-CR1 in patients with matched sibling donors in the intermediate and high-risk groups. Exceptions are:

- the AML subtype Acute Pro-Myelocytic Leukemia [APML: t(15;17)]
- children with Down Syndrome
- patients with AML, favorable risk

Multiple clinical trials (Testi AM, Biondi A et al, 2005; Ortega JJ, Madero L et al, 2005; Zhang L, Zhao H et al, 2008) provide evidence of the efficacy of All Trans-Retinoic Acid (ATRA) in the treatment of APML. These study results led to guidelines that restrict allo-HCT to relapses and refractory disease in APML. In Rao et al, pediatric patients with Down Syndrome and AML in CR1 who received Allo-HCT were found to have increased TRM without long-term benefits on OS. The publication concluded that there is no role for consolidation treatment with Allo-HCT in children with Down Syndrome with AML in CR1 (Rao A, Hills RK et al, 2005).

Areas of controversy include the potential benefit and role of transplantation in AML with FLT3-ITD mutations where the overall survival rates are 30%. There is

also evidence of a lack of benefit of allo-HCT in infants with AML (Pui CH, Carroll WL et al, 2011). The effect of UCB-HCT or allo-HCT in the above sub-types of AML is beyond the scope of this review.

Review Strategy for Efficacy of allo-HCT as a Treatment in Pediatric AML

As stated in Section 6.0 of this review the two-step approach to evaluating efficacy of UCB in pediatric AML was to first evaluate the benefit of allo-HCT in this disease and subsequently evaluate the benefit of UCB as an alternate donor source of allo-HCT.

One meta-analysis (Horan JT, Alonzo TA et al, 2008) and two randomized studies (Woods WG, Neudorf S et al, 2001; Gibson BE, Wheatley K et al 2005) were selected to evaluate the efficacy of MSD allo-HCT in the treatment of pediatric AML.

- The two randomized studies were chosen because they were large cooperative prospective clinical trials designed to assess the benefit of allo-HCT as compared to chemotherapy and auto-HCT.
- The meta-analysis was selected because it reviewed four large prospective pediatric cooperative group trials conducted in the United States, United Kingdom, Europe and Australia to evaluate the benefit of allo-HCT in pediatric AML. This meta-analysis compared allo-HCT to chemotherapy. Two of the trials in the meta-analysis were Woods et al and Gibson et al.

Review Strategy for Efficacy of UCB-HCT as a Treatment in Pediatric AML

To compare UCB as donor source to other allo-HCT donor stem cell sources, registry studies by Rocha V, Cornish J et al, 2001 and Eapen M, Rubinstein P et al, 2007 were reviewed.

- These retrospective registry studies had large sample sizes. The studies were conducted internationally. This combination of size and scope may provide improved reliability and generalizability of the results for use in this review of efficacy.
- As discussed in the review strategy for efficacy of UCB-HCT in pediatric ALL, these studies reported outcomes in acute leukemias as a group. However, these two studies are considered acceptable to include in this AML review because approximately half of the enrolled subjects had a diagnosis of AML.

6.6.3 Role of Allo-HCT in the Treatment of Pediatric AML in Remission

Comparison of MRD Allo-HCT to Auto-HCT or Chemotherapy in Pediatric AML (Woods WG, Neudorf S et al, 2001)

Woods 2001

Objective:
The objective of this study (CCG-2891) was to compare allo-HCT to one of two control groups with regard to long-term survival in pediatric subjects with AML in remission. These control groups were high-dose chemotherapy (HDCT) and auto-HCT.

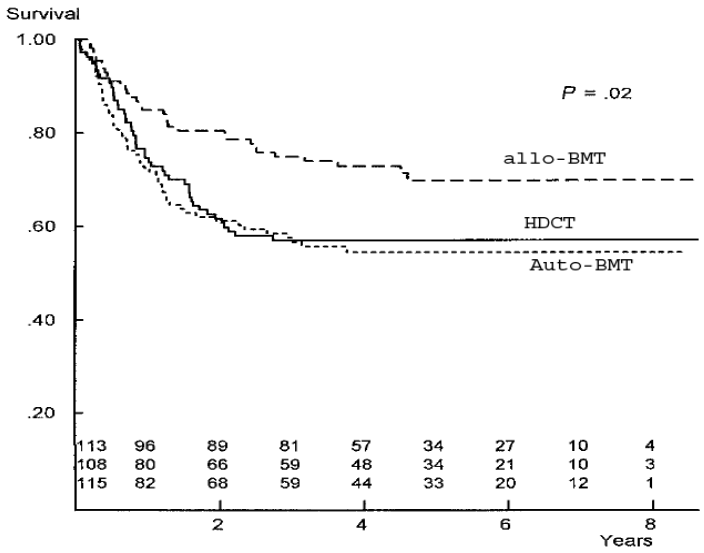
Design:
Subjects who achieved CR were eligible for allocation to allo-BM HCT if a MRD source was available. Following CR, those who did not have a MRD source were randomized to treatment with auto-BM HCT or HDCT. Survival analysis was based on an ITT (allocation to MSD allo-BMT vs. HDCT or auto-BM HCT). The study was conducted between 1989 and 1995.
Results:
Six hundred and fifty-two patients were in remission after completion of therapy. Of the 652 subjects in remission, 181 patients were to receive allo-BM HCT. Of the remaining 471 subjects in remission but without a MSD donor, 115 refused to be randomized between auto-BM HCT or HDCT. The remaining subjects were randomized to auto-BM HCT (n=177) and HDCT (n=179). There were statistically significant differences in 8-year DFS and OS in favor of the allo-BM HCT when compared to each of the two control groups.

Table 14: DFS and OS outcomes for Allo-HCT, Auto-BM-HCT and Chemotherapy (Woods WG, Neudorf S et al, 2001)

Outcomes*	Allo- BM HCT	Auto-BM HCT	Chemotherapy	p-value Allo- vs. Auto	p-value Chemo vs. Allo-HCT
All patients (n=537)	n=181	n=177	n= 179		
DFS	55%	42%	47%	0.001	0.01
OS	60%	48%	53%	0.002	0.05

- Outcomes are based on 8-year follow-up

Figure 7: OS Outcomes for Allo-HCT, Auto-BM HCT and Chemotherapy
(Woods WG, Neudorf S et al, 2001)



Allo-BMT = Allo BM HCT with a MSD
HDCT = High-dose chemotherapy
Auto-BMT = Auto-BM HCT

Study Conclusions:

- Allo-HCT for pediatric AML in CR1 was statistically significantly better (p=0.006) than auto-HCT or HDCT as consolidation therapy with 8-year follow-up for OS.
- The advantage to MSD allo-HCT was consistent when stratified for age, white blood cell count at diagnosis, FAB classification and cytogenetics.

Reviewer Comments and Conclusions:

- For patients with pediatric AML in CR1, allo-HCT as consolidation therapy provides better long-term outcomes as compared to auto-HCT or HDCT.
- The study was based on an ITT population determined by biologic randomization (depending on MRD donor availability). This is likely to reduce selection bias.
- Subjects in CR1 who received allo-HCT from MRD sources were not selected based on high-risk disease status. Risk-based selection of allo-HCT candidates is now the standard of care to determine if allo-HCT is an appropriate therapeutic plan in CR1.Thus, the applicability of the study conclusions to current practice remains to be determined.

- Despite the lack of a risk-based approach to therapeutic decisions, the patients who receive MSD allo-HCT had a statistically significant improvement in 8-year OS. The study reviewed cytogenetics at diagnosis, and the three groups were balanced. From the risk-based approach, the advantage of allo-HCT is in the intermediate-risk group. The low or favorable-risk and high-risk groups have similar outcomes, as detailed in the studies below.

Analysis of Risk-Based Outcomes Between MSD Allo-HCT and Auto-BM-HCT in MRC 10 (Gibson BE, Wheatley K et al 2005)

Gibson 2005

Objective:
The primary objective of the MRC AML 10 study was to reduce the relapse risk (RR) in pediatric AML. This study also compared long-term outcomes of allo-BMT (allo-HCT from BM source only) to auto-BM HCT (auto-HCT from BM source only) in CR1.

Study Design:
Between 1988-1995, subjects ≤ 14 years of age in CR1 with no MSD were assigned to the auto-BM HCT or no further therapy after four courses of aggressive chemotherapy. Risk-group stratification was determined by cytogenetics. There were 3 risk groups determined by cytogenetics at diagnosis and response to course one of treatment: Low-risk (LR), Standard-Risk (SR), and High-Risk (HR).

Results:
A total of 364 subjects were enrolled. Outcomes of only those subjects who achieved a remission and received a transplant will be included in the discussion of the results below. The assessment of efficacy of BM-HCT was based on an intention to treat (ITT) analysis, i.e., whether a MSD was available (donor) or not (no donor group). This assessment compared outcomes for the donor group (allo-BM HCT) versus the no donor group (auto-BM HCT or no further therapy) within each risk-based sub-group as well as for the entire group. Sixty-one of the 85 subjects with MSD received an allo-BM HCT. There was no statistically significant difference in survival at 10 years between subjects with (68%) versus without (59 %) a donor, HR=0.79, 95% CI=0.54-1.17, p=0.03). For those subjects receiving allo-BM HCT, the differences among the three risk groups with regard to both OS and DFS at 10 years from the time of CR were statistically significant. For those subjects who relapsed and likely received salvage therapy with re-induction followed by allo-BM HCT, the OS at 5 years for LR, SR and PR were 57%, 14% and 8%. These results were statistically significant.

Study Conclusions:

- The OS at 10 years was similar for allo-BM HCT, auto-BM HCT or no further therapy. The treatment-related deaths off-set the benefit of decreased relapse risk (RR) in the allo-BM HCT group.

- The MRC 10 trial for adults and children was analyzed to produce a risk-based approach to therapy use in subsequent MRC trials for all aged patients. Thirty-four percent of the patients were low-risk, 61% were Intermediate-risk and 7% were high-risk. OS at 10-years was 77%, 58% and 30%, respectively.

- The 57% OS at 5 years post-relapse for the LR group suggests that salvage therapy with allo-BM-HCT may be more appropriate in CR2 in the LR subjects. The post-relapse 5-year OS outcome for the high-risk group was low (8%). The sample size for this group was small (19% of all subjects).

Reviewer Comments and Conclusions:

- There outcomes for allo-HCT and chemotherapy were similar for subjects with AML in CR1. As with other studies that are described in the meta-analysis (Horan JT, Alonzo TA et al, 2008), the results suggest that low-risk subjects have acceptable long-term survival outcomes that may permit using allo-BM-HCT as a salvage option at relapse.

- Both the AML 10 (Gibson et al) and CCG 2891 (Woods WG, Neudorf S et al, 2001) studies compared OS outcomes between donor vs. no donor groups to evaluate the benefit of MSD allo-BMT HCT. However the results from these studies are different.
    - Unlike the CCG 2891 study, the AML 10 study did not suggest a benefit for MSD allo-BMT for the entire group. This difference may be due to the differences in post-transplant mortality associated with the AML 10 induction regimen, consisting of four induction courses, compared to the post-transplant mortality associated with the two induction courses in the CCG 2891.

    - In AML 10 the benefit of allo-BM HCT in reducing relapse may have been offset by the induction-related toxicity and peri-transplant mortality.

- This study provides justification for the use of risk-based therapy to determine the timing of MSD allo-HCT.

Meta-analysis of the Treatment of AML

Horan 2008 (Horan JT, Alonzo TA et al, 2008)

Objective:
The objective of this meta-analysis of the treatment of AML was to assess the Children's Oncology Group studies (POG 8821, CCG 2891, and CCG 2961) and the British MRC AML10 study to define prognostic and therapeutic risk categories.

Outcomes were used to define risk-categories for pediatric subjects with AML in CR1 in the context of efficacy of MRD allo-BM-HCT versus chemotherapy.

Study design:
Subjects were stratified into three risk categories (low, intermediate and high-risk) based on their cytogenetic profile at diagnosis and their response to induction therapy based on their percentage of remaining blasts after the first course of chemotherapy. Long-term outcomes of LFS and OS were compared based on assignment to MRD Allo-BM HCT or chemotherapy.

- Low-risk was defined as inv 16, t(8:21)
- High-risk was defined as monosomy 5, monosomy 7, 5q-, 3q abnormalities, ≥ 5 cytogenetic abnormalities or more than 15% blasts after first chemotherapy.

- Intermediate-risk was defined as those subjects who had cytogenetic results that were neither low-risk nor high-risk.

Results:
Of the 1,373 patients in first remission, eight hundred ninety-three patients received chemotherapy alone and 480 patients were assigned to allo-HCT. A summary of the results are provide in Table 15.

Table 15: Risk-Based Outcomes for BM HCT vs. Chemotherapy in Pediatric AML (Horan JT, Alonzo TA et al, 2008)

Sample Size and Outcomes* by risk category	BM HCT (%)	Chemotherapy (%)	HR (95% CI)	p-value
Overall group (Not-risk stratified and includes unclassified risk group)				
N	480	893		
DFS	56%	61%	0.89 (0.57-1.37)	0.58
OS	73%	71%	0.95 (0.57-1.59)	0.85
Low-Risk				
N	96	157		
DFS	63%	61%	0.89 (0.57-1.37)	0.58
OS	73%	71%	0.95 (0.57-1.59)	0.85
Intermediate-Risk				
N	204	411		
DFS	58%	39%	0.59 (0.46-0.76)	<0.001
OS	62%	51%	0.69 (0.52-0.90)	0.006
High-Risk				
N	9	38		
DFS	33%	35%	1.13 (0.38-3.38)	0.82
OS	33%	35%	0.87 (0.30-2.51)	0.80

*Outcomes reported are at 8 years. N = sample size

Conclusions:

- The study concluded that matched related donor allo-BM HCT provides a treatment benefit over chemotherapy for IR pediatric AML.

Reviewer Comments and Conclusions:

- The sample size was small for the HR group (n=47). Therefore, there is insufficient data to evaluate efficacy in the HR group. In general, the incidence of HR AML is less than 15 % of all AML (Pui CH, Carroll WL et al, 2011). Therefore, the relative sample sizes in this study reflect the relative incidences of the risk groups in the AML population.

- This retrospective meta-analysis is based on studies from three large international cooperative groups. The studies varied in study design, treatment regimens, and demographics. Individual subject data and study details are unavailable in this study report. Thus it is difficult to assess the impact of these variations on the study results.

- The meta-analysis includes studies that were conducted over a period of 15 years. Subject eligibility and selection practices based on risk-group stratification for allo-BMT evolved during this period. Individual study data and individual study criteria for subject selection are lacking in the report. Thus the conclusions from this analysis must be interpreted in light of these changes in risk stratification.

6.6.4 The Role of UCB-HCT in Pediatric AML: Background

As with the efficacy review of the literature for pediatric ALL, the discussion of UCB as a donor source will be restricted to studies that provide comparative data in AML or acute leukemia.

Studies evaluating UCB in pediatric AML are summarized in a review by Brunstein CG, Baker KS et al, 2007. These are retrospective studies lacking control groups. Therefore, these studies are not included in this review of published literature.

UCB as a Comparable Allogeneic Donor Source in Acute Leukemia

The studies by Rocha (Rocha V, Cornish J et al, 2001) and Eapen (Eapen M, Rubinstein P et al, 2007) compare UCB to various other donor sources for allo-

BM-HCT. These studies have been discussed in detail in the efficacy review of UCB compared to other donor sources in pediatric ALL (Section 6.5.7).
In summary, Rocha 2001concluded that UCB was comparable to matched unrelated donor allo-BM HCT with regard to LFS and OS in pediatric AML.
Eapen 2007 concluded that LFS outcomes were similar for matched UCB-HCT, mismatched UCB-HCT, matched unrelated BM HCT and mismatched unrelated BM HCT.

6.6.5 Summary Comments and Conclusions for the Role of Allo-HCT and UCB-HCT in the Treatment of Pediatric AML

- In the studies outlined above:
    - The MRC AML 10 trial (Gibson BE, Wheatley K et al 2005) and the meta-analysis study (Horan JT, Alonzo TA et al, 2008) suggest that allo-HCT is unlikely to provide long-term benefit over chemotherapy for subjects with AML in the low- (or favorable-) risk group. This is because the improved outcomes and lower toxicities associated with consolidation chemotherapy outweigh the risks of peri-transplant mortality from allo-HCT.
    - The MRC 10 trial and Horan meta-analysis suggest that outcomes appear to be similar between chemotherapy and allo-HCT for pediatric AML.
    - The Horan meta-analysis provides evidence to support the use of allo-HCT in intermediate-risk pediatric ALL.

- Based on the above published studies, the reviewer concludes that in pediatric subjects with AML in CR2:
    - In the absence of other post-remission therapy, allo-HCT is a suitable option for consolidation therapy. However, individual patients should be evaluated for their suitability for allo-HCT after assessment of their risks and benefits of allo-HCT compared to consolidation chemotherapy.
    - Based on review of the published literature, UCB may be comparable as a donor source to matched and mismatched unrelated BM and PBSC donor sources in the treatment of acute leukemia (AL) including AML. However disease-specific efficacy data from prospective studies in pediatric AML for UCB-HCT is lacking. The evidence comparing UCB to other donor sources comes from retrospective analyses and is subject to various biases.
    - Standard practice for this indication for allo-HCT has changed since the period of the retrospective studies (Rocha 2001, Eapen 2007) and the meta-analysis of Horan. The role of UCB as a donor source has

only been compared within the group of subjects in whom bone marrow transplantation is indicated.

- The efficacy of UCB as a treatment in AL is a "derived comparison" directly dependent on the evidence of efficacy of allo-HCT. UCB-HCT may not be indicated in certain sub-types of acute leukemia (e.g. low-risk pediatric AML) where recent advances have suggested a lack of benefit for allo-HCT.

6.6.6 Adult AML: Background

For adult AML patients with unfavorable cytogenetics achieving CR, the probability of disease recurrence is 80%. Since fewer than 20% of adult patients with high-risk adult AML are able to receive allo-HCT in CR2, transplants should preferentially be prior to relapse after CR1 (Rowe JM, 2009). Curative potential is approximately 25%-30% in a highly selected group of patients in CR2 (Schlenk RF, Dohner K et al, 2008). Approximately half of subjects in the LR AML group in CR1 have favorable long-term outcomes without allo-HCT. The majority of subjects in the IR group have normal cytogenetics. Thus, it became necessary to establish other predictive prognostic factors to select patients with normal cytogenetics who were likely to benefit from allo-HCT. Identification of molecular classification markers of AML such as NPM1, FLT3-ITD, CEBPA and c-kit have further defined the indication of allo-HCT to this group (Schlenk RF, Dohner K et al, 2008; Dohner K, Dohner H, 2008). This efficacy review for Adult AML will focus on the role of allo-HCT in patients with AML in CR1, and the comparability of UCB to other sources of allogeneic stem cells in subjects with AML.

6.6.7 General Approach to Treatment of Adult AML

The treatment of adult AML depends on risk categorization for post-remission therapy. Risk categorization is based on cytogenetic karyotyping and/or molecular typing. Three main risk categories exist in the current standard practice, including favorable, intermediate and high-risk groups. These risk categories are prognostic. With emerging biologic data, risk classification in the intermediate risk group has changed. These changes impact the interpretation of results from older studies when compared to more recent studies in adult AML. The groups within the risk categories may not be comparable across publications.

Review Strategy for Efficacy of allo-HCT as a Treatment in Adult AML

As stated in Section 5.2, this review takes a two-step approach to evaluating efficacy of UCB-HCT for AML. The first step is to evaluate the benefit of allo-HCT in adult AML. The second step is to evaluate the benefit of UCB as an alternate donor source of Allo-HCT.

- One meta-analysis (Koreth J, Schlenk R et al, 2009) and two randomized studies (Burnett AK, Wheatley K et al, 2002 and Basara N, Schulze A et al, 2009) were selected to evaluate the efficacy of allo-HCT (MRD) as compared to a no MRD donor control group. This constitutes our first step in the review process to evaluate the efficacy of allo-HCT in the treatment of adult AML. The treatments offered to the no donor group differed between studies and included observation, auto-HCT, and conventional chemotherapy.

    - The meta-analysis was selected because it allowed for analysis across many studies, included international sites, and the retrospective studies included in the analyses were selected by independent reviewers. All of these factors were expected to reduce bias and provide a larger sample population.

    - The two other studies were selected because they were prospective randomized controlled studies. The study by Burnett 2002 was the first study to evaluate the efficacy of allo-HCT in risk-based groups. The study by Basara 2009 evaluates the efficacy of allo-HCT in the high-risk group.

Review Strategy for Efficacy of UCB-HCT as a Treatment in Adult AML

Two retrospective studies by Rocha V, Labopin M et al, 2004 and Atsuta Y, Suzuki R et al, 2009 were selected to compare the efficacy of UCB-HCT to matched unrelated allo-HCT donor sources. This comparison constitutes the second step of our review process, as stated in section 5.2.

- The study by Rocha 2004 was selected because it was a registry studies that compared UCB-HCT from international cord blood registries to matched controls from bone marrow registries. Results from analyses using control groups and multiple sites are expected to be more reliable.

- The study by Atsuta 2009 is from a single registry with a matched control group in Japan. The Japanese population is more genetically homogeneous than the populations included in other international registries, which decreases the likelihood of GvHD and peri-transplant mortality as competing risks to long-term outcomes.

6.6.8 Role of Allo-HCT for Adults with AML in CR1

The role of allo-HCT for adults with AML in CR1 is reviewed in the context of the Burnett and Basara studies and the meta-analysis by Koreth. It should be noted

that data from the Burnett study was included in the meta-analysis. It is reported separately here because the study had a considerable impact in excluding the use of allo-HCT for patients in CR1 who are favorable-risk. Three meta-analysis studies have been published evaluating the role of allo-HCT in AML in CR1. These studies include:

- Koreth J, Schlenk R et al, 2009
- Cornelissen JJ, van Putten WLJ et al, 2007
- Yanada M, Matsuo K et al , 2005

The Koreth study includes the majority of the studies considered in Cornelissen and Yanada. Therefore, detailed reports for the meta-analyses by Cornelissen and Yanada are not provided in this review.

Koreth 2009 (Koreth J, Schlenk R et al, 2009)

This study (Koreth J, Schlenk R et al, 2009) is a meta-analysis of outcomes in adult AML risk categories in donor vs. no donor groups.

Objective:
The objective of the meta-analysis was to assess RFS and/or OS outcomes in donor vs. no-donor groups. The no donor groups included auto-HCT and/or consolidation chemotherapy.

Design:
Twenty-four retrospective trials were selected by two independent reviewers based on study characteristics, interventions and outcomes. Enrollment periods for these international studies were from 1982-2006. Adult subjects with AML in CR1 were assigned to undergo allo-HCT or non-allo-HCT treatment (auto-HCT, chemotherapy or observation) based on donor availability. The cytogenetic risk criteria used were based on existing practice guidelines for risk stratification. There were only minor variations in risk stratification criteria between studies. RFS outcomes based on all cytogenetic risk groups were reported in eighteen trials. RFS outcomes for favorable-, intermediate-, and high-risk AML were reported in ten, fourteen and fourteen trials, respectively. OS outcomes based on cytogenetic risk groups were reported in fifteen trials.

Results:
Of the 6007 subjects analyzed, 5951 subjects were included in the RFS analysis and 5606 subjects were included in the OS analysis. Cytogenetic risk analysis was available in 3638 subjects, including 547 FR, 2499 IR, and 591 HR subjects.

Table 16: Meta-analysis of RFS and OS Outcomes by Risk Category for Donor vs. No-Donor Group in Adult AML (Koreth J, Schlenk R et al, 2009)

Outcome	Overall group HR (95% CI) Donor (n=1909) vs. No-Donor (n=3225)	Favorable-Risk HR (95% CI) Donor (n=188) vs. No-Donor (n=359)	Intermediate-Risk HR (95% CI) Donor (n=864) vs. No-Donor (n=1635)	High -Risk HR (95% CI) Donor (n=226) vs. No-Donor (n=366)
RFS	0.80 (0.74-0.86) P<0.01	1.06 (0.80-1.42) P=0.68	0.76 (0.68-0.85) P<0.01	0.69 (0.57-0.84) P<0.01
OS	0.90 (0.82-0.97) P<0.01	1.06 (0.64-1.76) P=0.81	0.84 (0.71-0.99) P=0.03	0.60 (0.40-0.90) P=0.01

Study Conclusions:

- The meta-analysis of the overall group showed a statistically significant benefit for RFS and OS in favor of allo-HCT for adult AML. The authors further state that for allo-HCT, there is a statistically significant benefit for subjects with intermediate- and high-risk AML. There was no benefit in favorable-risk patients.

Reviewer Comments and Conclusions:

- The treatment of AML in CR1 changed from 1982 to 2006. The enrollment characteristics of later studies included in this analysis tended to restrict allo-HCT options to intermediate- and high-risk groups. Overall, the study conclusions are consistent with the current treatment of AML in CR1, but the individual trials in the analysis varied with regard to the time for patient selection, chemotherapy backbone, risk-stratification and timing of MSD allo-HCT.

- Cytogenetic and molecular risk profiling in AML is an evolving field that can further stratify outcomes. Molecular risk profiling was not available at the time of the above studies. It is therefore unclear whether the results favoring allo-HCT in the intermediate-risk group could be the result of differences in molecular prognostic factors.

Burnett 2001 (Burnett AK, Wheatley K et al, 2002)

This study compares donor vs. no donor groups with regard to outcomes in adult AML patients who were treated on MRC AML-10.

Objective:
The objective of the study (MRC AML-10) was to evaluate the role of allo-HCT compared to other post-remission therapies (auto-BMT or chemotherapy) in AML.

Design:
The study enrolled patients ≤ 55 years of age, including pediatric ages, from UK, Ireland and New Zealand. All subjects had to be in CR1 to proceed to allo-HCT, auto-HCT or chemotherapy. The enrollment period was from 1988 and 1995. Subjects who achieved CR1 were assigned to allo-HCT if they had an HLA-matched sibling donor. Those without a MSD underwent randomization to either auto-HCT or consolidation chemotherapy. Risk categorization was based on cytogenetic karyotyping.

Results:
The majority of the patients in the analysis were adults. Of the 1063 subjects achieving CR1, 428 had a MSD, and 269 of these patients underwent allo-HCT. Patients with favorable-risk and MSD did not always receive allo-HCT because of the comparable benefit and decreased risk of chemotherapy consolidation. Outcome analysis was based on donor vs. no-donor groups.

Table 17: LFS and OS by Donor vs. No Donor Group in AML
(Burnett AK, Wheatley K et al, 2002)

Outcome	Overall group Donor (428) vs. No-Donor (877)	Favorable-risk cytogenetics t(8:21) and inv (16) Donor (n=51) vs No-Donor (n=94)	Intermediate-risk cytogenetic Donor (n=230) vs No-Donor (n=483)	High-risk cytogenetics Donor (n=23) vs. No-Donor (n=60)	Unknown cytogenetics Donor (n=77) vs. No-Donor (n=139)
DFS*	49 vs. 41% p=0.02				
OS*	54 vs. 48% P=0.1 HR=0.88 (95% CI 0.75, 1.03)	59 vs. 72% HR=1.76 (95% CI 0.96, 3.25)	54 vs. 42% HR=0.76 (95% CI 0.62, 0.94)	22 vs. 30% HR=1.14 (95% CI 0.64, 2.01)	48 vs. 45% HR=0.89 (95% CI 0.61, 1.29)

*All point estimates are at 10 yrs from CR.

Study Conclusions:

- The author's conclusions were that for subjects with favorable-risk and high-risk characteristics, there were no DFS and OS benefits to consolidation with allo-HCT.

- Subjects with intermediate-risk cytogenetics may benefit from allo-HCT with improved OS.

Reviewer Comments and Conclusions:

- This study was one of the first to use a risk-stratification in the analysis of their results. This risk-based system was based on diagnostic cytogenetics and did not direct therapeutic decisions.

- This study provides supportive evidence that AML patients with favorable-risk cytogenetics, based on the definition in the study, in CR1 should not be offered allo-HCT. Subjects with intermediate-risk benefit from allo-HCT with improved OS and lower relapse rates.

- The changes to risk-stratification from the time of the above study to current practice should be taken into consideration before recommending allo-HCT for the individual subject.

- There was insufficient evidence from this study to support the use of allo-HCT in the high-risk group.

Basara 2009 (Basara N, Schulze A et al, 2009)

This study evaluates the role of allo-HCT in high-risk AML.

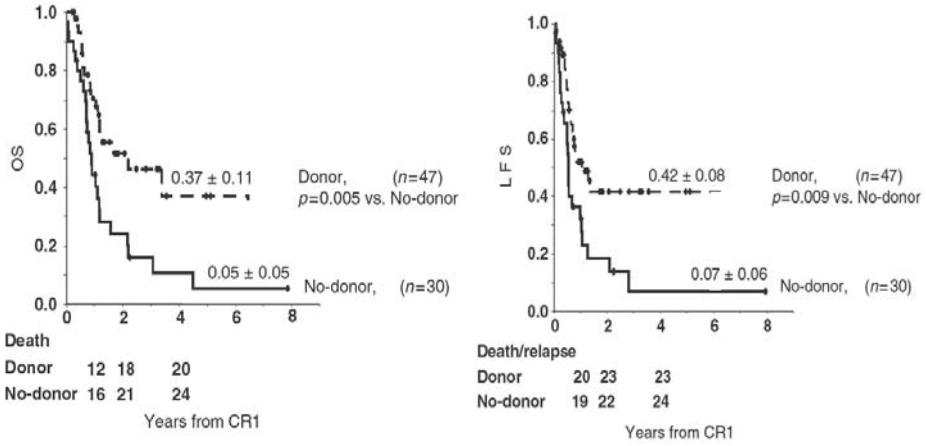
Objective:
The objective of this study was to evaluate the impact of matched related and unrelated allo-HCT on DFS and OS in high-risk AML in CR1.

Study design:
This was a retrospective review of subjects in East German Study trials AML 96 and AML 02. High-risk determination was based on accepted karyotypes for categorization. Allo-HCT was done after consolidation chemotherapy.

Results:
Of the 138 HR patients, 77 achieved CR1 and were eligible for HCT. Median duration of follow-up was 19 months. Results for the DFS and OS analyses per donor versus no donor group (ITT) and per treatment (allo-HCT vs. chemotherapy or auto-BMT) were statistically significant in favor of allo-HCT.

The TRM in the allo-HCT group did not differ significantly from treatment related mortality in the chemotherapy group.

Figure 8: Two-Year DFS and OS for Donor vs. No Donor Group in HR AML
(Basara N, Schulze A et al, 2009)



Study Conclusions:

- The study concluded that matched allo-HCT from related or unrelated BM source provided superior OS and LFS outcomes for high-risk AML in CR1.

- The treatment related mortality from chemotherapy was not different from the TRM in allo-BMT. The outcomes related to the treatments were similar. The OS and LFS benefit for allo-HCT was probably related to reduction in the relapse rates.

Reviewer Comments and Conclusions:

- The study by Burnett et al was not conclusive regarding the role of allo-HCT in high-risk adult AML. The meta-analysis by Koreth et al and this study (Basara et al) provide evidence to support the benefit of Allo-HCT with regard to OS in high-risk adult AML.

6.6.9 Summary Comments and Conclusions for the benefit of Allo-HCT in Adult AML

- Allo-HCT provides long-term benefit in adult subjects with intermediate- and high-risk AML. Allo-HCT is not superior to chemotherapy in subjects with low-risk adult AML.

- Stratification of these risk groups has evolved from the time that these studies were conducted to the present. Thus, the recommendations for allo-HCT should also be weighed in the context of the suitability of the individual subject based on these changes in risk stratification.

6.6.10 UCB-HCT Adult AML: Background

Discussions of the efficacy of UCB-HCT compared to various other donor sources in acute leukemia have been provided under Section 6.5.13 for Rocha 2004 (Rocha V, Labopin M et al, 2004), Laughlin 2004 (Laughlin MJ, Eapen M et al, 2004), Atsuta 2009 (Atsuta Y, Suzuki R et al, 2009) and Eapen 2010 (Eapen M, Rocha V et al 2010). The discussion in this section will focus on efficacy data specifically for AML for the studies by Atsuta 2009 and Rocha 2004.

Efficacy of UCB-HCT Compared to Other Donor Sources for Allo-HCT

Rocha 2004 (Rocha V, Labopin M et al, 2004)

This is a brief summary of the data provided regarding adult AML and UCB-HCT. The objective of this retrospective analysis was to compare UCB-HCT with mismatches in up to two HLA loci to fully matched unrelated BM (UBM-HCT) donor sources.
Forty-six percent of a total of 98 subjects with Acute Leukemia who received single-unit UCB-HCT were diagnosed with AML. Fifty-four percent of 584 subjects with Acute Leukemia who received unrelated fully matched Allo-HCT were diagnosed with AML. The difference in two-year LFS, comparing UCB-HCT (32%) and UBM-HCT (42%), was not statistically significant.

Study Conclusions:

- The study concluded that LFS at two years was comparable between UCB-HCT and Unrelated BM-HCT in AML.

Reviewer Comments and Conclusions:

- There were more subjects with advanced disease (beyond CR2) in the UCB-HCT group than in the unrelated BM-HCT group. More subjects in the UCB-HCT arm had received auto-HCT as prior therapy. The number of prior therapies is an adverse prognostic factor. Thus, the UCB-HCT group had more subjects with unfavorable prognostic factors.

- This evidence supports the conclusion that UCB may have similar outcomes to fully matched unrelated allo-HCT in adult AML.

Atsuta (Atsuta Y, Suzuki R et al, 2009)
The details of this study have been provided under Section 6.5.13

The objective of this retrospective analysis study was to compare UCB-HCT to unrelated matched allo-HCT in adults with AL. The study included 477 subjects with AML receiving allo-HCT following CR1, CR2, relapse or induction failure, between 2000-2005.
One hundred and seventy-three subjects received UCB-HCT, and 311 subjects received BM HCT. The two groups were comparable with regard to disease status. Risk categories were favorable, normal, other and unknown,

Table 18: OS, LFS in AML According to Disease Status at Transplantation for UCB-HCT and UBM-HCT (Atsuta Y, Suzuki R et al 2009)

Outcome	UCB-HCT (%) n= 173	UBM-HCT (%) n=311	p-value (UCB-HCT vs. UBM-HCT)
2-yr OS	43%	60%	p<0.001
2-yr LFS	36%	54%	p<0.001

UBM = Unrelated fully matched BM donor
n = sample size

Study Conclusions:

- In patients with AML who received UCB-HCT, early mortality is high, and improvement in supportive measure could improve outcomes.

- The 2-year OS and LFS fro unrelated BM-HCT were statistically significantly better than UCB-HCT (p<0.001). See Table 21.

Reviewer Comments and Conclusions:

- The number of patients in the UCB-HCT arm with favorable cytogenetics was almost half that in the UBMT arm. The patients in the UCB-HCT arm

had more advanced disease. These are adverse prognostic factors which could have negatively affected the relapse rates and the long-term outcomes.

- The group receiving UCB-HCT had better hematopoietic recovery and chronic GvHD of the extensive type. Thus, peri-transplant mortality is unlikely to have impacted the OS outcomes.

- The evidence from this study suggests that unrelated matched allo-HCT is superior to UCB in AML. However, this conclusion should be interpreted with caution due to imbalances in adverse prognostic factors between the two treatment groups.

6.6.11 Summary Comments and Conclusions for the Role of Allo-HCT and UCB-HCT in Adult AML

- Allo-HCT provides long-term benefit in Adult AML for subjects with intermediate- and high-risk AML. Allo-HCT is not superior to chemotherapy in subjects with favorable-risk adult AML.

- Changes to stratification to the risk groups (favorable or low, intermediate and high) have evolved from the time. The studies that were conducted to validate these risk groups were conducted in a different therapeutic era. Thus, the recommendations regarding the use of allo-HCT should be weighed in the context of the suitability for the individual patient, with consideration of available risk information.

- UCB-HCT may be considered an acceptable alternative to matched unrelated allo-HCT for treatment of AML, based on the evidence from the Rocha 2004 study in Acute Leukemia and from the Laughlin 2004 study (discussed in the section under Adult ALL). The results of the Atsuta 2009 study favoring allo-HCT from matched unrelated donors over UCB is interpreted with caution due to imbalances in adverse prognostic factors between the two arms.

6.7 Indications: Chronic Myelogenous Leukemia (CML) and Other Hematological Malignancies

The evidence of effectiveness of UCB-HCT as an alternative to a matched related or unrelated donor transplant for hematological malignancies is based primarily on data in acute leukemias. The feasibility of obtaining data for each

hematological malignancy is limited due to the small population sizes. The general practice of the use of allo-HCT in hematological malignancies is based on its efficacy in the treatment of acute leukemias. The accepted medical practice is to utilize UCB-HCT in specific diseases where allo-HCT is indicated and no other stem cell donor is available. In the case of UCB, cell dose and HLA matching are considered (Stanevsky A, Goldstein G et al, 2009, Wall DA, Chan KW, 2008, Smith AR, Wagner JE, 2009) when deciding on the donor.

6.7.1 CML: Background

Chronic Myelogenous Leukemia (CML) represents approximately 15% of adult leukemias, and there are 4000-5000 new cases a year in the United States (Howlader N, Noone AM et al, 2011). CML occurs in all age groups. The incidence of CML increases with age. The median age at diagnosis is 66 years. Advances in cytogenetics and molecular characterization have enabled the clinician to identify the Philadelphia chromosome and the *BCR-ABL* chimeric gene. Tyrosine kinase inhibitors (TKIs) produce long-term outcomes in CML without allo-HCT. Ninety percent of the CML patients have the Ph+ chromosome, and an additional 5% can be detected using FISH for the *BCR-ABL* gene. These patients will respond to targeted treatment with TKIs with favorable long-term outcomes. These changes pose challenges regarding the evaluation of efficacy of allo-HCT in specific groups of subjects with CML. The challenges include:

- Limited sample sizes for studies of allo-HCT in patients who are not eligible for treatment with TKIs (TKI refractory CML or have Philadelphia chromosome-negative CML) (Druker BJ, Lee SJ, 2005).

- Previously published literature that supports the use of allo-HCT in CML. These publications did not compare allo-HCT to TKI therapy. They also did not consider cytogenetic and molecular characterization. Therefore, the efficacy review for CML did not include an extensive review of the published literature from a period prior to the availability of TKIs and cytogenetic and/or molecular characterization.

General Approach to Management of CML

CML in the pediatric population occurs after age four and is rare compared to the incidence in the adult population. Treatment principles are the same as in adults. The discussion for the treatment of pediatric CML will refer to the treatment in the adult CML population.

Following FDA approval of imatinib mesylate (a TKI) in 2001, the use of allo-HCT in CML decreased. Although allo-HCT is considered curative (Goldman JM, Mijhail NS et al, 2010), the risk vs. benefit issues of allo-HCT outweigh those of imatinib. Imatinib has been shown to result in prolonged hematologic, cytogenetic

and molecular remissions (Deininger M, O'Brien et al 2009). Allo-HCT is no longer recommended as first-line treatment in chronic phase (NCCN Guidelines v2.2012 Chronic Myelogenous Leukemia). With the development of other TKIs that target other *BCR-ABL* mutations, second-line treatments with these therapies are also considered acceptable prior to consideration of allo-HCT.

Role of Allo-HCT in CML: Current Practice

Thus, despite reduction in morbidity and mortality from TRM, the role of allo-HCT is restricted to patients with specific mutations of *BCR-ABL* (T3151) that predict resistance to TKIs or patients who have failed TKIs or have other unfavorable *BCR-ABL* mutations.

Review Strategy for Efficacy of allo-HCT as a Treatment in CML

As stated in Section 5.2, this review is a two-step approach to evaluating the efficacy of UCB-HCT in CML. The first step is to evaluate the benefit of allo-HCT in CML. The second step is to evaluate the benefit of UCB as an alternate donor source of allo-HCT.

- To evaluate data for the role of allo-HCT as first-line therapy in CML, the study by Hehlmann (Hehlmann R, Berger Ute et al, 2007) was reviewed. No additional prospective and well-controlled study of the role of Allo-HCT in second CP was identified.

- A retrospective analysis by Boehm (Boehm A, Walcherberger B at al, 2011) was reviewed to assess whether subjects undergoing allo-HCT (related and unrelated BM donor) in the post-TKI era could serve as historical controls for single-arm studies with UCB as a donor source.

6.7.2 Comparison of Allo-HCT to Drug Therapy as First Line Therapy in Chronic Phase of CML (Hehlmann R, Berger Ute et al, 2007)

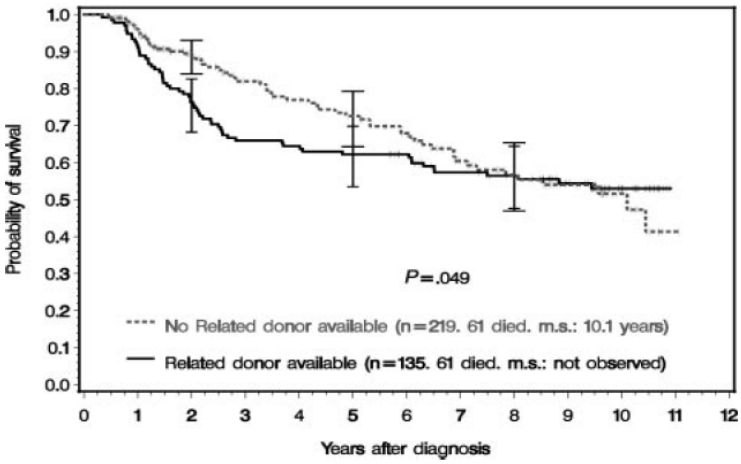
Hehlmann 2007

Objective:
The objective of this study was to compare matched related allo-HCT to IFN-gamma with regard to OS in subjects with newly diagnosed CML. Therapy with IFN-gamma was later modified to best available drug treatment, which included imatinib after 2000. To be eligible for the randomization, patients had to be eligible for allo-HCT.

Study design:
This was a prospective study from 1996 through 2001. There were two groups: subjects with matched related donors (MRD) and subjects with no MRD. Subjects who were in Chronic Phase (CP) with MRD received allo-HCT. Subjects in CP without MRD in whom a matched unrelated donor (MUD-HCT) was identified received an allo-HCT from that donor if they were unresponsive to best available drug therapy. If no MUD was found, they received best available drug treatment, which after 1999 included imatinib.

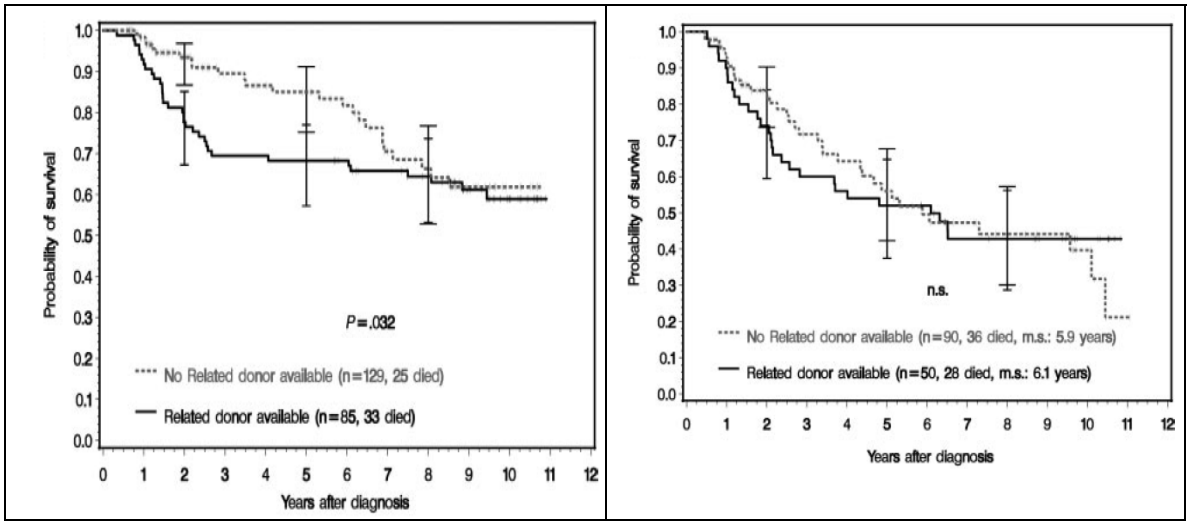
Results:
The results of the comparison of MRD to best available therapy are illustrated in Figure 17. Three hundred fifty-four eligible patients were analyzed in the entire group and then stratified by prognostic risk categories (low-, intermediate- and high-risk) (Hasford J, Pfirrmann M et al, 1998). Median follow-up is 8.9 years. Sixty-two of 122 subjects in the no donor arm received imatinib therapy; the remaining subjects received the best available therapy, which consisted mostly of interferon. The differences in the OS at 8 years between the two groups (donor vs. no donor group) were statistically significant for the low-risk subgroup (45 vs. 56%) and in the overall groups (57% vs. 56%). There was no difference between the donor and no donor groups with regard to OS in the intermediate and high-risk groups. Sample sizes were smaller for this intermediate and high-risk group than for the low-risk group.

Figure 9: OS for Subjects with Available MRD Compared to Subjects without MRD. (Hehlmann R, Berger Ute et al, 2007)



Overall group [Low, intermediate and High-risk (HR)]

Figure 10: OS for Low-Risk, and Non-Low-Risk Groups with Available MRD-HCT Compared to Those without MRD-HCT
(Hehlmann R, Berger Ute et al, 2007)



Low-risk (LR) subjects **Intermediate and HR subjects**

Study Conclusions:

- In this study, the results are statistically significant in favor of imatinib (or best available therapy) in the low-risk group and the overall group. The limited sample sizes for the intermediate and high-risk groups may have contributed to the results seen in these groups.

- The survival curves for donor vs. no donor in the intermediate and high-risk groups cross each other in the later phases of follow-up, with a downward trend in mortality for the no donor arm. An analysis of OS at 11 years suggests statistically significant results in favor of the no-donor group. It may be possible that an extended period of observation may detect a benefit for allo-HCT. However the number of subjects at risk is small, making it difficult to draw any meaningful conclusions.

Reviewer Comments and Conclusions:

- The introduction of imatinib therapy may have contributed to the late-phase plateau in the survival curves for the overall group.

- In this study, approximately half of the subjects in the no donor arm received drugs other than TKIs. This raises the possibility that the statistically significant results for OS in the no donor group could have

been the result of therapies other than TKIs. However multiple studies have established the superiority of imatinib over interferon in CML (Deininger M, O'Brien et al 2009). Therefore, it is unlikely that the improved OS in the no donor group in this study was driven by the subjects who received interferon or drugs other than TKIs.

- The conclusions from this study are applicable in the TKI era. Thus there is no role for allo-HCT as first-line therapy of CML in CP in the TKI era. It may be reasonable to reserve allo-HCT for specific groups in whom TKIs are not a viable options (TKI refractory disease and Ph-negative CML). This review of the literature did not find studies that compared the benefit of allo-HCT to therapies other than TKIs for such patients in whom TKIs are not a viable option.

- The use of imatinib or best available drug treatment is superior to allo-HCT in newly diagnosed patients with CML in CP.

6.7.4 Outcome of Allo-HCT in CML in the post-TKI era (Boehm A, Walcherberger B et al, 2011)

Boehm 2011

Objective:
The objective of this study was to evaluate OS and other transplant-related outcomes in subjects who received allo-HCT from BM or PBSC.

Design:
This was a retrospective analysis from a single center. Enrollment was from 1963-2007; however OS in specific cohorts is analyzed based on period of transplant. The study included MRD or matched or mismatched unrelated donor (URD) sources.

Results:
The discussion of the results is limited to subjects who received imatinib prior to HCT. These subjects were imatinib failures, had imatinib toxicity, or had high-risk disease (e.g., CP2 or greater). Seven of these subjects had sibling donor allo-HCT while the remainder underwent URD Allo-HCT. OS was 66% at a median follow-up time of 19 months. As seen in Figure 12, OS results for the imatinib group and the group that did not receive imatinib (predominantly in the period prior to 2001) prior to allo-HCT are similar.

Figure 11: OS Outcomes in Adult CML Undergoing Allo-HCT Performed in Specific Years (Boehm A, Walcherberger B et al, 2011)

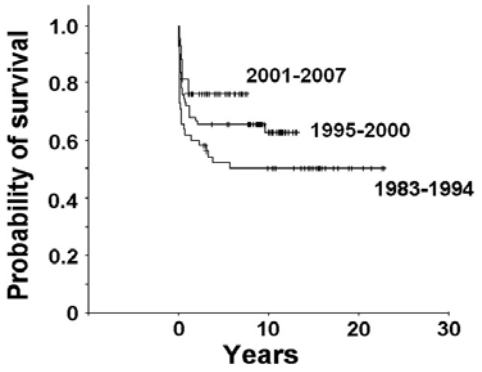
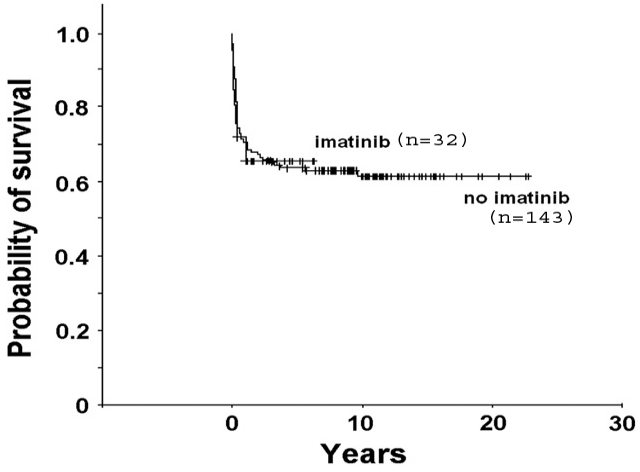


Figure 12: OS Outcomes in CML Subjects with and without Imatinib Exposure Prior to Allo-HCT (Boehm A, Walcherberger B et al, 2011)



Study Conclusions:

- The authors concluded that prior imatinib exposure did not impact the OS outcomes for allo-HCT transplant.

Reviewer Comments and Conclusions:

- The differences in outcomes among the time periods suggest that historical data from the pre-TKI era should not be used as controls for comparison to outcomes in more recent UCB studies.

- The survival data from the 32 subjects in the post-TKI era who received allo-HCT could be considered as historical controls for the purpose of comparing UCB-HCT to allo-HCT (with MRD and URD donors). This would be interpreted within the context of a median

follow-up period of 19 months. Such a control group would include subjects who by current guidelines are considered candidates for allo-HCT (high-risk or intolerant or refractory to imatinib and in disease stages beyond CP1).

- The above data illustrate a problem with retrospective analysis to determine efficacy of allo-HCT in CML, when the standard treatment paradigm for CML has changed.

6.7.5 Summary Comments and Conclusions for Role of Allo-HCT in CML

- There is no role for allo-HCT as first-line therapy in CML.
- Allo-HCT is considered an appropriate therapy in patients who have failed TKI therapy and have no further options for curative potential other than allo-HCT. The curative potential for allo-HCT in advanced disease has been established in a study conducted in the pre-TKI era (Goldman JM, Majhail NS et al, 2010).
- Due to the shift in the standard treatment paradigm for CML, selection of an appropriate allo-HCT historical control group for comparison to UCB-HCT will be difficult.

6.7.6 Review Strategy for Efficacy of UCB-HCT as a Treatment in CML

This is the second step to evaluate the benefit of UCB as an alternate donor source of allo-HCT in patients with CML.

- Studies comparing UCB to other donor sources were not available.
- Outcomes from one more recent single-arm study using UCB allo-HCT (Nagamure-Inoue T, Kai S et al, 2008) were reviewed. The study was assessed to determine if a study that consisted of subjects with prior TKI treatment could be compared to historical controls from the study by Boehm.

Retrospective single-arm study of Umbilical Cord Blood (UCB) in CML (Nagamura-Inoue T, Kai S, et al, 2008)

Nagamura-Inoue 2008

Objective:
The objective of this study was to evaluate prognostic factors for UCB-HCT and to determine if UCB-HCT is an appropriate therapy for CML.

Design:
Retrospective study from the Japan Cord Blood Bank Network in subjects receiving UCB-HCT after prior therapies from 1997-2006. Both pediatric and adult subjects were included.

Results:
Eighty-six subjects who did not have a related or unrelated matched donor were selected. Prior treatments included imatinib, Interferon-alpha (IFN-α), chemotherapy and other therapies. The median age was 39 years. Thirty-eight of these subjects were in chronic phase (29 in CP2). The remaining subjects had more disease advanced beyond CP. The median TNC dose was 2.5 x 10e7/kg. Event-free survival (EFS) assessments included graft failure, relapse or death in patients achieving a CR. Factors associated with favorable risk for LFS outcomes included TNC >$3x10^7$/kg and CP or AP stage of disease. OS outcomes were affected by disease stage at the time of UCB-HCT. The estimated 2-year EFS, LFS and OS for all subjects were 34%, 38% and 53%. At 2 years, the probability of OS and LFS for subjects in CP were 71% and 52% respectively.

Figure 13: K-M Estimates of OS, LFS, and EFS Following UCB-HCT for Subjects with CML (Nagamura-Inoue T, Kai S, et al, 2008)

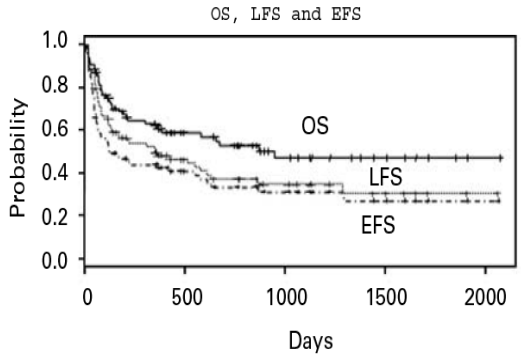
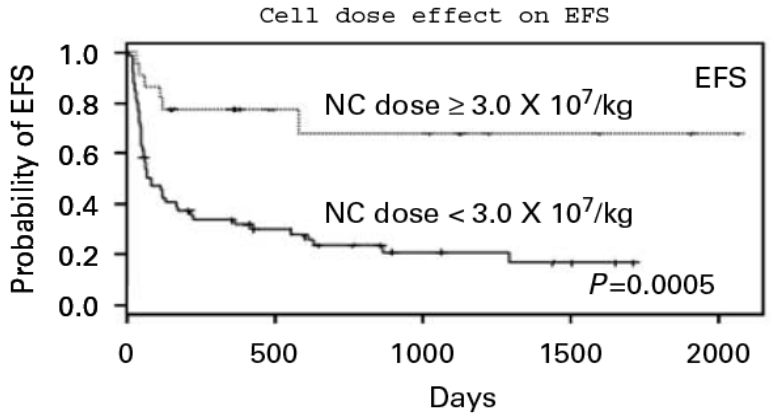
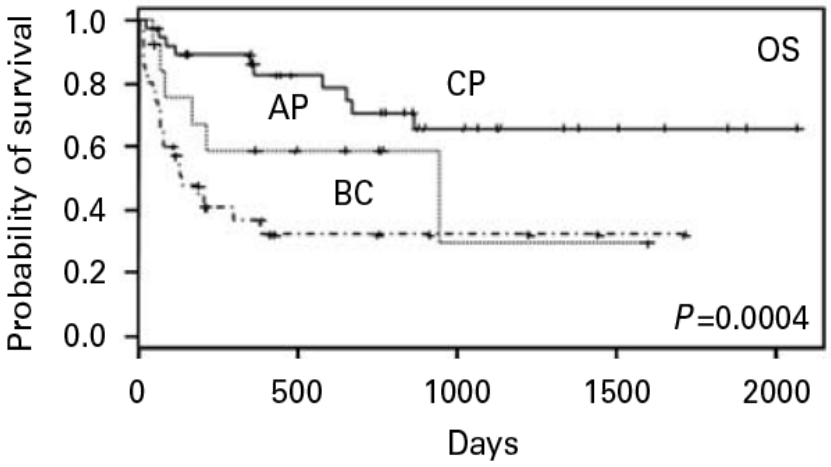


Figure 14: K-M Estimates of EFS in CML Based on TNC /kg
(Nagamura-Inoue T, Kai S, et al, 2008)



NC=nucleated cell

Figure 15: **K-M estimates of EFS by CML disease stage**
(Nagamura-Inoue T, Kai S, et al, 2008)



Study Conclusions:

- The subjects in this study met the current guidelines for allo-HCT. These results suggest that 2-year OS rates of 71% in the group who received UCB-HCT is comparable to 2-year OS rates of 44-77% in CP with unrelated allo-HCT from published studies.

Reviewer Comments and Conclusions:

- For subjects in CP, the overall survival at 2 years (71%) in this study using UCB-HCT is comparable to OS (76%) in the Allo-BMT group in the study by Boehm et al. With the limited data available in CML and the above studies, the OS outcomes may be comparable between UCB-HCT and other cell sources for Allo-HCT. The evidence from published literature is weak due to the absence of direct comparisons and the absence of data regarding detailed subject characteristics.

- UCB-HCT may be considered for CML patients who are intolerant or resistant to TKIs (T3151 mutation) and do not have a MRD or an available alternative suitably matched unrelated donor. UCB-HCT is not recommended for CML patients in CP who have not received treatment with TKIs.

6.7.7 Summary Comments and Conclusions for Role of Allo-HCT and UCB-HCT in CML

- There is no role for allo-HCT as first-line therapy in CML.

- Allo-HCT is considered an appropriate therapy in patients who have failed TKI therapy and have no further options for curative potential other than allo-HCT. This curative potential for allo-HCT in advanced disease has been established in a study conducted in the pre-TKI era (Goldman JM, Majhail NS et al, 2010).

- Changes in the standard treatment paradigm pose a challenge for the selection of an appropriate historical allo-HCT control group for comparison to UCB-HCT for the treatment of CML.

- Comparison using a historical control group of allo-HCT provides some evidence of comparability of UCB to other donor sources, especially in subjects with CP2 or beyond. The utility of UCB-HCT in accelerated phase or blast crisis is unclear.

- The evidence for effectiveness of UCB-HCT in CML is restricted to single-arm retrospective reports such as Nagamura et al. However, the available data may be sufficient to conclude that the benefit of UCB-HCT is comparable to Allo-HCT in subjects in CP2.

6.7.8 Review Strategy for Efficacy of UCB as a Treatment in Other Hematological Malignancies

As stated in Section 5.2, this review takes a two-step approach to evaluating the efficacy of UCB-HCT in other hematological malignancies. The first step would be to evaluate the benefit of allo-HCT in other hematological malignancies. The second step is to evaluate the benefit of UCB as an alternate donor source of allo-HCT. However, randomized studies and adequate comparative studies evaluating the role of allo-HCT in hematological malignancies other than for acute leukemia and CML are not available.

A single prospective study by Kurtzberg (Kurtzberg J, Prasad VK et al, 2008) is discussed below. This study does not evaluate long-term outcomes. It does provide evidence of hematopoietic reconstitution in various pediatric hematological malignancies. The primary objective of this trial was to assess overall survival (OS) at 180 days. However, considering that the general purpose of UCB-HCT is for hematopoietic reconstitution, this study is being considered for review.

Outcomes of Unrelated UCB in Pediatric Hematological Malignancies
(Kurtzberg J, Prasad VK et al, 2008):

Kurtzberg 2008

Objective:
The objective of this study was to determine survival outcomes at 180 days after transplant for unrelated UCB-HCT in children with primarily hematological malignancies.

Design:
Prospective multi-center study to evaluate OS at 180 days, engraftment, rate of relapse at two years, and two-year survival probabilities.

Results:
191 subjects were evaluated of 193 enrolled. One hundred nine subjects had ALL; 51 had AML; 13 had MDS; 7 had CML; 6 had lymphoblastic non-Hodgkin Lymphoma; 2 subjects had MDS with congenital agranulocytosis; and 1 subject had JMML. A minimum cell dose of $1x10^7$/kg was required and mismatches at up to two HLA loci were permitted. OS was 67.4% at 180 days and 49.5% at 2 years. The cumulative incidence of neutrophil recovery at Day 42 was 79.9%. Failure to engraft rate was 12%.

Study Conclusions:
- The OS at 180 days and the engraftment rate for UCB are comparable to other sources of allo-HCT.

Reviewer Comments and Conclusions:

- Thus hematopoietic reconstitution rates with UCB-HCT in hematological malignancies are comparable to other sources of allo-HCT.

Table 19 below presents the results for neutrophil recovery in the docket dataset. The cumulative incidence of neutrophil recovery at day 42 was similar for the docket dataset [all diagnoses except Hodgkin Disease (HD)] and the Kurtzberg 2008 study. These results support the efficacy of UCB for hematopoietic reconstitution to other hematological malignancies. Please see Dr. Przepiorka's safety review.

Table 19: Hematologic Recovery in Hematological Malignancies (Docket Data)

Table 1: Hematopoietic Recovery by Indication (TNC≥2.5)			
	N	Median time to ANC>500[+]	CumInc at Day 42 (%, 95%CI)[+,*]
ALL	363	27 days	78.4% (74.8-82.3%)
AML	301	26 days	75.8% (70.6-80.3%)
CML	40	30 days	69.2% (52.2-81.2%)
HD	7	42 days	57.1% (17.2-84.7%)
HIST	31	19 days	87.1% (69.2-95.0%)
MDS	65	27 days	70.3% (57.5%-79.9%)
MPD	12	23 days	75.0% (40.8-91.2%)
NHL/CLL	24	25 days	87.0% (64.8-95.6%)
OTHER	19	24 days	78.9% (53.2-91.5%)

6.7.9 Summary Comments and Conclusions for the Role of Allo-HCT and UCB in CML and Hematological Malignancies other than the Acute Leukemia

- Prospective controlled studies comparing long-term outcomes of allo-HCT and chemotherapy do not exist for hematological malignancies other than acute leukemia and CML.

- Single-arm studies of UCB-HCT with small sample sizes exist but have limited long-term outcome data.

- At best, there may be evidence of efficacy of UCB in adult CML subjects in second chronic phase.

- If the general purpose of UCB-HCT is considered to be hematopoietic reconstitution, then the evidence for effectiveness based on hematopoietic recovery in acute leukemia may be considered supportive for effectiveness in hematological malignancies other than leukemia. However, this review focuses on the assessment of long-term outcomes for efficacy rather than hematopoietic recovery.

6.8 Analysis of Clinical Information Relevant to Dosing Recommendations

6.8.1 Evidence to Support a Specific Cell Dose for UCB Use in Hematological Malignancies

In two of the four studies discussed below, dose was predetermined as a factor in the analysis. The Eapen 2010 study had a minimum cell dose of 2.5 x 10e7 TNC/kg and the Atsuta 2009 study examined efficacy in adult acute leukemias at median dose of $2.5x10^7$ TNC/kg.

The degree of HLA disparity is likely to impact the minimum cell dose that may be needed to produce a favorable efficacy outcome. Therefore, to provide support for a specific cell dose for UCB in the treatment of hematological malignancies, the effect of HLA disparity on cell dose should be considered. These four registry studies assessed the relationship of HLA matching and cell dose to outcome (LFS and OS) in hematological malignancies: Cohen YC and Scaradavou 2011; Eapen 2007; Eapen 2010; Barker 2010.

- The Cohen study (Cohen YC and Scaradavou A et al. 2011) did not find an effect of HLA disparity on OS. However, OS results were unfavorable for cell doses of $< 2.5 \times 10^7$ TNC/kg. LFS was not evaluated in the Cohen study.

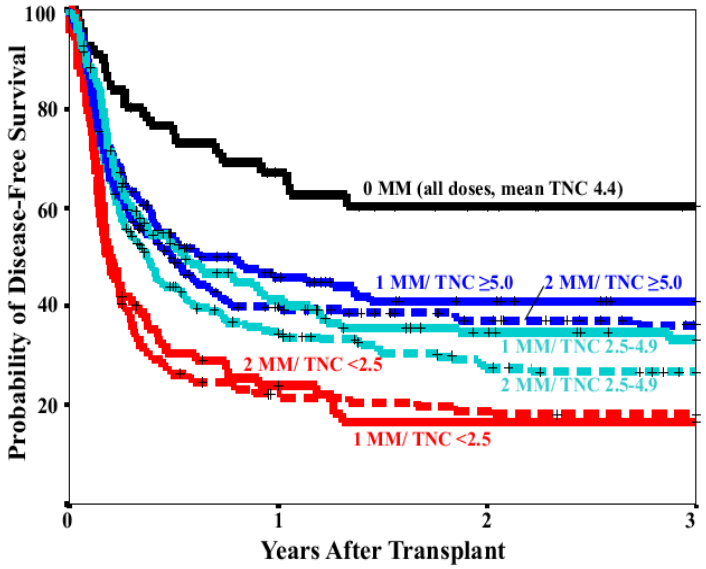
- The Eapen studies in pediatric and adult leukemia (2007 and 2010) evaluated the effect of varying degrees of HLA disparity and cell doses for UCB on outcomes compared to varying degrees of HLA disparity for bone marrow sources. The Eapen 2010 study (adults) aimed at selecting for $\geq 2.5 \times 10^7$ TNC/kg as the minimum cell dose for eligibility. Neither study found an effect of dose on LFS.

- The Barker study (Barker and Scaradavou et al 2010) compared outcomes in groups with varying degrees of HLA disparity and varying UCB cell doses. The study used a single HLA locus

mismatch and cell dose of 2.5 - 4.9x10^7 TNC/kg for the reference group.

- In the Barker study, the matched UCB group had the most favorable LFS outcomes, while the groups mismatched at 1 or 2 HLA loci receiving <2.5x10^7 TNC/kg, and the group with 3 HLA loci mismatches for UCB at any cell dose, had worse outcomes than the reference group (1 mismatch and cell dose ≥2.5x10^7 TNC/kg). LFS outcomes from the Barker study by dose are summarized in Figure 17 below.

Figure 16: Probability of Disease-Free Survival by Dose
(Barker and Scaradavou et al 2010)



Reviewer Comments and Conclusions:

- The Barker and Cohen studies support a relationship between HLA disparity and cell dose on outcomes in adult hematological malignancies. However, the results are not consistent across all four studies discussed above.

6.9 Sub-populations

6.9.1 Evidence in the Geriatric Population

The evidence of the efficacy of allo-HCT and UCB-HCT in hematological malignancies is predominantly in patients younger than 55 years of age. The study by Majhail (Majhail NS, Brunstein CG et al, 2011) is reviewed to evaluate efficacy of UCB in older subjects. In an attempt to decrease TRM, reduced intensity conditioning (RIC) regimens were used.

Majhail 2011

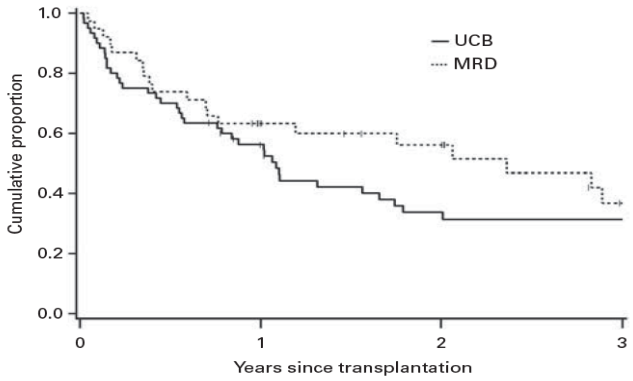
Objective:
The objective of this study was to compare MSD allo-HCT to UCB-HCT with regard to OS in subjects over age 55 years.

Design:
This was a prospective study of 98 consecutive subjects undergoing either MSD-HCT (n=38) or UCB-HCT (n=60) for AML or MDS between 2001 and 2009. MSD grafts were fully matched, while UCB matching was at 4-6/6 HLA loci. 95% of UCB recipients received two UCB units with a median cell dose of $4x10^7$ TNC/kg. All subjects received the same reduced intensity chemotherapy (RIC) regimen. The median age for subjects receiving MSD was 63; for UCB, the median age was 61 years.

Table 20: OS Comparing MSD vs. UCB in older subjects after RIC
(Majhail NS, Brunstein CG et al, 2011)

Outcome	MSD (n=38)	UCB (n=60)	p-value
OS at 3 years	37%	31%	0.21
LFS at 3 years	34%	22%	0.23

Figure 17: OS Outcomes after RIC Comparing UCB vs. MSD in Older Subjects (Majhail NS, Brunstein CG et al, 2011)



Study Conclusions:

- The results of this study suggest that UCB-HCT is comparable to MSD-allo-HCT with respect to LFS and OS in older subjects with AML and MDS who received RIC.

Reviewer Comments and Conclusions:

- This study provides supportive data for consideration of UCB as an alternate donor source for subjects who are >55 years and who are eligible for allo-HCT for the treatment of hematological malignancies. In this study, all recipients received RIC which would also affect OS and DFS. Safety data for this group has not been evaluated in this review.

9 Appendices

9.1 Literature Review

The literature search was conducted to identify historical experience and prospective clinical trial experience for hematologic malignancies. The search focused on acute leukemias because the published literature contained more information on the role of hematopoietic stem cell transplantation for acute leukemias than for other disorders. The searches were conducted through PubMed.

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