FDA BRIEFING DOCUMENT

Cellular, Tissue, and Gene Therapies Advisory Committee

September 22, 2011

BLA 125397

HemaCord (Hematopoietic Progenitor Cells-Cord)

Applicant: New York Blood Center

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

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Table of Abbreviations

AAP	American Academy of Pediatrics
ALD	(X-linked) Adrenoleukodystrophy
ALL	Acute lymphocytic leukemia
Allo	Allogeneic
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
Auto	Autologous
BLA	Biologics License Application
BM	Bone marrow
BMT	Bone marrow transplant
BRMAC	Biological Response Modifiers Advisory Committee
CBU	Cord blood unit
CFR	Code of Federal Regulations
CI	Confidence interval
CIBMTR	Center for International Bone and Marrow Transplant Research
CLL	Chronic lymphocytic leukemia
CMC	Chemistry, manufacturing, and controls
CML	Chronic myelogenous leukemia
COBLT	Cord Blood Transplantation (study)
CR	Complete remission
CTGTAC	Cell, Tissue, and Gene Therapies Advisory Committee
DFS	Disease-free survival
DMSO	Dimethyl sulfoxide
EBV	Epstein-Barr virus
EFS	Event-free survival
ES	Engraftment syndrome
FA	Fanconi anemia
FR	Federal Register
GVHD	Graft versus host disease
GVT	Graft versus tumor
HCT/P	Human cell, tissue, and tissue-based products
HLA	Human leukocyte antigen
HPC-C	Hematopoietic progenitor cells – cord
HSCT	Hematopoietic stem cell transplant
IND	Investigational New Drug application
IOM	Institute of Medicine
IST	Immunosuppressive therapy
LFS	Leukemia-free survival
MPS I	Mucopolysaccharidosis I
NAT	Nucleic acid test
NCI CTC	National Cancer Institute Common Toxicity Criteria
NHL	Non-Hodgkin lymphoma
NIMA	Noninherited maternal allele

NMDP	National Marrow Donor Program
NYBC	New York Blood Center
OS	Overall survival
PBSC	Peripheral blood stem cell
PIR	Pre-engraftment immune reaction
PTLD	Post-transplant lymphoproliferative disorder
RD	Related donor
SAA	Severe aplastic anemia (acquired)
SCID	Severe combined immunodeficiency
SCT	Stem cell transplant
SCTOD	Stem Cell Therapeutic Outcomes Database
SD	Standard deviation
SE	Standard error
SEER	Surveillance, Epidemiology and End Results Program
SEM	Standard error of the mean
TNC	Total nucleated cells
TRM	Treatment-related mortality
UBM	Unrelated bone marrow
UCB	Umbilical cord blood (unrelated, unless otherwise specified)
URD	Unrelated donor (bone marrow)

1. INTRODUCTION

The purpose of this CTGTAC meeting is to discuss BLA 125397**,** New York Blood Center's application for HemaCord (Hematopoietic Progenitor Cells-Cord).

The New York Blood Center submitted a Biologics License Application for HemaCord (Hematopoietic Progenitor Cells-Cord, HPC-C) for the use of allogeneic hematopoietic stem cell 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.

The applicant cited Docket 97N-0497 for the efficacy data to support this application. The applicant also submitted a review of its own safety outcomes dataset to evaluate safety of the product. This briefing document includes summaries of the reviews of the relevant docket material and information available in the public domain, and a summary of the FDA review of the applicant's safety data.

2. BACKGROUND ON FDA REGULATION OF CORD BLOOD

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) [http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm187144.pdf]. 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 1: History of Development of Regulatory Policy for Cord Blood

1997	Human Cells, Tissues, 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, which will 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.

3. PRODUCT INFORMATION

New York Blood Center (NYBC) has submitted a licensing application for minimally manipulated unrelated allogeneic placental/umbilical cord blood. NYBC has applied for licensure of units that have used a consistent manufacturing procedure that has been in place since 2006. Compliance of these units with quality standards set forth in the guidance document and also with appropriate regulations, such as good manufacturing practices, is currently under review by the agency. We are not asking the advisory committee to discuss any manufacturing related questions. However, a brief description of the product manufacturing and testing is provided below.

3.1 Overview of HPC-C Processing

The process used for collection and processing of HPC-C at NYBC is described in this section.

Mothers who consent to donate their newborn's cord blood for public banking are screened and tested for communicable infectious diseases. Cord blood is collected from mothers who screen and test negative for the listed infectious disease markers. NYBC has arrangements with six local hospitals and two out-of-state hospitals to collect cord blood and dedicated couriers to transport the collected cord blood to their manufacturing facility.

The cord blood is processed by volume reduction and partial red cell and plasma depletion. The final cell suspension (20 ml) is cryopreserved under conditions designed to preserve cell viability. The cell suspension if formulated by addition of 5 ml of 50% DMSO in 5% Dextran 40, so that the final concentration of DMSO is 10% and that of Dextran is 1%, is frozen at a controlled rate, and is stored in liquid nitrogen (-196°C).

The HPC-C bag is placed and maintained inside a protective metal canister for freezing and storage. HPC-C units are cryopreserved in two-compartment freezing bags. The larger compartment contains 80% of the cell suspension (20 ml) and the smaller contains 20% (5 ml).

For shipment to the end user, HPC-Cs are enclosed in labeled stainless steel canisters and protected by plastic foam thermal sleeves, and shipped frozen in special shipping containers (Dry-Shippers) designed to maintain a controlled environment and a very low temperature ($\leq$ -150°C). Attachments to each shipment provide complete identification of the product, its contents and intended recipient and detailed instructions regarding the thawing of the product, dilution and re-suspension of the cells and infusion to the intended recipient.

3.2 Product Testing

NYBC's BLA application contained information/data on their approach to meeting the recommended tests and results described in Section V. Chemistry, Manufacturing and Controls of the HPC-C licensure guidance. The table below is reproduced from Section V. Chemistry, Manufacturing and Controls of the HPC-C licensure guidance. NYBC performs testing and uses the acceptance criteria found in this table.

Table 2: Testing of HPC-C[1]

Product Characteristics[2]	Testing	Sample (Type and Timing)	Results of Product Testing
Safety	Infectious diseases – Testing Required. (21 CFR 1271.45 through 1271.90)	Maternal peripheral blood obtained within 7 days of cord blood collection – Type and Timing Required. (21 CFR 1271.80(a) and (b))	All tests negative except non-treponemal test for syphilis when confirmatory test is negative. (Cytomegalovirus (CMV) results are recorded.)
			CMV – Report
	Sterility – Bacterial and fungal cultures – Testing Required. (21 CFR 211.165(b), and 21 CFR 610.12)	HPC-C (pre-cryopreservation) **	No growth
	Hemoglobin	Cord blood*	No homozygous hemoglobinopathy
Purity and Potency[3]	Total nucleated cells (TNC)	HPC-C (pre-cryopreservation)	≥ 5.0 x 10^8 TNC ***/ unit HPC-C
	Viable nucleated cells	HPC-C (pre-cryopreservation)	≥ 85% viable nucleated cells
	Viable CD34+ cells (flow cytometry)	HPC-C (pre-cryopreservation)	≥ 1.25 x 10^6 viable CD34+ cells ****/ unit HPC-C
Identity	Human leukocyte antigen (HLA) Typing	Cord blood	Report
	Confirmatory HLA typing	Attached segment of HPC-C	Confirms initial typing
	Blood Group and Rh Type	Cord blood	Report

[1] Testing, Sample (Type and Timing), and Results are recommended unless specifically noted as required.
[2] The PHS Act requires a demonstration that the product is safe, pure, and potent.
[3] Other purity and potency assays may be considered under the BLA.
** Cord blood = a sample of unmanipulated cord blood. A red cell sample or other cord blood aliquot obtained after volume reduction may be used for testing with appropriately validated reagents or test systems.*
*** Sample may be obtained before or after addition of the cryoprotectant.*
**** Based on 20 kg recipient, a target dose of ≥ 2.5 x 10^7 nucleated cells/kg and ≥ 70% post-thaw recovery = 1.7 x 10^7 nucleated cells/kg.*
***** Based on CD34+ cells ≥ 0.25% of TNC prior to freezing.*

In addition to the testing noted above, NYBC performs additional donor and product testing as summarized in the table below.

Table 3: NYBC Additional Donor and Product Testing

Testing	Sample Type	Results of Product Testing
Donor screening tests Hepatitis B virus nucleic acid test (HBV-NAT) West Nile Virus NAT Cytomegalovirus NAT Trypanosoma cruzi (antibody)	Maternal peripheral blood and cord blood	Negative; in case of discrepant results, maternal test results are used.
HLA typing	Maternal peripheral blood and cord blood	Mother and cord must share haplotype.
Colony forming units	post processing samples and on integral segments post thaw at the time of release	Report results as growth or no growth.

4. SUMMARY OF EFFICACY INFORMATION

4.1 Nature and Scope of Efficacy Review

The Applicant referenced the material in the docket in support of the requested indications. This briefing document contains a summary of the efficacy information from the docket, updated with relevant information from the literature.

The datasets submitted to the docket were not the results of prospective, controlled studies. Rather, the datasets document experience with unrelated cord blood transplantation, reported in whatever detail and format the submitters elected. Limitations of these data include incomplete documentation of diagnostic criteria and assessments, lack of individual detail on patient characteristics such as disease-specific prognostic factors, and data errors that may, in particular, affect the survival times calculated for certain diseases. Since the principal outcomes provided by submitters were related to engraftment and survival, the datasets lacked information about other types of outcomes that may relate to benefit. No control groups were included with the datasets. The literature review for this BLA was designed to complement the docket dataset by providing: control data for comparison to the docket data, perspective on issues that could not be adequately assessed with the docket data, and updated information relevant to product efficacy.

4.2 Hematological Malignancies

Background

Hematological malignancies are a diverse group of neoplasms. Table 4 below provides the disease types, incidence, median age at diagnosis, distribution by sex, and 5-year survival rates.

Table 4: 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 56.1% of all hematological malignancies.
Hodgkin's 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's lymphoma

* Howlander and Noone et al., 2011

Prognosis is variable and dependent on the specific disease, stage, cytogenetic factors, response to treatment, and stem cell transplant options. If left untreated, many of these disorders, including AML and ALL, are fatal (Applebaum and Forman et al., 2008). Available treatments for hematological malignancies include chemotherapy, targeted therapies, and bone marrow transplantation, including autologous and/or allogeneic stem cell transplant (Allo-SCT).

Allogeneic Stem Cell Transplantation in Hematological Malignancies: Clinical Practice

Allogeneic stem cell transplant (Allo-SCT) 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-SCT 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. As the clinical experience with Allo-SCT evolved, and with improvements in transplant-related mortality (TRM), the role of Allo-SCT in clinical practice was generalized from acute leukemias to other hematological malignancies. With this increasing role of Allo-SCT in the treatment of hematological malignancies, and a limited inventory of suitable stem cell sources, the clinical practice of Allo-SCT evolved from using bone marrow to using peripheral blood and umbilical cord blood as stem cell sources.

Lymphomas constitute nearly 56% of all hematological malignancies. However, the role of Allo-SCT in lymphoma is limited, due in part to the availability of other curative therapies, the availability of sibling donors, and the toxicities associated with the conditioning regimens. Currently, acute leukemias, predominantly AML and ALL, constitute the most common hematological malignancies in which Allo-SCT is used as a treatment option.

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 improved TRM. With these improvements in TRM, Allo-SCT is now 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-SCT.

Umbilical Cord Blood Transplantation in Hematological Malignancies: Evidence of Effectiveness

Both bone marrow and umbilical cord blood (UCB) contain hematopoietic progenitor cells, and transplantation from either source is expected to act through a graft vs. tumor effect. Therefore, UCB transplantation is expected to support hematopoietic reconstitution and provide disease-specific outcomes similar to the effects of bone marrow transplantation.

Early studies of cord blood transplantation were primarily to evaluate whether cord blood could provide adequate progenitor cells to support engraftment (Broxmeyer and Douglas et al. 1989). Encouraging results from these studies led to the development of cord blood banking and a registry-based collection of data, while attempting to collect and store cord blood units under specific guidelines. Early studies of cord blood transplants in hematological malignancies were predominantly in the pediatric age group. These studies confirmed favorable engraftment outcomes, reduced risk of GVHD and overall mortality that was comparable to unrelated bone marrow transplants (Rubinstein and Carrier et al. 1998; Rocha and Wagner, Jr. et al. 2000; Rocha and Cornish et al. 2001).

Subsequent registry studies (Laughlin and Eapen et al. 2004; Rocha and Labopin et al. 2004) analyzing patients with adult acute leukemia suggest that UCB could be an acceptable alternative

to unrelated bone marrow transplantation. A summary of these two studies is provided in Table 5 below.

- The Laughlin and Rocha studies compared the rates of disease-specific survivals between UCB and other stem cell sources in adult subjects. The comparator arm in each study was unrelated donor sources.

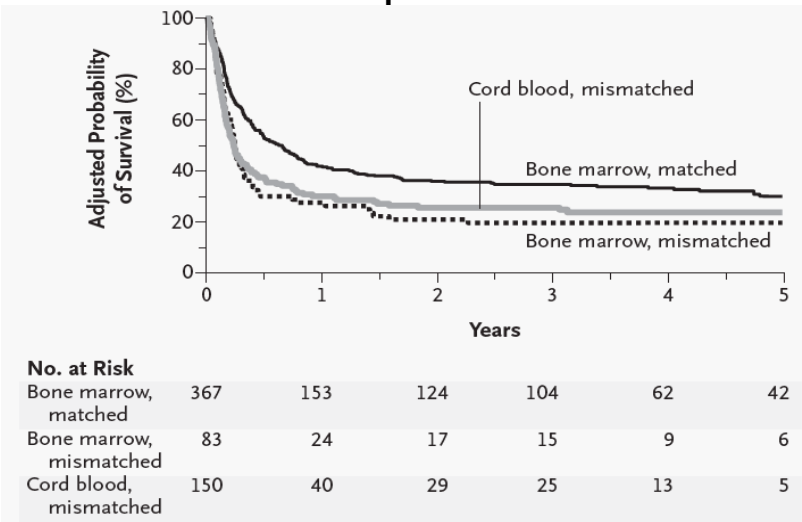
- In the Laughlin study the median TNC dose/kg for the Matched BM (24 x 10^7) and mismatched BM (22 x 10^7) groups were ten times the median dose in the Cord Blood group (2.2 x 10^7)

Table 5: UCB vs. UBM in AML and ALL

Registry/Author Age range (yrs)	Source	Disease AML / ALL (%)	LFS	OS	Conclusions and outcome summary
IBMTR/NCBP Laughlin 2004 16-60 yrs	UCB (150)	39% / 30%	3yr LFS: 23 %	3yr OS: 26%	M-UBM has highest LFS and OS.
	M-UBM (367)	31% / 22%	3yr LFS: 33 %	3yr OS: 35%	
	MM-UBM (83)	33% / 20%	3yr LFS: 19 %	3yr OS: 20%	
EBMT Rocha 2004 24-32 yrs	UCB	46% / 54%	2yr LFS: 33%	2yr OS: 36%	No difference in LFS
	M-UBM	54% / 46%	2 yr LFS: 38%	2yr OS: 42%	

UCB = Umbilical Cord Blood mismatched at 1-2 loci
M-UBM = Matched Unrelated Bone Marrow (Donor Cells)
MM-UBM = Mismatched Unrelated BM (mismatched at one locus or – two loci)

Figure 1: Survival after Transplant with UCB vs. Bone marrow



Source: Laughlin and Eapen et al. 2004: OS

Review of the docket data, the published studies by Laughlin et al and Rocha et al (above), and recommendations of the CTGT Advisory Committee formed the basis for the issuance of the

FDA Guidance *Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancie*s (FDA 2009).

As part of the current BLA review, an updated literature review identified additional studies comparing UCB to other sources of stem cells for hematopoietic reconstitution and long term outcomes in hematological malignancies. The purpose of this review of updated literature was to examine the evidence that exists in studies that have a large sample size, recent updates, and direct controls. Four selected studies are summarized in Table 6 below.

- Three of the four studies are from registries and thus are expected to provide a multi-center perspective (Eapen and Rubinstein et al. 2007; Eapen and Rocha et al. 2010; Atsuta and Suzuki et al. 2009).

- The data from the Tomblyn study is based on a single-institution experience and includes subjects who received related and unrelated bone marrow transplants, thereby providing perspective on the place for UCB in the spectrum of donor sources for Allo-SCT transplants (Tomblyn and Arora et al. 2009).

- The Japanese study (Atsuta) was selected because the study enrollment period is fairly recent (2000-2005) and attempts to evaluate donor graft sources with regard to outcomes, considering AML and ALL as separate groups. The Atsuta study compared UCB to fully matched unrelated bone marrow (Atsuta and Suzuki et al. 2009).

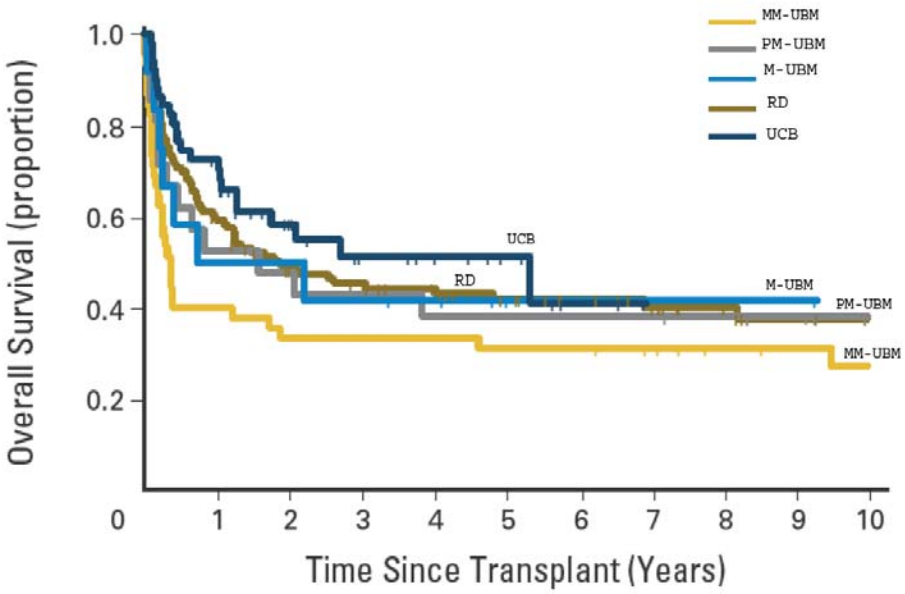
Table 6: UCB vs. Bone Marrow Transplantation in Acute Leukemia, recent published studies

Registry source/Author/ Age range	Stem cell source based on HLA disparity (n)	Disease (n)	LFS probability (%)	OS probability	Outcome summary
CIBMTR (Pediatric) Eapen and Rubinstein et al. 2007 Age 0-16 yrs	M UCB (35)	AML (16) ALL (19)	5-yr LFS: 60%	Not provided	LFS highest with M UCB; LFS with MM UCB similar to LFS with M UBM and MM UBM.
	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%		
CIBMTR, NCBP, EBMT and Eurocord-Netcord (Adult) Eapen and Rocha et al. 2010 Age 16-50+ yrs	M – MM UCB-2 (161)	***UCB*** AML: 46% ALL: 54% ***PBPC*** AML: 59% ALL: 41% ***BM*** AML: 58% ALL: 42%	2-yr LFS*: 44%	Not provided	LFS with UCB sources similar to LFS with matched and mismatched non-UCB sources. The minimum cell dose for eligibility was 2.5 x10^7/kg.
	M PBPC (632)		2-yr LFS*: 50%		
	MM PBPC (256)		2-yr LFS*: 39%		
	M UBM (332)		2-yr LFS*: 52%		
	MM UBM (140)		2-yr LFS*: 41%		

Registry source/Author/ Age range	Stem cell source based on HLA disparity (n)		Disease (n)	LFS probability (%)	OS probability	Outcome summary
University of Minnesota Tomblyn and Arora et al. 2009** Median Age 13 yrs (included adults)	RD (113)		ALL in CR1 & 2	5-yr LFS: 40%	5-yr OS: 42%	Median cell doses were not provided. Long-term outcomes similar across all donor sources.
	M UBM (12)			5-yr LFS: 42%	5-yr OS: 42%	
	PM UBM (21)			5-yr LFS: Not provided	5-yr OS: 38%	
	MM UBM (45)			5-yr LFS: 27%	5-yr OS: 31%	
	UCB (51)			5-yr LFS: 49%	5-yr OS: 51%	
Japanese registry study Atsuta and Suzuki et al. 2009 Median Age: 38 yrs for both AML and ALL groups	AML	UCB (173)	AML and ALL in remission, induction failure, relapse and unknown disease states.	AML LFS 2yrs, UCB vs. M-UBM 42% vs. 54% (p=0.04) HR=1.5 (CI 1.1, 2.0) P=0.012	AML OS 2yrs UCB vs. M-UBM 48% vs. 59% (p=0.010) HR: 1.5 (CI 1.0, 2.0) P=0.028	Median cell dose (TNC/kg x 10^7) 2.44 for AML and 2.48 for AML. Subjects with AML who received M-UBM had higher LFS and OS than subjects who received UCB. More subjects with relapsed disease at the time of transplant (a known poor prognostic factor) were in the UCB arm for AML, which could explain the worse outcomes. Subjects with ALL who received UCB had LFS and OS similar to subjects who received M-UBM.
		M-UBM (311)				
	ALL	UCB (114)		ALL LFS 2yrs, UCB vs. M-UBM 46% vs. 44% (p=0.41) HR=1.2 (CI 0.9-1.18) P=0.28	ALL OS 2yrs UCB vs. M-UBM 52% vs. 53% (p=0.99) HR=1.1 (CI: 0.9-1.6) P=0.78	
		M-UBM (222)				

M UCB = Matched UCB
MM UCB-1L = Mismatched UCB at 1/6 HLA loci with low cell dose (low cell dose was $\leq 3x10^7$ TNC/kg for Eapen 2007)
MM UCB-1H = Mismatched UCB at 1/6 HLA loci with high cell dose (high cell dose was $> 3x10^7$ TNC/kg for Eapen 2007)
MM UCB-2 = Mismatched UCB at 2/6 HLA loci with any cell dose for Eapen 2007)
M-MM UCB = for CIBMTR/NYCBP/EBMT-Eurocord (Eapen 2010) and Japanese Registry studies, included matched and mismatched up to 2 HLA loci. Cell doses for Eapen 2010 were at or above $2.5x10^7$ TNC/kg.
M UBM = Unrelated BM Matched at 8/8 HLA Loci
MM UBM = Matched at 6/8 and 7/8 for Eapen 2007 (pediatric) and 7/8 for Eapen 2010 (adult)
MM PBMC = Mismatched PBMC matched at 7/8 HLA loci
MR BM = Matched related BM
MM UBM = Mismatched Unrelated BM
RD = Related Donor
PM – UBM = Partially Matched Unrelated Bone Marrow (mismatched in up to one locus, depending on extent of HLA resolution)
HR = Hazard ratio
* 2-yr LFS for patients undergoing transplant in remission; data for subjects in relapse or induction failure were excluded.
** Allo-SCT in CR1 and CR2 (1990-2005)

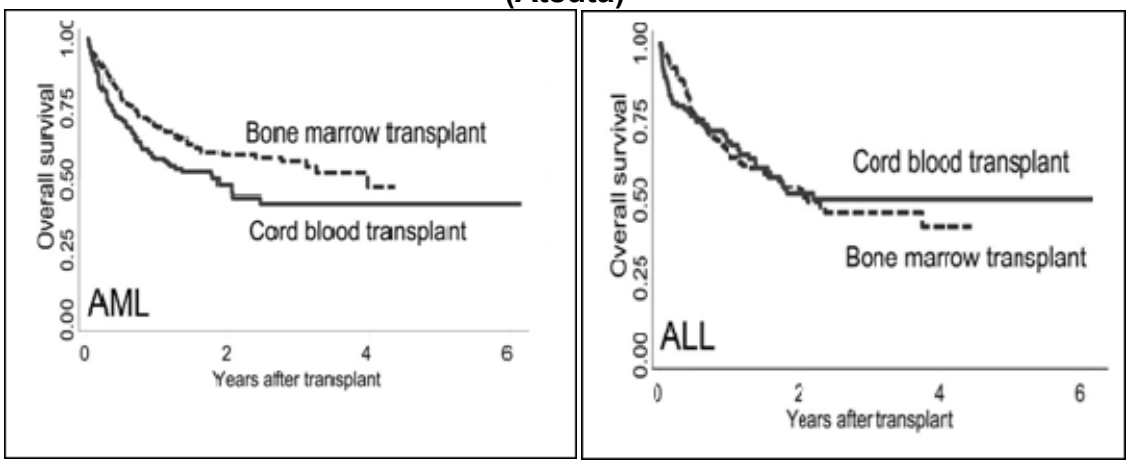
Figure 2: Survival in Allo-SCT in CR1 and CR2 for ALL by graft source (Tomblyn)



MM – UBM = Mismatched Unrelated Bone Marrow
M – UBM = Matched Unrelated Bone Marrow
PM – UBM = Partially Matched Unrelated Bone Marrow (mismatched in up to one locus, depending on the extent of HLA resolution)
RD = Related Donor
UCB = Umbilical Cord Blood

Source: Minnesota (Tomblyn and Arora et al. 2009)

Figure 3: Survival in Allo-SCT for AML and ALL, cord blood vs. bone marrow (Atsuta)



Source: Japanese Registry Study (Atsuta and Suzuki et al. 2009)

As illustrated by these four studies (Table 6; Figure 2; Figure 3), recent evidence supports the previous conclusion that UCB is similar in effectiveness to bone marrow transplantation as a treatment for acute leukemias.

Limitations of the evidence of effectiveness

The evidence of effectiveness of UCB 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 and the general acceptance of any form of Allo-SCT as treatment for specific diseases. However, the extent to which the evidence of the effectiveness of UCB in acute leukemias supports the use of UCB in patients with other hematological malignancies is unclear.

Evidence to support a specific cell dose for UCB use in hematological malignancies

Of the four studies discussed in Table 6 above, the Eapen 2010 study and the Japanese studies examined efficacy in adult acute leukemias at median doses above $2.5x10^7$ TNC/kg.

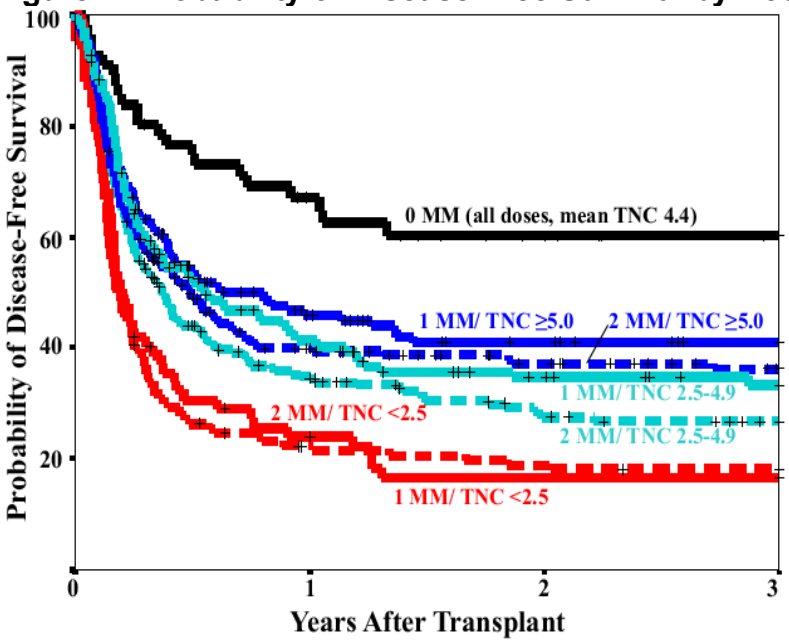
The degree of HLA disparity is expected to impact the minimum cell dose that may be needed to produce a favorable efficacy outcome. Therefore, to provide support for a specific cell dose for UCB in the treatment of hematological malignancies, the effect of HLA disparity on cell dose should be considered. Four registry studies assessed the relationship of HLA matching and cell dose to outcome (LFS and OS) in hematological malignancies: Cohen and Scaradavou et al. 2011; Eapen and Rubinstein et al. 2007; Eapen and Rocha et al. 2010; Barker and Scaradavou et al. 2010.

- The Cohen study 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 compared groups with varying degrees of HLA disparity and cell doses of UCB with regard to outcomes, using a single HLA locus mismatch and cell dose of 2.5 - $4.9x10^7$ TNC/kg as 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 $\geq 2.5x10^7$ TNC/kg). LFS outcomes from the Barker study by dose are summarized in Figure 4 below.

Figure 4: Probability of Disease-Free Survival by Dose



Source: Barker and Scaradavou et al. 2010

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.

4.3 Nonmalignant Indications – General Considerations

Diseases Evaluated

The cord blood guidance listed several nonmalignant conditions as proposed indications for unrelated cord blood. Some of those indications are specific diseases (Hurler syndrome, Krabbe disease, adrenoleukodystrophy, and beta-thalassemia), whereas other indications are categories of disease (primary immunodeficiency and bone marrow failure) that could include numerous different conditions. For the latter group of indications, this briefing document provides information from the docket only on those specific conditions that were substantially represented in the docket datasets.

For the primary immunodeficiency diseases, the docket datasets contained the numbers of cases shown in Table 7.

Table 7: 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

For bone marrow failure diseases, the docket datasets contained the conditions listed in Table 8.

Table 8: 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
Schwachman-Diamond syndrome	1

Consequently, the review for primary immunodeficiency focused on SCID, and the review for bone marrow failure diseases focused on Fanconi anemia and severe aplastic anemia.

Docket and Literature Review

The data provided in the docket reflected essentially only uncontrolled experience with UCB transplantation. A literature search was performed to look for historical data in an attempt to identify appropriate control populations. A major limitation when using such controls is the inability to control bias, because it is difficult, if not impossible, to establish comparability of the treatment and control groups.

Literature was also reviewed to identify any additional substantial experience using UCB for the indications of interest and to determine if there was evidence regarding effects of UCB on clinical outcomes other than the outcomes provided in the docket datasets.

The principal clinical efficacy outcome provided by the 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, which 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.

4.4 Hurler Syndrome

Mucopolysaccharidosis I (MPS I) is an autosomal recessive lysosomal storage disorder caused by deficiency of alpha-L-iduronidase (IDUA) due to 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 is usually 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.

Baseline Data

In the docket datasets, diagnostic information other than the diagnosis was not provided. Thus, eligibility criteria for the series and the criteria for classification of the phenotype are unknown. Most (60%) of the cases came from one dataset, in which diagnoses of Hurler-Scheie also appeared, indicating that a distinction between the two had been made in that dataset.

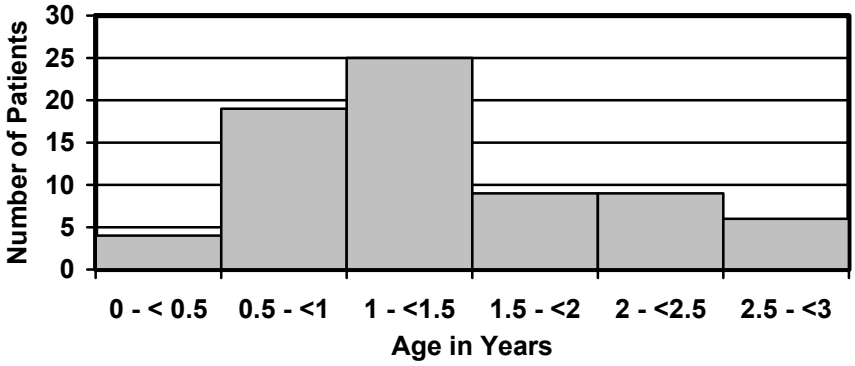
Basic demographics for the Hurler patients in the pooled datasets are shown in Table 9 below, together with basic treatment data. Demographic information other than age was not provided in one of the datasets.

Table 9: 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
10th, 25th, & 75th 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)

* Dose was unknown for 2 patients (3%)

Figure 5: Age Distribution of Hurler Syndrome Patients – Docket Data



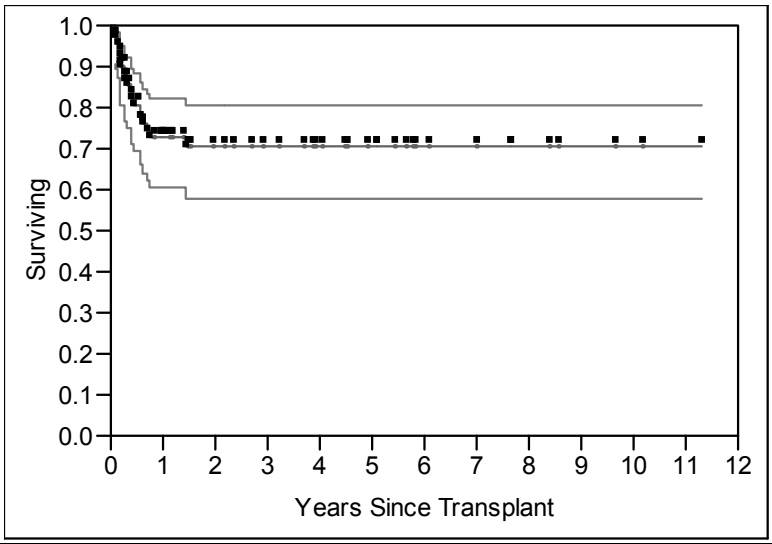
The age distribution appears to be as expected for patients early in the course of Hurler syndrome. The older patients may represent those for whom UCB transplant was delayed until a year or more after diagnosis, but might also be an indication that some patients with Hurler-Scheie syndrome have been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

Analysis of Primary Endpoint

Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown in Figure 6 below for the 71 analyzable Hurler syndrome patients from the pooled docket datasets. There is approximately 27% mortality by the end of the first year. The loss to follow-up is heaviest at around 1 year. After the first year, additional mortality is very low, but the numbers at risk decline progressively. Median follow-up is 1.1 years; 75th quartile of follow-up was 4.5 years.

Figure 6: Survival (± CI) Following UCB Transplant for 71 Hurler Patients – 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

Relationship Between Dose and Survival

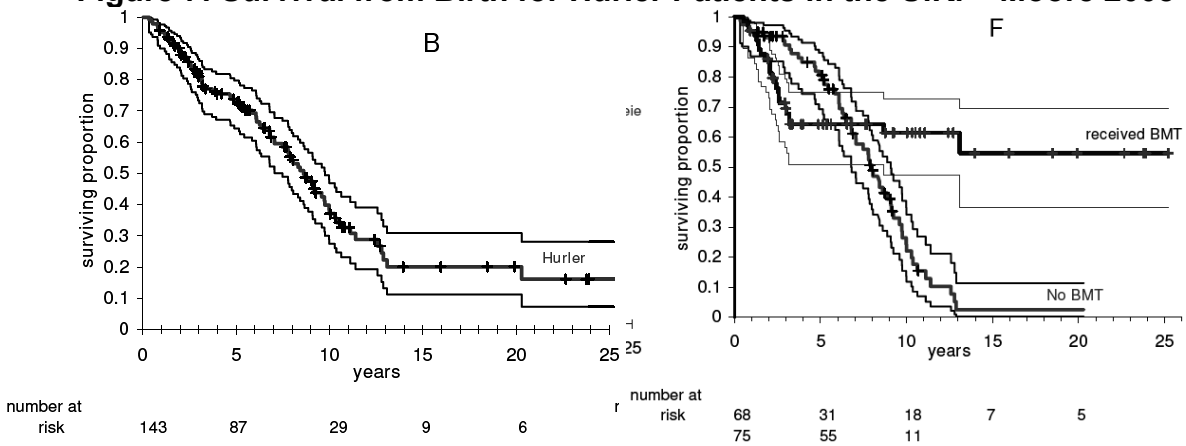
A proportional hazards model found no significant relationship between TNC dose and survival (nominal p = 0.97) with an estimated 0.2% *increase* in hazard for each increase in dose of 10^7 TNC/kg. There was no patient with a dose < 2.5 x 10^7 TNC/kg, so a subgroup analysis for that dose range could 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.

Historical Control Data

The most useful historical control data come from an analysis by Moore (Moore and Connock et al. 2008). The authors obtained information from a longitudinal data set maintained in the U.K. for over 20 years by the Society for Mucopolysaccharidosis Disease. 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 143 cases is shown as display B in Figure 7, below. Because 65 Hurler syndrome patients

received bone marrow transplant (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 Figure 7.

Figure 7: Survival from Birth for Hurler Patients in the U.K. – 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. The assumption of proportional hazards is not supported when survival curves cross so dramatically, 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.

Moore also showed an overall survival curve for Hurler-Scheie patients. This is not reproduced here, but 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 above, one docket dataset had evidence that suggested it made the distinction, but, in the other two, only the term "Hurler syndrome" appeared, and the diagnostic criteria used for making the diagnosis and deciding on the phenotype were not stated.

Given the dates of the Moore study, the exposure to laronidase in the control population was probably none to minimal. The data for the No BMT experience are reasonably consistent with the natural history reported in less detail by previous authors, who cited an average age at death of 6.25 years, with a range of 1.3 to 10.9 years, in a series of 27 Australian patients (Wraith and Rogers et al. 1987). The Moore data appear to be the most complete and detailed historical data available.

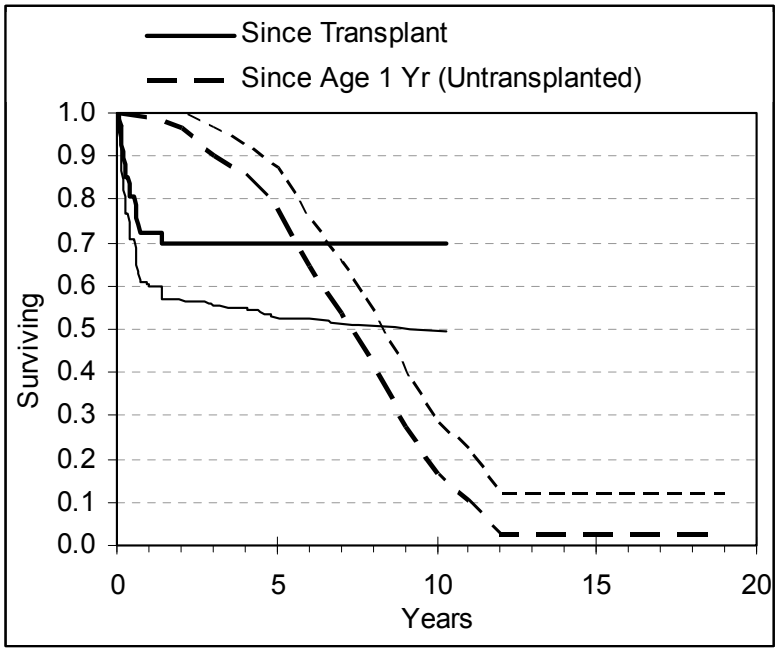
Comparisons with Historical Control Data

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. In an attempt to compare the active treatment and historical control experiences more directly, the Moore control experience was visually extracted from the published graphic. Because the median age at transplant was just over 1 year, the Moore data were also adjusted to approximate survival after

transplant, rather than survival from birth. As noted earlier, there are concerns about the reliability of the follow-up times reported for some Hurler syndrome patients in the dockets datasets. An adjustment was made in an attempt to compensate: for surviving patients in the docket for which there was a question about the reliability of their follow-up times, the times were discounted (by a factor of 1/3 for follow-up under three years and by 1 year for follow-up over 3 years) to approximate a time to last visit; time to death was not adjusted for those who died. In addition, confidence intervals for the UCB survival curve were estimated using a hybrid technique that is less prone to being conservative in the tails of distributions subject to heavy censoring (Borkowf 2005).

The superposition of the adjusted Moore data and the post-transplant UCB experience is shown in Figure 8. The estimated survival is very similar to that without adjustment, but the UCB confidence limits extend almost 10% lower by the right end of the curve:

Figure 8: 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 docket 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.

Sources: UCB (Transplant) data from docket datasets, control (Untransplanted) data modified from Moore and Connock et al. 2008 (see text)

Although the lack of individual patient data for the historical controls precludes 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 follow-up 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 anti-conservative because it ignores the uncertainty in the control group.)

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 long periods of observation for the BMT patients produce a hazard ratio estimate that is an averaged 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.

Analysis of Secondary Endpoints

For patients in one dataset, additional data were provided regarding 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 10: Enzyme Results for Hurler Syndrome Patients – Docket Data

	Pre-transplant (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 using the docket datasets because no other disease-specific outcome data were included.

Published Reviews and Expert Opinion

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). More recent reviews of the uses of cord blood are found in Smith and Wagner 2009 and Prasad and Kurtzberg 2010. The latter review regarded the use of UCB in severe phenotypes of MPS I as standard of care, and provided a list of references in support; these are described below.

Published Experience with UCB in Hurler Syndrome

The most relevant additional experience from the literature is summarized below:

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

This article reports on 20 patients with Hurler syndrome transplanted with unrelated cord blood at Duke University between 1995 and 2002, and it presumably represents a subset of the patients already considered in the review docket datasets. 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 compound heterozygous for mutations associated with the severe phenotype of MPS I. 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 article did not provide an objective comparison to untransplanted Hurler syndrome control data.

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

This article reports on the COBLT study sponsored by NHLBI, in which UCB transplant was performed in 69 patients with lysosomal and peroxisomal storage disorders, almost all of whom were transplanted at Duke University. The population included 21 patients with Hurler syndrome, 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 Hurler syndrome patients. However, it did include 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 in non-Caucasians and in those who received units as part of an expanded access program.

Dusing and Thorpe et al. 2007a (n=18), Dusing and Thorpe et al. 2007b (n=21)

These two articles report on Hurler syndrome patients who received UCB transplant. Although they appear to be based on a selected subset of the patients presented in the docket datasets, they offer some information on outcomes other than survival. The authors found that the transplanted 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. 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. The authors noted that information about 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.

Prasad and Mendizabal et al. 2008 (n=45)

This report describes 159 patients who received UCB transplantation at Duke University, including 45 patients with Hurler syndrome. This appears to consist of patients whose data were also submitted to the docket and therefore does not provide additional evidence regarding survival; the survival experience for Hurler syndrome was similar to that already reported above in Figure 6. The report does offer some additional outcome information. 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 did not identify how the diagnosis of Hurler syndrome was established, and no comparisons to untreated Hurler syndrome control data were provided.

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 University and Eurocord experience. About half of the patients appear to be the same as those represented in the docket, with the remaining patients coming from 18 international centers and one U.S. site. 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%, with six having autologous reconstitution and 5 having graft failure. Survival beyond 3 years is 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, and 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 (> 7.6×10^7) cell dose.

Hurler Syndrome – Observations and Limitations

The evidence of efficacy of UCB transplantation in Hurler Syndrome has substantial limitations. Based on the limited 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. Survival outcomes with UCB seem to resemble those seen with BMT, but the follow-up experience is not as extensive for UCB. Changes in enzyme levels have been reported, but their clinical meaningfulness is unclear. The evidence from the published literature regarding the effect of UCB on survival and other aspects of the Hurler syndrome is limited by the lack of objective controls and possible selection or reporting bias. No clear relationship was seen between cell dose and survival over the range of doses used.

4.5 Krabbe Disease

Krabbe disease (globoid cell leukodystrophy) is an autosomal degenerative neurologic disease caused by deficiency of the enzyme galactocerebrosidase (GALC) 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 (Kemper and Knapp et al. 2010).

The early infantile onset form presents with symptoms 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 spasms. They 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 early infantile onset type (Wenger and Rafi et al. 2000). However, of the cases in the Krabbe Family Database, 71% or fewer had onset in the age range 0 to 6 months (Duffner and Jalal et al. 2009).

There is no approved drug or biologic therapy for Krabbe disease. No specific therapy is available for the symptomatic infantile onset form, but published reports (Escolar and Poe et al. 2005) suggest HSCT before onset of symptoms can be beneficial.

Baseline Data

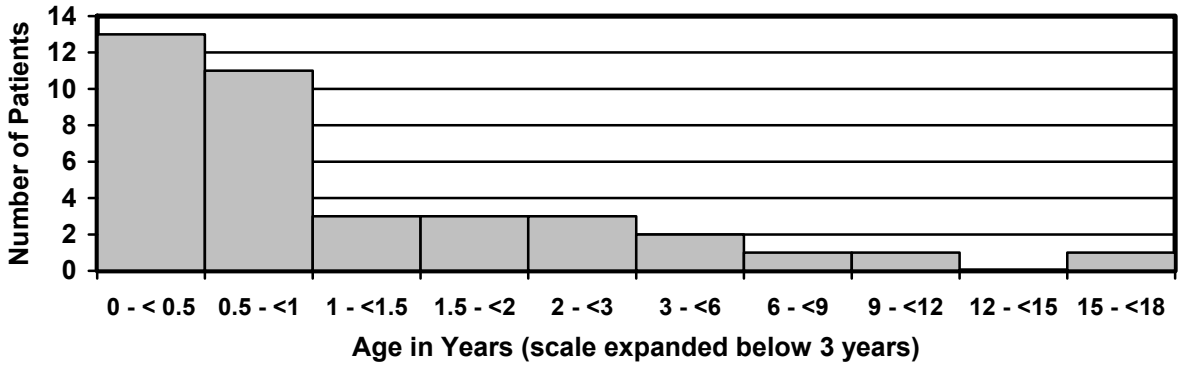
Diagnostic information, other than simply the diagnosis of Krabbe disease, was not provided in the docket datasets. Thus, eligibility criteria for the series and the criteria for classification of phenotype, particularly the early infantile onset phenotype, are unknown. Although the Lansky scores (see below) recorded in one dataset gives 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. Almost all of the cases came from the dataset for which there is a question about the reliability of the follow-up times.

Basic demographic data for the Krabbe disease patients in the pooled datasets are shown in Table 11 below, together with basic treatment data. Demographic information other than age was not provided in one of the datasets.

Table 11: Demographics and Treatment Data for Krabbe Patients – Docket Data

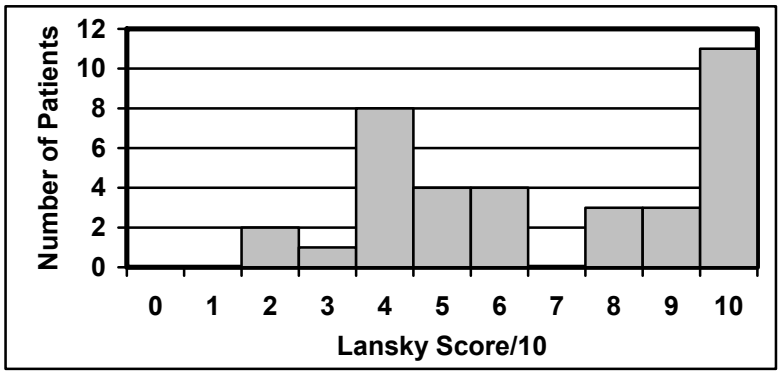
Total N	38
Age in Years	
Mean (SD)	1.8 (3.2)
Median (Range)	0.7 (0.05 – 16.7)
Gender	
Male	58% (22)
Female	39% (15)
Unknown	3% (2)
Race	
Caucasian	79% (30)
African or African/American	11% (4)
Hispanic or French/Hispanic	5% (2)
Unknown	5% (2)
Dosing ($x10^7$ TNC/kg prefreeze)	
Median	16.5
10th, 25th, & 75th 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)

Figure 9: Age Distribution for Krabbe Disease Patients – Docket Data



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 in only one dataset. The distribution of scores for those 36 patients is shown in Figure 10.

Figure 10: Lansky Score Distribution for Krabbe Disease Patients – Docket Data



(Lansky score was only reported for the 36 patients one of the datasets.)

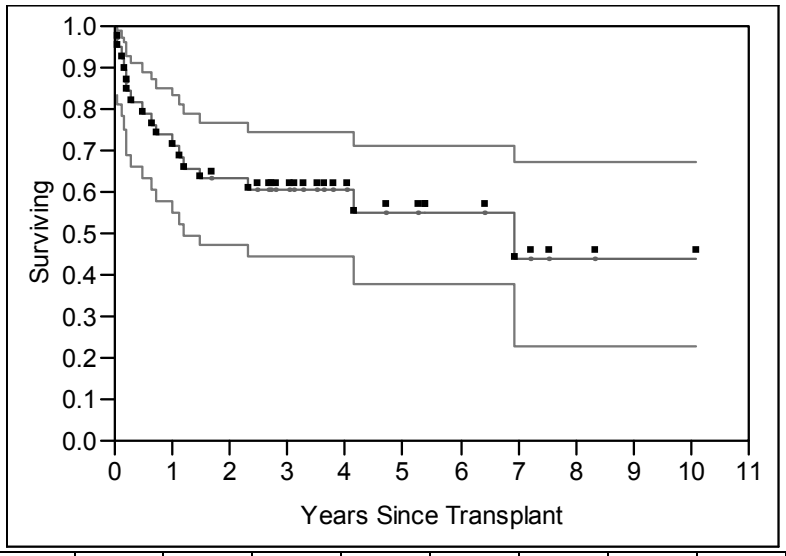
Just under half of the patients had a Lansky score of 80 (active but tires more quickly) or better. The rest fell in the range of 20 (often sleeping) to 60 (minimal active play) with a mode of 40 (mostly in bed). It is noteworthy that there were 8 patients (21% of the total) who were 2 years or older, and 3 who were 6 years or older. Of the 6 patients aged 2 years or older who had a Lansky score, all had a score of 60 or better. Thus, it appears there was a substantial representation of phenotypes other than early infantile onset type.

Analysis of Primary Endpoint

Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown in Figure 11 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. The median follow-up was 2.8 years.

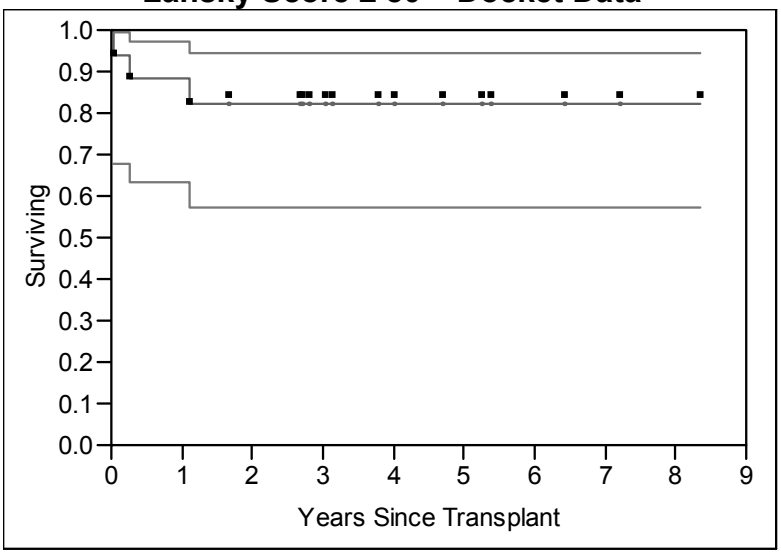
Figure 11: Survival (± CI) Following UCB Transplant in 38 Krabbe Disease Patients – Docket Data



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 was analyzed separately as an approximation to selecting an asymptomatic or minimally symptomatic population. Survival outcomes tended to be better for this subset. The survival experience for the group is shown in Figure 12.

Figure 12: Survival Following UCB Transplant in 17 Krabbe Disease Patients with Lansky Score ≥ 80 – Docket Data



There were 8 patients in the dataset who were age 2 years or older and presumably represented milder phenotypes. A separate plot for these 8 is not shown, but it was observed that 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.

Relationship Between Dose and Survival

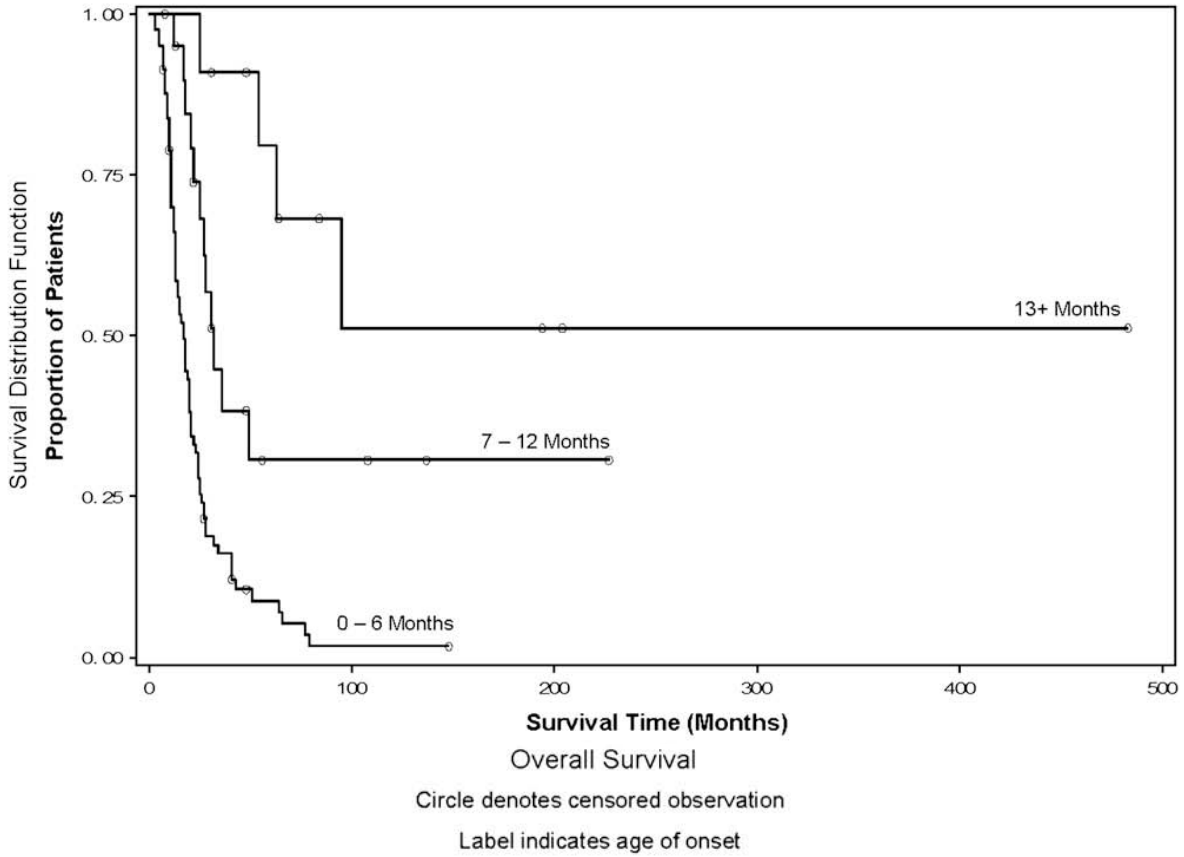
A proportional hazards model found no significant relationship between TNC dose and survival (nominal $p = 0.21$), with an estimated 3.5% decrease in hazard for each increase in dose of 10^7 TNC/kg. There was only one patient with a dose $< 2.5 \times 10^7$ TNC/kg (this was a 16 year old who received 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 16.5×10^7 TNC/kg showed a trend toward improved survival at doses above the median, but the difference was not statistically significant (nominal $p = 0.14$).

Historical Control Data

One of the earliest substantial 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, 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 curves were not significantly different.) These 114 cases included 81 cases with symptom onset at or before 6 months, 22 with symptom onset from 7 through 12 months, and 11 with onset at 13 months or later. An analysis of survival by age of symptom onset showed evident differences between these groups (Figure 13). The survival analyses 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 13: 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 mo. Age at onset 7-12 mo. (n = 22): mean survival = 88.81 mo. (SEM = 24.10), median = 32 mo. Age at onset 13+ mo. (n = 11): mean survival = 278.75 mo. (SEM = 89.02), median > 483 mo. (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. [Patients who had HSCT were not included in the analysis].
Source: Duffner and Jalal et al. 2009

This analysis underscores the high variability in phenotype and the value of age of symptom onset in estimating prognosis. Although the group of patients with onset at age 6 months or earlier has the highest mortality, a visual estimate from Figure 13 shows that about 16% survive for 4 years (48 months).

There have been a small number of publications that deal with approaches to distinguishing phenotypes that might bear on ability to predict prognosis. Loes and Peters et al. 1999 reported that certain MRI findings were seen only in early onset disease, while other findings were more common in older onset patients, but their definition of early onset included symptoms before age 2 years, rather than 6 months. The authors did not explicitly evaluate the ability of

presymptomatic MRI to predict clinical course. Husain and Altuwaijri et al. 2004 observed that nerve conduction abnormalities may be seen before other neurophysiologic findings in early onset disease, but that nerve conduction abnormalities were less common and less predictable in late onset disease. The authors did not propose that such studies could predict phenotype in asymptomatic patients. Escolar and Poe et al. 2006 developed a clinical staging system that identified a group with higher mortality or more severe disability following transplant. However, none of these papers clearly proposes a practical method for predicting natural history in untransplanted asymptomatic infants, and any prediction method would need some independent confirmation of discrimination ability in order to correct for training set bias.

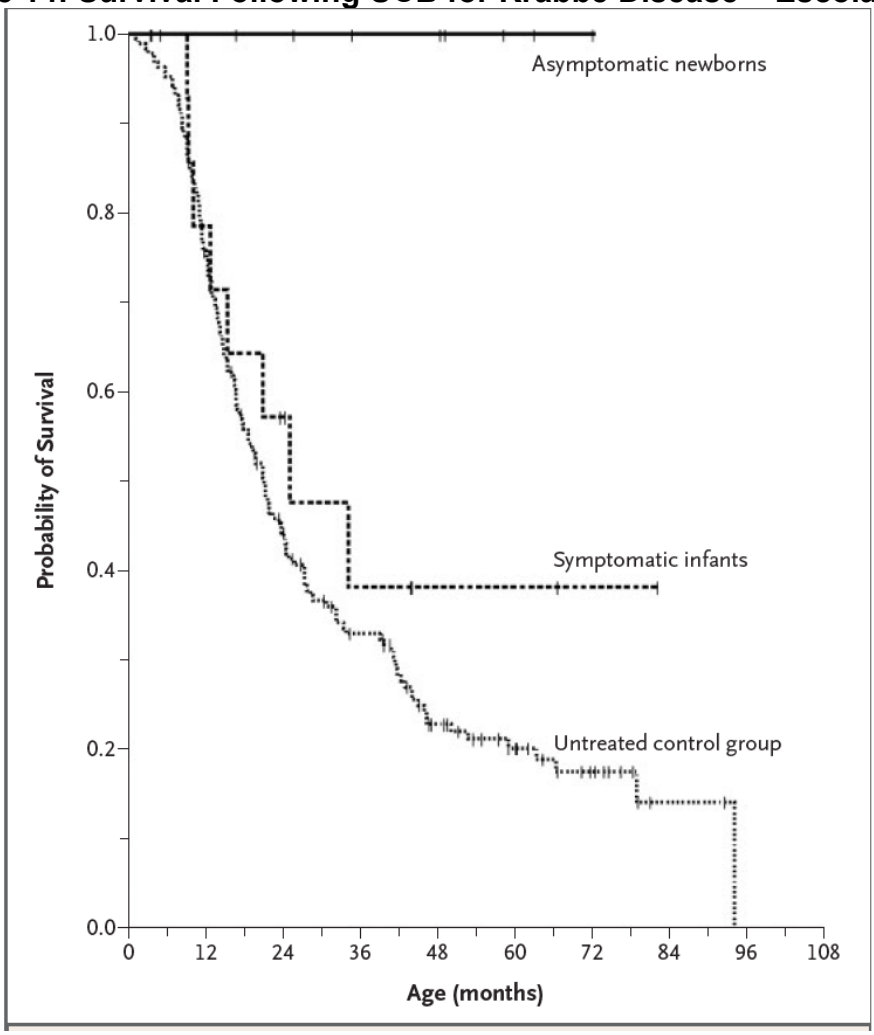
Comparisons with Historical Control Data

The overall experience for the 38 patients in the docket dataset yielded 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 13. In the absence of knowing the age of symptom onset for the docket data, but considering the ages reported as age of 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.

A subset of the Krabbe disease patients in one of the datasets 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 database that were collected through 1/28/05. Further details on the selection of the control group were not provided. The survival curves from the publication are reproduced below in Figure 14.

The corresponding 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. One of the other datasets in the docket showed a death in a Krabbe disease neonate two weeks after transplant. Thus, the favorable experience reported by Escolar cannot be confirmed exactly with the docket data, and, with the additional early deaths added to the experience, the estimated effect of treatment on survival 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 in the review of published experience, below.

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



Kaplan–Meier Estimates of the Probability of Overall Survival among Patients with Krabbe Disease.
Shown are Kaplan–Meier estimates of survival among all 11 asymptomatic newborns with Krabbe 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

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 or 9 months, it 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 survival 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, as 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. The Escolar report does not describe how patients were selected to include as controls. In the small group of patients who were transplanted before symptom onset, the clinical phenotype is undetermined. Absent a randomized comparison to provide statistical comparability, or a series that is consecutive, minimally 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 comments above) is still subject to the concerns raised by the use of an external control population.

Analysis of Secondary Endpoints

For patients in one dataset, an affiliated dataset provided 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 12: Enzyme Results for Krabbe Disease Patients – Docket Data

	Pre-transplant (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 pre-transplant 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 using the docket datasets because no other disease-specific outcome data were included.

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 controversial. In their presentation of the Krabbe Family Database, Duffner and Jalal et al. 2009 provide the following remarks:

> 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)

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 certainty that the asymptomatic patients actually would have developed the early infantile onset phenotype.

A review by Prasad in 2010 (Prasad and Kurtzberg 2010) regarded UCB as standard of care for Krabbe disease, and provided a list of references in support; these are described below.

Published Experience with UCB in Krabbe Disease

The most relevant additional experience from the literature is summarized below:

Martin and Carter et al. 2006 (n=16)

This article reports on the COBLT study sponsored by NHLBI in which UCB transplant was give to 69 patients with lysosomal and peroxisomal storage disorders, almost all of whom were transplanted at Duke University. The population 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 did 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 in non-Caucasians and in 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 University, including 36 patients with Krabbe disease. This report appears to consist of patients whose data were also submitted to the docket and therefore does not provide additional evidence regarding survival; the survival experience for Krabbe disease was similar to that already reported above in Figure 11.

Duffner and Caviness, Jr. et al. 2009

This is report of a workshop on outcomes 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 University were presumably nearly all UCB. The report is of note because it provides outcome information other than survival. Results are cited 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)

Krabbe Disease – Observations and Limitations

The evidence of efficacy of UCB transplantation in Krabbe disease has substantial limitations. Based on the limited data submitted to the docket, the overall survival experience appears to overlap that of candidate historical controls; variability of the phenotype and uncertainty about the phenotypes of patients in the docket datasets makes control selection challenging. Changes in enzyme levels have been reported, but their clinical meaningfulness is unclear. Published literature seems to indicate no benefit once symptoms develop, but suggests presymptomatic transplantation is effective in improving survival. The evidence for the latter is limited by difficulty in determining phenotype prior to symptom onset and by the recent observations that transplanted patients are still severely affected. Published data on the effect of UCB on other aspects of Krabbe disease is limited by lack of objective controls and possible selection or reporting bias. No clear relationship between TNC dose and survival was observed over the range of doses used.

4.6 Adrenoleukodystrophy (ALD)

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 to 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 transporting 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 can be the clinical manifestation 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).

Baseline Data

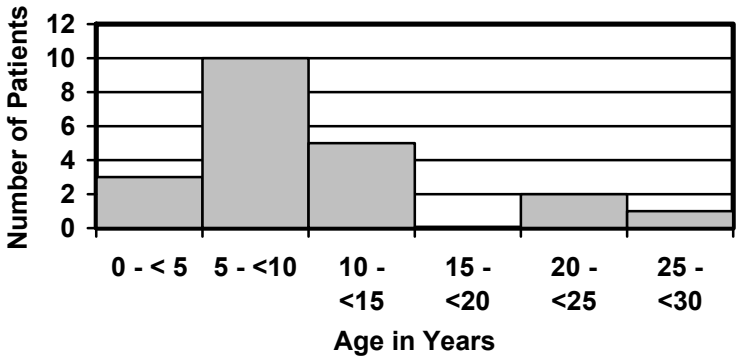
In the datasets, diagnostic information other than the diagnosis of ALD was not provided. Thus, eligibility criteria for the series and the criteria for classification of the phenotype are unknown. Although the Lansky scores recorded in one dataset give some indication of patient status, there is no explicit representation of whether or not a patient had neurologic symptoms at the time of UCB transplantation. A majority (62%) of the cases came from the dataset for which there is a question about the reliability of the survival times.

Basic demographics for the ALD patients in the pooled datasets are shown in Table 13 below, together with basic treatment data. Demographic information other than age was not provided in one dataset.

Table 13: 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
10th, 25th, & 75th 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)

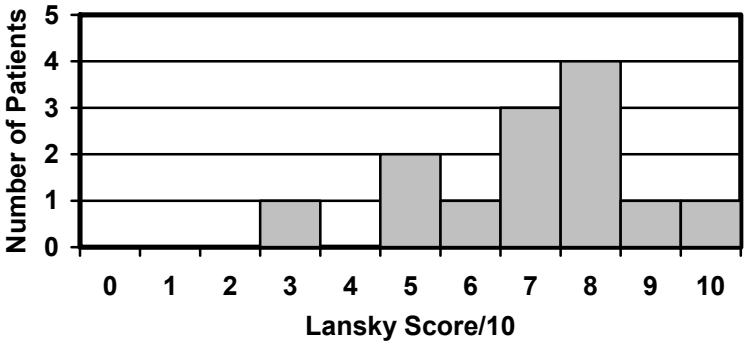
Figure 15: Age Distribution for ALD Patients – Docket Data



The presence of three patients who were 20 years or older raises some question 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 in previous sections. The score was recorded in only one 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 data indicate there was a fairly broad range in clinical status at time of transplant.

Figure 16: Lansky Score Distribution for ALD Patients – Docket Data



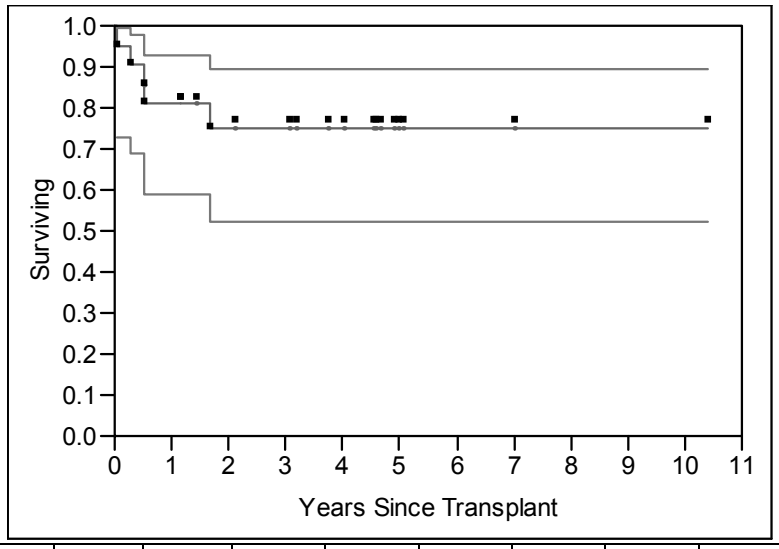
(Lansky scores were available only for the 13 patients one of the datasets.)

Analysis of Primary Endpoint

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 pooled docket datasets. There is about 19% mortality by the end of the first year. The estimated fraction surviving at 5 years is 75%, but the number at risk is very low at 5 years and beyond. Median follow-up was 3.2 years.

Figure 17: Survival (± CI) Following UCB Transplant 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 patient who was 26 years old at the time of transplant; the second longest survival, censored at 7.0 years following transplant, was in the patient who was 9 years old at the time of transplant. Survival at

5 years and beyond came only from the dataset for which is there is concern about the reliability of the follow-up times for censored observations.

The three patients older than 20 were not typical for the childhood cerebral phenotype. An additional analysis of the data, but including only the 18 patients age 14 years and younger, found survival outcomes fairly similar to those depicted in Figure 17.

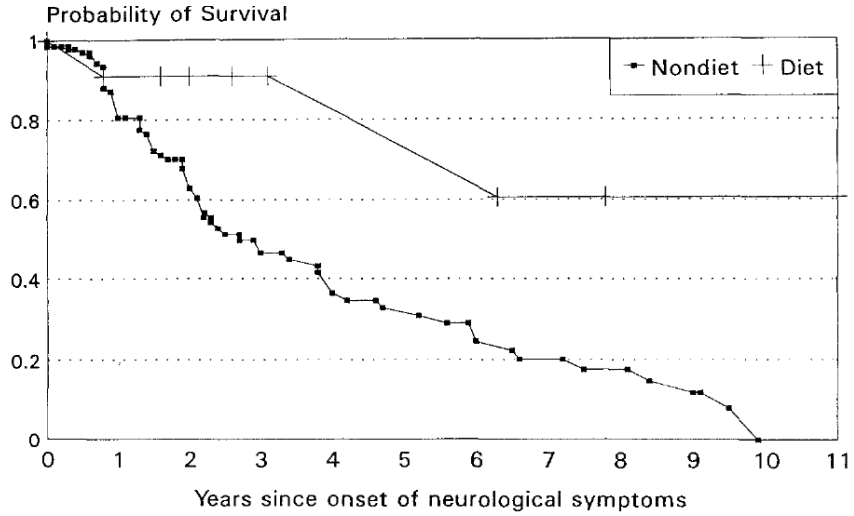
Relationship Between Dose and Survival

A proportional hazards model found no statistically significant relationship between TNC dose 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 a higher dose. 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 with improved late survival for doses above the median, but the difference was not statistically significant (nominal p = 0.14).

Historical Control Data

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 analysis showed progressive failure over a course of 10 years following the onset of neurologic symptoms (Figure 18). The 5-year survival was about 30%.

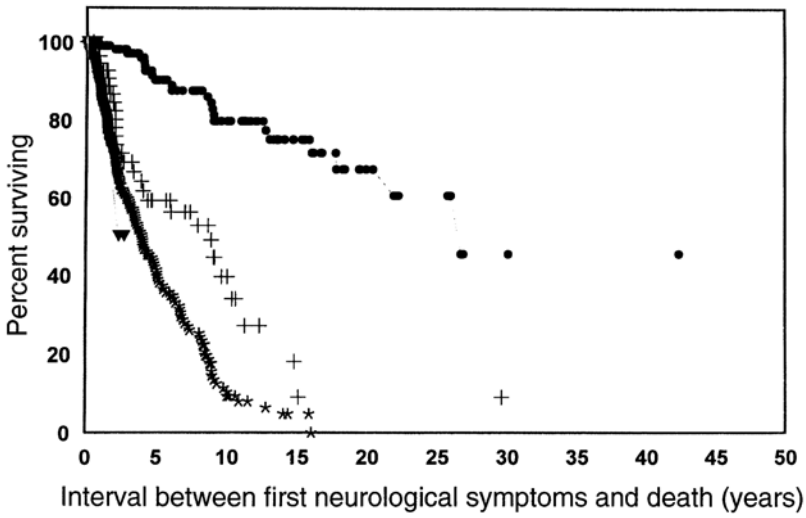
Figure 18: Survival Following Onset of Neurologic Symptoms in 139 Untreated ALD Patients – Moser 1995



Probability of survival from onset of neurologic symptoms to death. Untreated [no diet] (n=139) and treated [diet] (n=11) symptomatic adrenoleukodystrophy patients.
Source: Moser 1995

In a subsequent publication, Moser presented a larger series including 257 patients with the childhood cerebral phenotype, along with data on other phenotypes (Moser 1997). However, the source and selection criteria for these data are not made clear in the publication. It is difficult to estimate from the graph in the publication (see
Figure 19), but the 5-year survival following onset of symptoms in the childhood cerebral form appears to be approximately 40%.

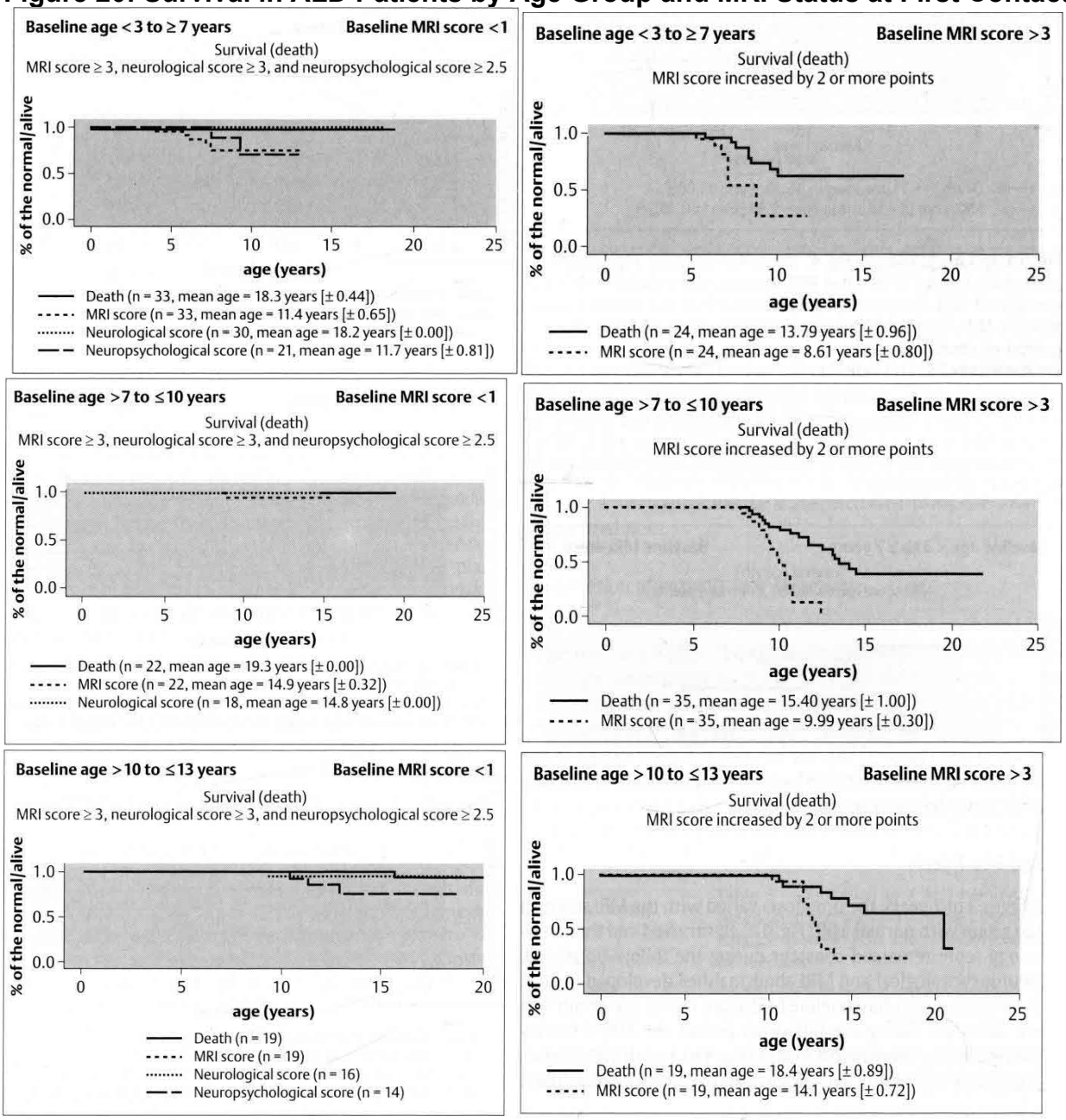
Figure 19: Survival Following Onset of Neurologic Symptoms in ALD Patients – Moser 1997



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 the effect of age and MRI findings on prognosis (Moser and Loes et al. 2000). In the 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 20 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).

Figure 20: Survival in ALD Patients 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). 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 entire group, the 5-year survival after onset of symptoms was 66%. For the subset with early stage disease, the 5-year survival was 54% after first abnormal MRI in those who did not receive HSCT, but 5-year survival was 95% in those who were transplanted.

Figure 21: Survival from Onset of Symptoms in ALD Patients – Mahmood 2007

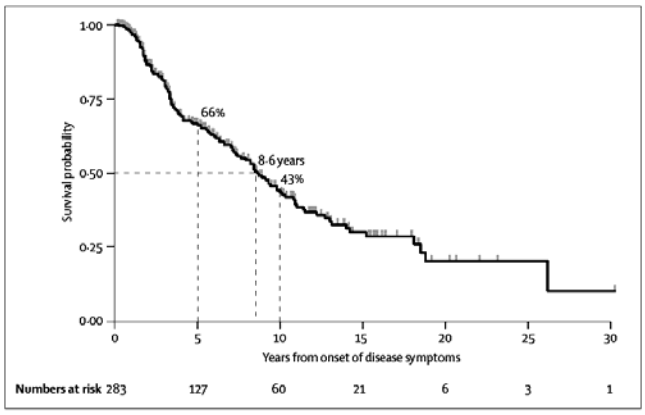


Figure 2: Kaplan-Meier estimate of survival for 283 boys with childhood cerebral X-linked adrenoleukodystrophy after development of neurological symptoms (cognitive, behavioural, or neurological symptoms)

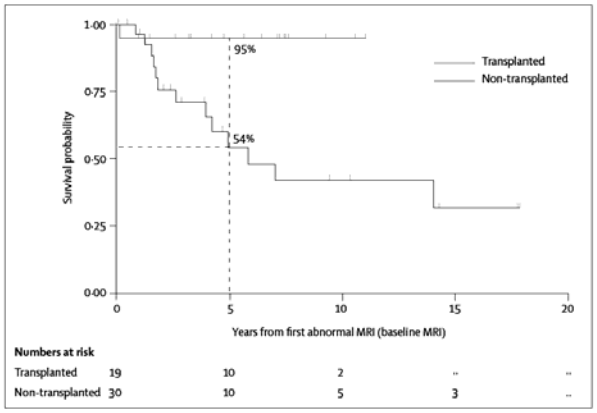


Figure 4: Kaplan-Meier estimates of survival for 19 transplanted patients with early stage cerebral adrenoleukodystrophy and for 30 non-transplanted patients with early stage cerebral adrenoleukodystrophy (ie, neurological deficit score of 0 or 1 and MRI severity score less than 9) Survival was different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

Source: Mahmood and Raymond et al. 2007

Comparisons with Historical Control Data

No additional analytical comparisons were undertaken using the ALD data. The lower limit of the estimated 5-year survival from the docket dataset is about 50% (Figure 17), which is not too different from estimated 5-year survival following onset of symptoms reported for most historical control groups. 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, it appears to be worse than survival in diagnosed patients who have not developed MRI abnormalities (Figure 20). Although the recent analysis by Mahmood estimated higher survival in patients who underwent HSCT compared to no HSCT, the UCB survival outcomes from the docket datasets are not that closely in agreement with those reported by Mahmood for HSCT; in fact, for the first few years where the follow-up experience is more complete, the UCB results in the docket seem closer to those of the untreated group.

Analysis of Secondary Endpoints

No other efficacy endpoints or disease-specific outcome data were included in the docket datasets.

Published Reviews and Opinions

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 as controversial for metabolic storage disorders. A 2010 review by Prasad (Prasad and Kurtzberg 2010) regarded UCB as standard of care for adrenoleukodystrophy, and

provided a list of references in support; the two most relevant are included in the description of published experience below.

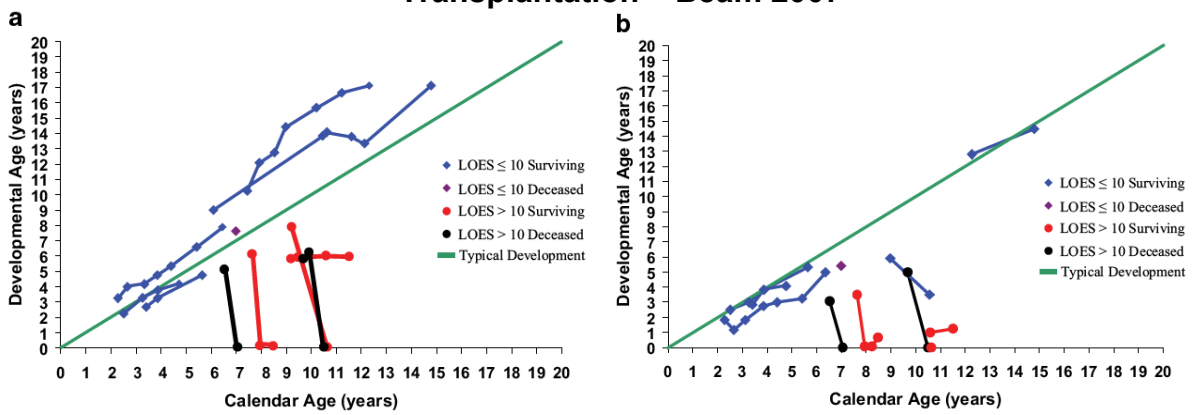
Published Experience with UCB in Adrenoleukodystrophy

The most relevant additional experience from the literature is summarized below:

Beam and Poe et al. 2007 (n=12)

This was a retrospective analysis of 12 patients with ALD referred to Duke University for transplantation. This presumably consists of patients whose data were also included in docket submission, so it does not provide additional survival information. (The survival at 6.25 months and beyond was 67%, which is slightly lower but consistent with the experience shown in Figure 17). The article does offer some information on outcomes other than survival, namely, serial cognitive and motor development observations. A graphic from the article is reproduced below (colors referenced in caption refer to graphics as originally published):

Figure 22: 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

From analyses aimed at determining whether baseline observations predicted outcomes after transplantation, the authors found that pre-treatment MRI-based Loes score was correlated with post-transplant cognitive and motor development, but baseline neurophysiologic studies were not predictive.

By the nature of the population studied, this analysis did not address prediction of disease course in patients who are 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 20. The article did not provide control cognitive and gross motor data from an untransplanted ALD population for comparison.

Prasad and Mendizabal et al. 2008

This is a report of 159 patients who received UCB transplantation at Duke University, 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 that the rate of engraftment with high (>90%) donor chimerism was 85%.

ALD – Observations and Limitations

The evidence of efficacy of UCB transplantation in ALD has substantial limitations. Based on the limited data submitted to the docket, the overall survival experience 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. In the report of an epidemiologic study suggesting better outcomes with BMT vs. no BMT in ALD, the docket survival experience more closely resembled the no BMT group. Published data on the effect of UCB on aspects of ALD other than survival is limited by lack of objective controls and possible selection or reporting bias. No clear relationship between TNC dose and survival was observed over the range of doses used.

4.7 Primary Immunodeficiency Disease – SCID

Severe combined immunodeficiency (SCID) is caused by mutations 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 specific 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.

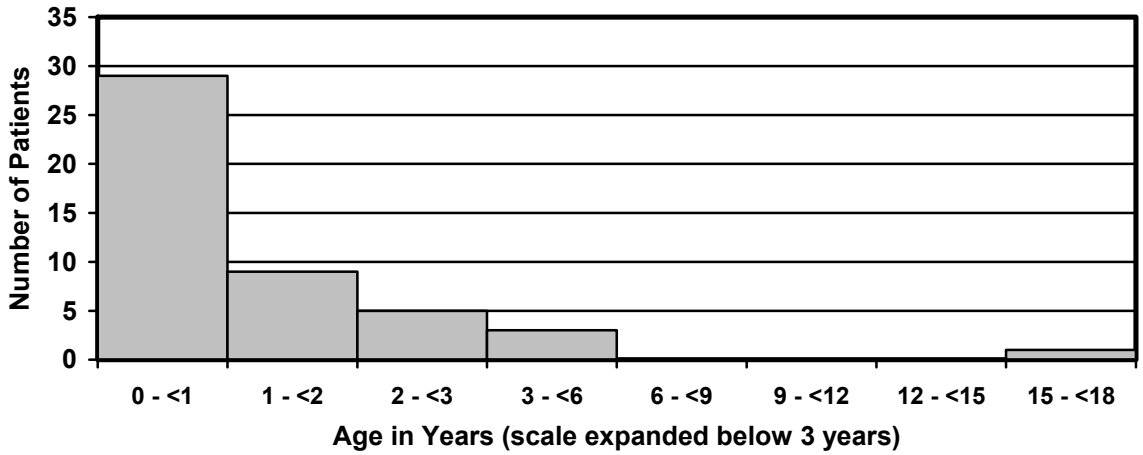
Baseline Data

A case report that was submitted to the docket is described in a subsequent section. Basic demographic information for the SCID syndrome patients in pooled docket datasets are shown in Table 14 below, together with basic treatment data. Demographic information other than age was not provided in one dataset.

Table 14: Demographics and Treatment Data for SCID Patients – Docket Data

Total N	47
Age in Years	
Mean (SD)	1.2 (2.5)
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
10th, 25th, & 75th 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)

Figure 23: Age Distribution for SCID Patients – Docket Data



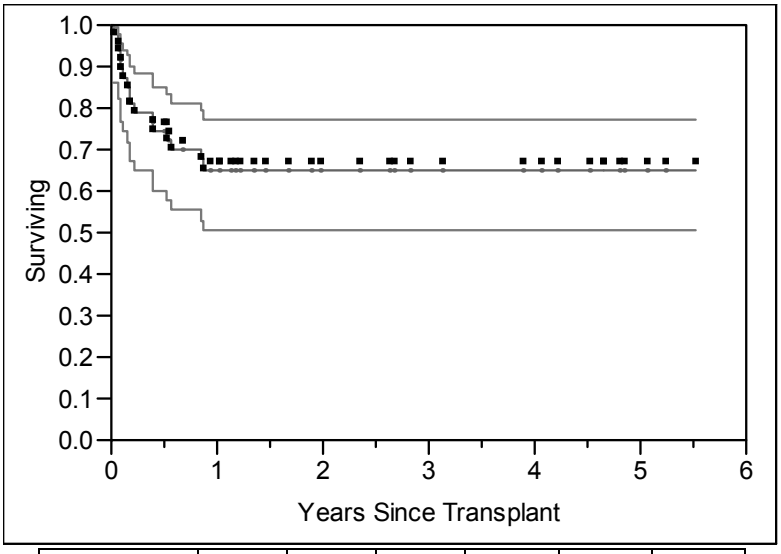
Most of the cases came from the database that only reported age as integer years, so a breakdown of ages below one year is not practical. The presence in the dataset of 9 patients who are 2 years or older is not expected for patients exhibiting the usual findings of SCID. The presence of a 17 year old with SCID is hard to interpret as other than a data entry error.

Analysis of Primary Endpoint

Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown in Figure 24 below for the 47 SCID patients from the pooled docket datasets. There is approximately 35% mortality by the end of the first year, but mortality is low thereafter. Median follow-up was 1.1 years; 75th quartile of follow-up was 3.1 years.

Figure 24: Survival (± CI) Following UCB Transplant for 47 SCID Patients – Docket Data



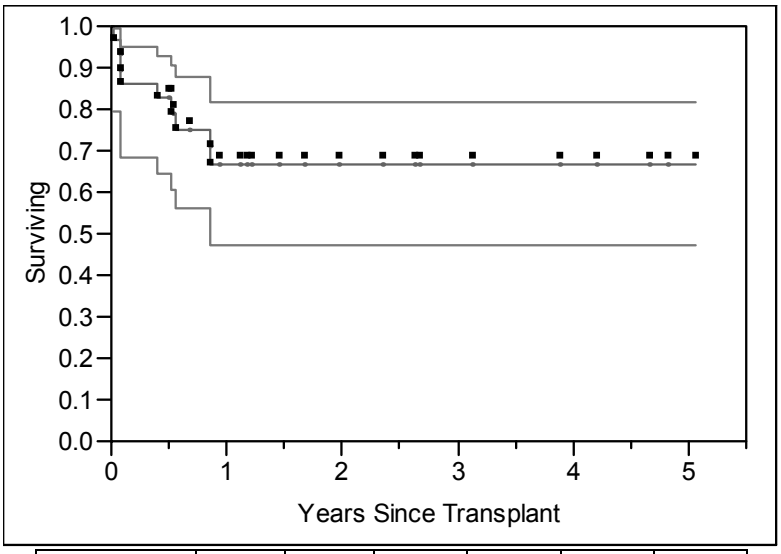
Year	0	1	2	3	4	5
Survival	1.00	0.65	0.65	0.65	0.65	0.65
No. at Risk	47	26	16	12	10	3

Relationship Between Dose and Survival

A proportional hazards model found no significant relationship between TNC dose and survival (nominal p = 0.33) with an estimated 1.9% decrease in hazard for each increase of 10^7 TNC/kg. There were no patients 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 p = 0.28).

Since the presence of patients 2 years and older raises questions about the appropriateness 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 to those for the entire group:

Figure 25: Survival (± CI) Following UCB Transplant for 29 SCID Patients < 1 Year Old – 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

Case Report

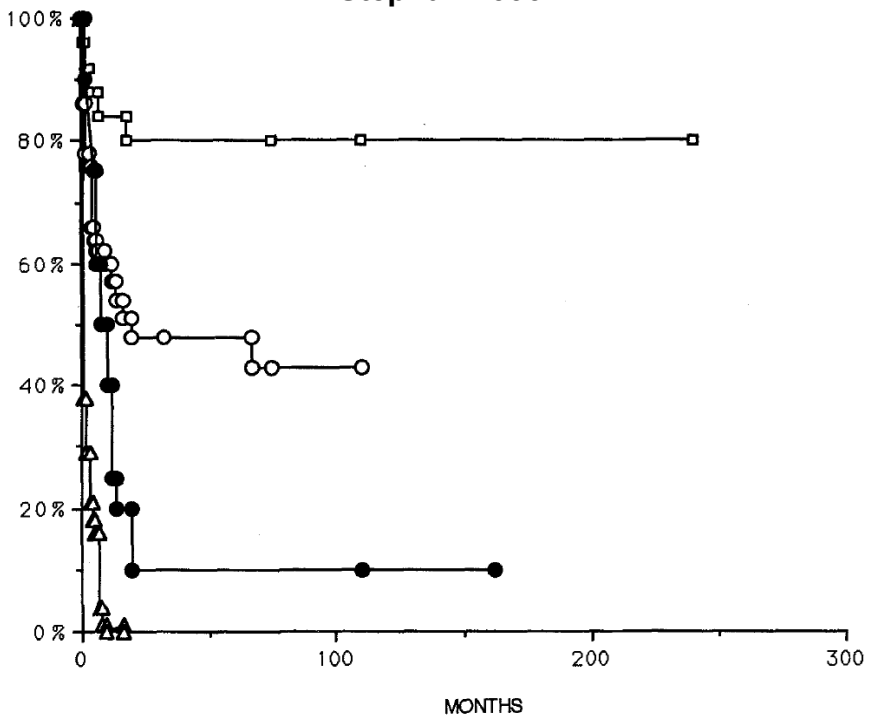
The submissions to the docket included a copy of a published case report (Jaing and Lee et al. 2006) of an infant with SCID who received unrelated UCB transplantation. The male infant was admitted at 5 months of age with a diagnosis of SCID. He had hypogammaglobulinemia and lymphopenia, with T cell count 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 TNC/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 to be in "very good clinical condition without medications."

Historical Control Data

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." If one makes the interpretation that "the first months of life" would fall within the first year of life, the report gives an observed survival rate of 0 out of 434, and the upper 2.5% confidence limit for the 1-year survival probability would be 0.0085. Even if it is allowed that 4 may have survived for a year (~1%, which might have been worthy of mention), the upper confidence limit for 1-year survival probability would be 0.0235. The case series report does not provide specific data, but that experience appears to be highly incompatible with any patient being alive in "very good clinical condition without medication" at 19 months of age.

A series of 22 SCID patients who did not undergo HSCT was reported by Stephan from a large series of 117 SCID cases referred to a Paris hospital between 1970 and 1992 (Stephan and Vlekova et al. 1993). Survival outcome is shown in Figure 26.

Figure 26: Survival in SCID Patients 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

Individual data were not provided in that report, but the graphic indicates all non-transplanted patients died by about 18 months. For just this small series, the 2.5% upper confidence limit for the probability of survival past 18 months is 0.154.

Comparisons with Historical Control Data

With the conservative assumption that censoring is treated as death, the 9 survivors in the docket datasets at 2 years, out of 29 UCB treated SCID patients <1 year of age, differs with nominal $p < 0.00001$ from the experience of no survivors out of the 456 combined untreated cases reported by Hitzig and Stephan. The nominal significance would still be $p < 0.001$ under the rather extreme sensitivity analysis assuming two of those 9 survivors among the docket UCB transplant cases are assumed to have died and the 2-year survival rate for the historical controls is taken to be 5%. The statistical significance is even greater for the corresponding analyses using the entire

experience in all 47 patients in the docket; however, the appropriateness of the control experience is less clear in that case.

Analysis of Secondary Endpoints

No disease-specific outcome data were included in the docket datasets.

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.

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.

SCID – Observations and Limitations

Although there are limitations of the data submitted to the docket, those data provide strong evidence of efficacy in prolonging survival in SCID. Despite approximately 1/3 mortality in the first year following UCB, the survival experience is in striking contrast to the near uniform early fatality in SCID seen in two historical control groups. Although age distribution in the docket dataset and the lack of documentation of diagnosis limit the ability to evaluate how comparable the docket patients are to the control groups, the apparent effect remains statistically and clinically strong when subjected to various sensitivity analyses. No clear relationship was seen between cell dose and survival over the range of doses used.

4.8 Bone Marrow Failure – Fanconi Anemia

Fanconi anemia (FA) is (mostly) an 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 can have limb and organ malformations and are at increased risk for leukemia and other neoplasms. The common mechanistic feature is defective production of a multi-protein 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.

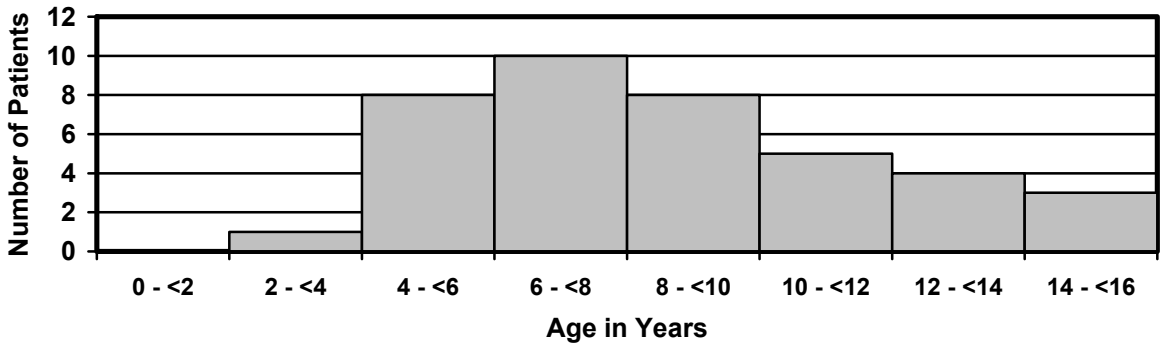
Baseline Data

Basic demographics for the FA patients in pooled docket datasets are shown in Table 15 below, together with basic treatment data. Demographic information other than age was not provided in one of the datasets.

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
10th, 25th, & 75th 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)

Figure 27: Age Distribution for Fanconi Anemia Patients – Docket Data

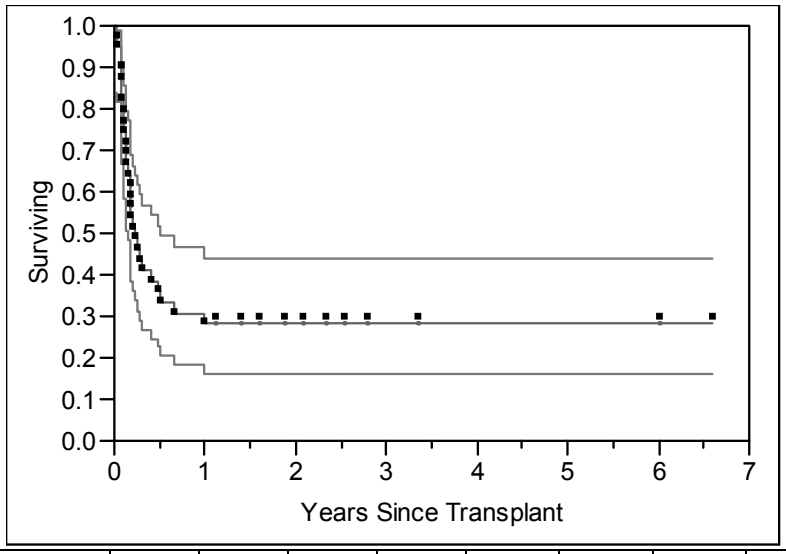


Analysis of Primary Endpoint

Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown in Figure 28 below for the 39 FA patients from the pooled docket datasets. The estimated mortality in about 64% at 6 months and 72% by the end of the first year, but survival levels off thereafter. The number at risk at 3 years and beyond is low. Median follow-up was 0.2 years.

Figure 28: Survival (± CI) Following UCB Transplant for Fanconi Anemia Patients – 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

Relationship Between Dose and Survival

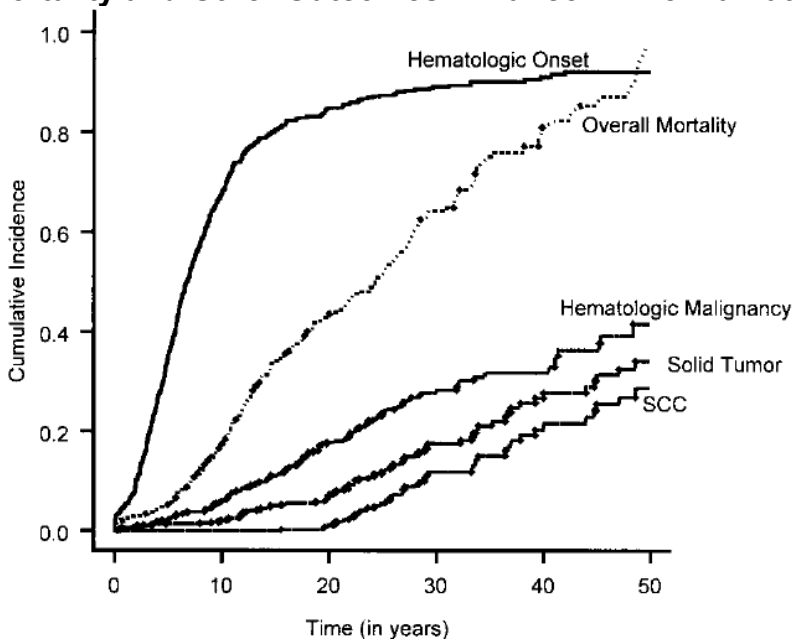
A proportional hazards model found a relationship between TNC dose and survival (nominal p = 0.013) with an estimated 15% decrease in hazard for each increase of 10^7 TNC/kg. There were 9 patients with a dose < 2.5 x 10^7 TNC/kg. An analysis comparing these 9 patients to those with

TNC doses ≥ 2.5 showed decreased survival (11% at 3 months) with the lower dose (nominal p = 0.036), but the survival experience with the higher dose was similar to that of the overall group. 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)

Historical Control Data

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 the 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 29.

Figure 29: 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 < 100×10^9/L, Hgb < 10 g/dL, or ANC < 1×10^9/L]
Source: Kutler and Singh et al. 2003

The article provided only a display of 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 platelets < 100×10^9/L, Hgb < 10 g/dL, or absolute neutrophil count (ANC) < 1×10^9/L. Of this group, 215 had data on follow-up after receiving HSCT. Using a Cox regression model, 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 16).

Table 16: 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

Since the fraction of patients receiving HSCT was only 37% of the total defined as having BMF, it is possible that the results of the survival analysis reflect 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 seem to run counter to the notion that HSCT could be expected to provide a dramatic sustained survival benefit in most patients.

Comparisons with Historical Control Data

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.

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 its determination; the IOM report cited evidence from several small case series and bone marrow transplant experience.

A more recent review addressing the use of cord blood is found in Smith and Wagner 2009, which commented that unrelated donor bone marrow, with improved conditioning regimens, was the gold standard in FA, but that UCB was a reasonable alternative. The authors cited more recent UCB experience, including that described below.

Published Experience with UCB in Fanconi Anemia

The most relevant experience from the literature is summarized below:

Gluckman and Rocha et al. 2007 (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 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%, 2 or 3 mismatches in 48%. Reduced intensity conditioning regimens 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 favorably related to survival were recipient negative CMV serology, use of fludarabine in conditioning regimen, and infused TNC ≥ 4.9×10^7/kg.

Ruggeri and Peffault de Latour et al. 2008 (n=8)

This is a report 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 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.

Fanconi anemia – Observations and Limitations

The evidence of efficacy of UCB transplantation in Fanconi anemia has substantial limitations. Based on the limited data submitted to the docket, the 72% one-year mortality following UCB transplant exceeds the mortality in any available historical control group, even if accumulated over several years. Although the UCB transplanted patients may reflect a select group regarding prognosis, prognosis could not be evaluated from the docket data, and it is unclear how an appropriate control group might be obtained.

Published literature in Fanconi anemia, generally confirms a high mortality following UCB transplant. Published literature even suggests hematopoietic stem cell transplantation (not necessarily UCB) is associated with several-fold increased hazard for mortality, but the observational nature of the study with that finding limits its interpretability.

From analysis of the docket datasets, survival appeared to be related to TNC dose, with patients who received a dose < 2.5 x 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.

4.9 Bone Marrow Failure – (Acquired) Severe Aplastic Anemia

For purposes of this section, severe aplastic anemia (SAA) is taken to encompass 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 definitions, proposed in Camitta and Thomas et al. 1979 or Myers and Davies 2009, are closely similar but differ in using criteria for absolute reticulocyte count or (Howard and Naidu et al. 2004) differ in the marrow cellularity criteria. 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 approved therapy for patients with SAA who are unsuitable for bone marrow transplantation. Other immunosuppressive therapies (antithymocyte globulin and cyclosporine) are also used to treat SAA.

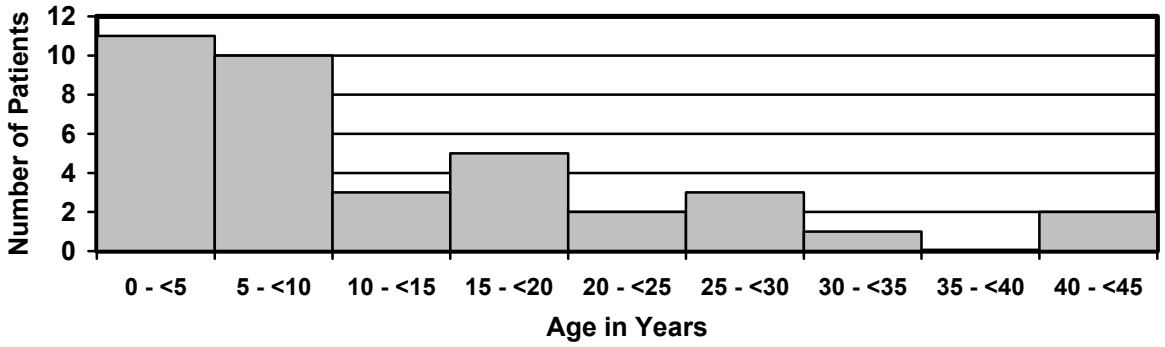
Baseline Data

Basic demographics for all the severe aplastic anemia patients in the pooled docket datasets are shown in Table 17 below, together with basic treatment data. Demographic information other than age was not provided in one of the datasets.

Table 17: 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
10th, 25th, & 75th 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)

Figure 30: Age Distribution for Severe Aplastic Anemia Patients – Docket Data



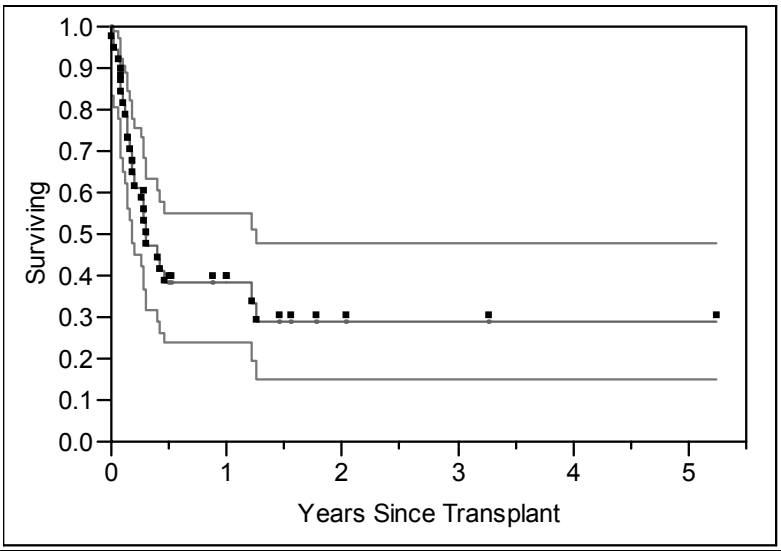
Analysis of Primary Endpoint

Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown in Figure 31 below for the 37 patients with severe aplastic anemia 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. Median follow-up was 0.3 years.

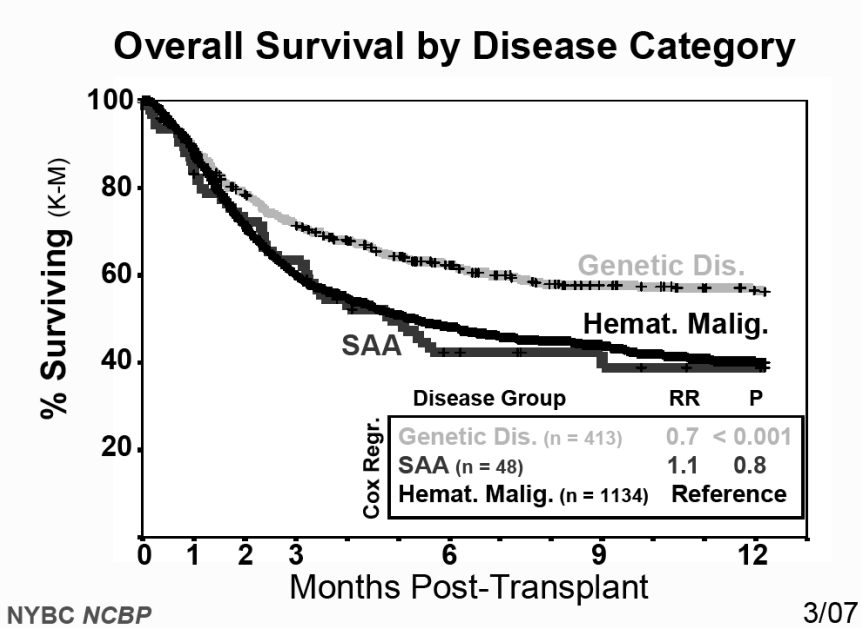
Figure 31: Survival (± CI) Following UCB Transplant for SAA Patients – Docket Data



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 32. The population used for the analysis presumably overlaps with patients represented in one of the datasets submitted to the docket, but the corresponding docket dataset had only 20 cases with a diagnosis coded as "SAA," whereas the summary analysis included 48. The results show less than 40% survival after a year, which is slightly higher than the survival probability estimated from the analysis of the docket datasets.

Figure 32: Survival in SAA Patients (& Other Conditions) Following UCB – Summary Results from NYBC



Source: Docket documents FDA-2006-D-0157-DRAFT-0064, -0065)

Relationship Between Dose and Survival

A proportional hazards model using the docket datasets found a significant relationship between TNC dose and survival (nominal p = 0.021) with an estimated 15% decrease in hazard for each increase of 10^7 cells/kg. 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 p = 0.0620), but the survival experience with the higher dose was similar to that of the overall group. 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).

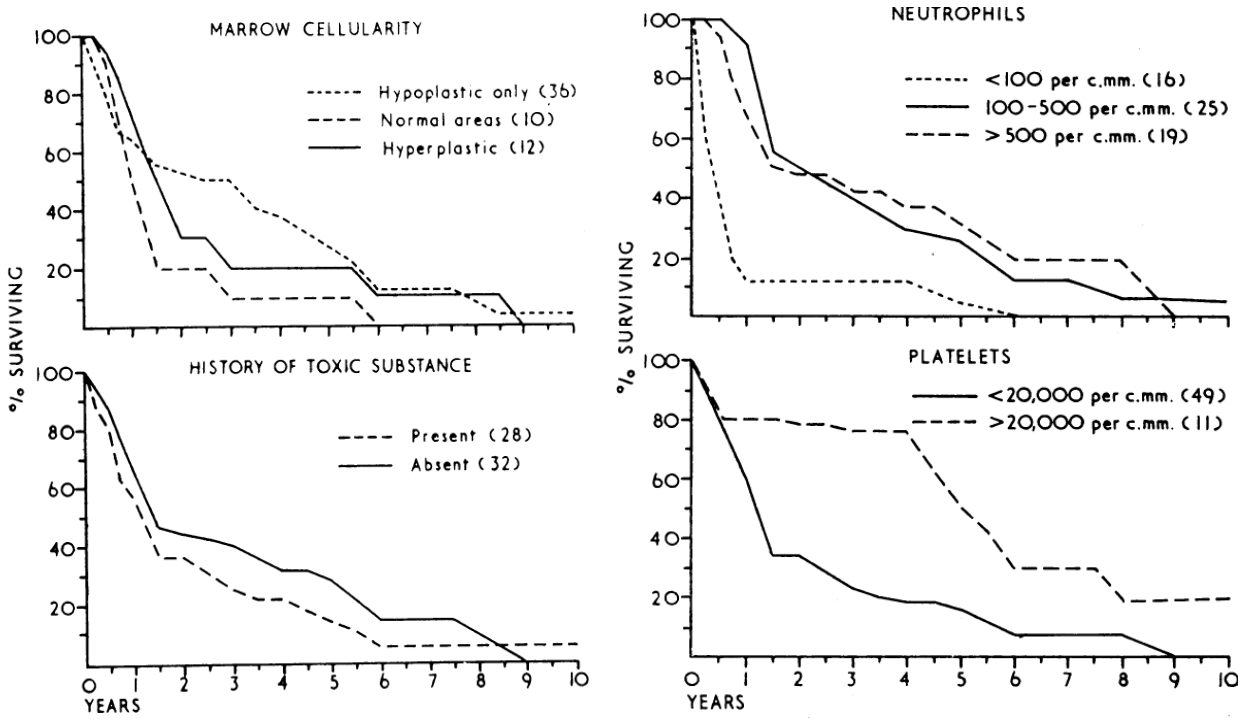
Historical Control Data

In contrast to the nonmalignant 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. Results of some of the more substantial or noteworthy reports are presented below; others are only summarized briefly. The earlier reports come close to providing data that can be regarded as reflecting natural history. Reports of large series 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 for aplastic anemia 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 33: Survival in 60 Patients with Acquired Aplastic Anemia – Lewis 1965



Source: Lewis 1965

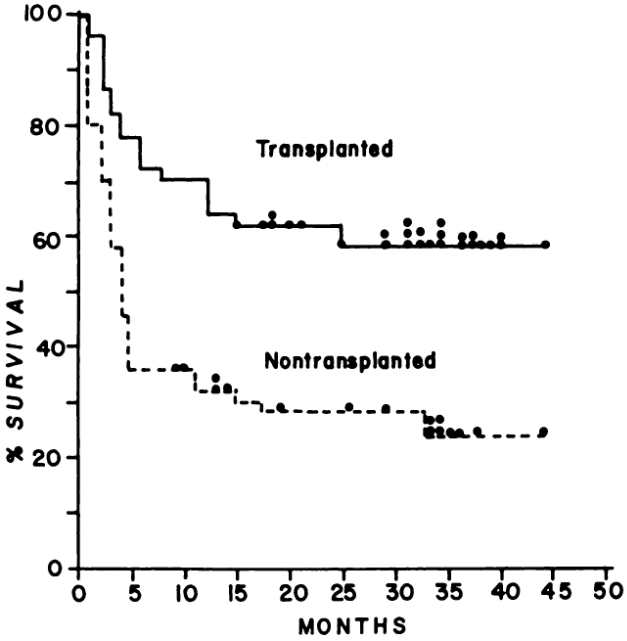
The report illustrated how prognosis can vary depending on cell counts. Overall survival appeared to be 55% to 65% at 1 year and 35% to 45% at 2 years.

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. Transcribing from the tabulated data, the survival at 1 year was estimated as approximately 24%.

In a study of 101 patients with aplastic anemia seen in Utah between 1944 and 1972 (Williams and Lynch et al. 1978), the survival was about 50% after 1 year and 45% after 2 years. The use of HSCT was not described, but in view of the time period covered it is unlikely to have been substantial.

In what appears to be an extension of a study reported in 1976 (Camitta and Thomas et al. 1976), Camitta reported on a series of patients prospectively "randomized" 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 34), which was within the range of the previous historical results.

Figure 34: Survival Following Sibling BMT or No BMT in SAA Patients – Camitta 1979



Source: Camitta and Thomas et al. 1979

A series of patients in England with SAA, excluding FA, was reported by Mir (Mir and Geary 1980); none was treated with HSCT. 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%.

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 patients who had only supportive care had estimated survival through 2 years of 25%.

Figure 35: Survival in Children with SAA – Halperin 1989

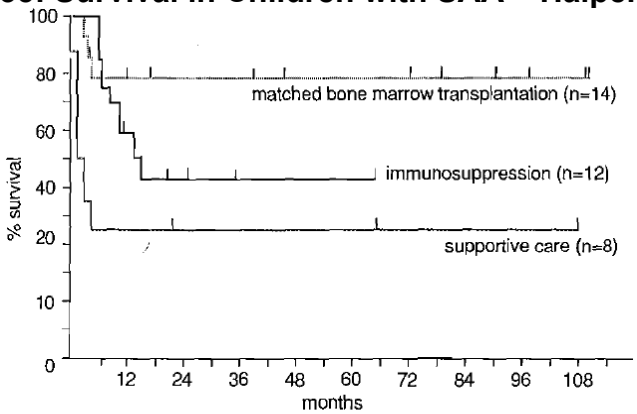
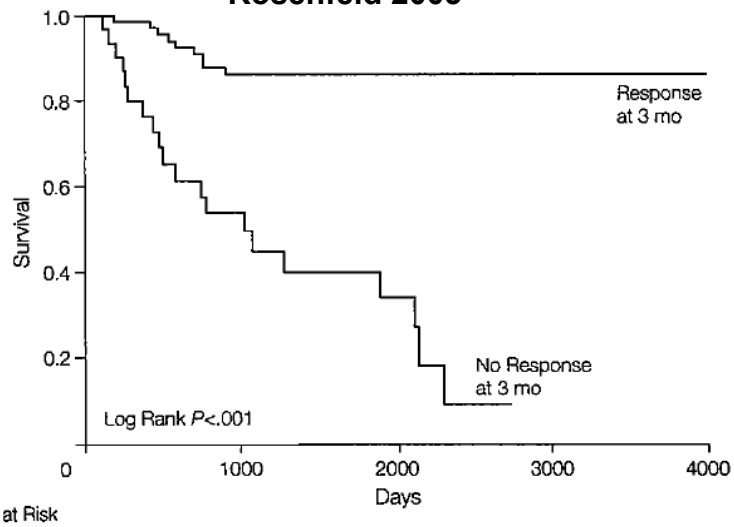


FIG. 1. Survival curves for children with severe acquired aplastic anemia treated with allogeneic histocompatible bone marrow transplantation, immunosuppression with antithymocyte globulin and/or high-dose corticosteroids, or supportive care. Ticks indicate latest follow-up examination of each patient.

Rosenfeld and Follmann et al. 2003 reported on 122 patients who received 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 by 3 months, the 5-year survival was 40%, compared to 86% in responders (Figure 36).

Figure 36: Survival in SAA Patients Not Responding to Anti-Thymocyte Globulin – Rosenfeld 2003



No. at Risk					
Response	74	52	27	8	1
No Response	31	13	5	0	0

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.

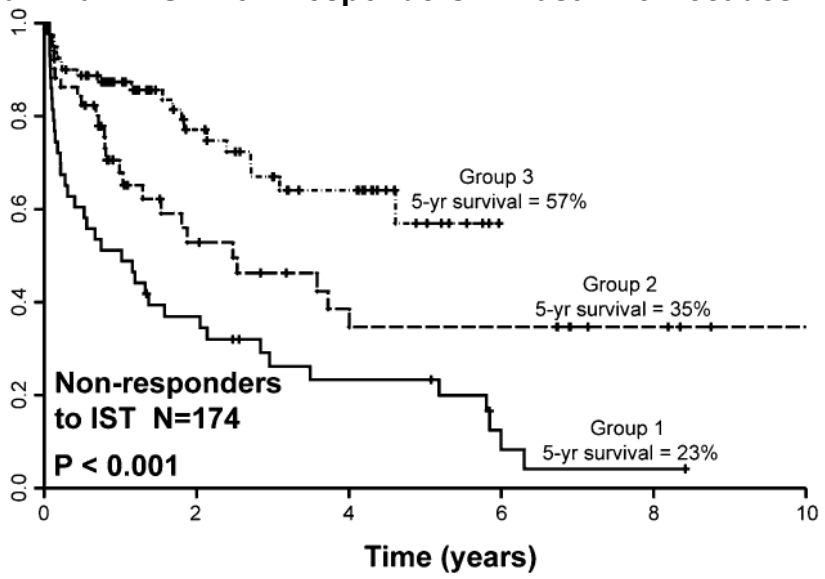
[There was 13% mortality prior to the 3-month evaluation. Four non-responders have matched, unrelated BMT; all died. Three responders had matched, related BMT; one survived.]

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.

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 37: 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

Comparisons with Historical Control Data

The survival experience for SAA in the docket datasets (38% survival at 1 year, 29% at 2 year) 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 34) 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.

Analysis of Secondary Endpoints

No other disease-specific outcome data were included in the docket datasets.

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). However, neither review explicitly addressed recommendations regarding acquired severe aplastic anemia.

Peffault de Latour and Purtill et al. 2011 reported on a large retrospective analysis of UCB experience in SAA (described further below). The authors also assessed the cumulative evidence and drew the following conclusion:

> 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)

Published Experience with UCB in Severe Aplastic Anemia

The most relevant additional experience from the literature is summarized below. There are several moderate-sized series in which outcomes appear notably better than the docket experience and these are presented briefly, but the two largest series have survival rates that are more similar to the docket results:

<u>Mao and Zhu et al. 2005 (n=9)</u>

This is a report of 9 adults, average age 25 years transplanted in China with UCB for SAA after failing one course of IST. At a median follow-up of 32 months, 7 patients (78%) were alive.

<u>Chan and McDonald et al. 2008 (n=9)</u>

This is a report of 9 children, median age 9 years, treated in Texas with UCB for SAA after failing at least one course of IST. With a median follow-up of 34 months, 7 patients (78%) remained alive.

<u>Yoshimi and Kojima et al. 2008 (n=31)</u>

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%).

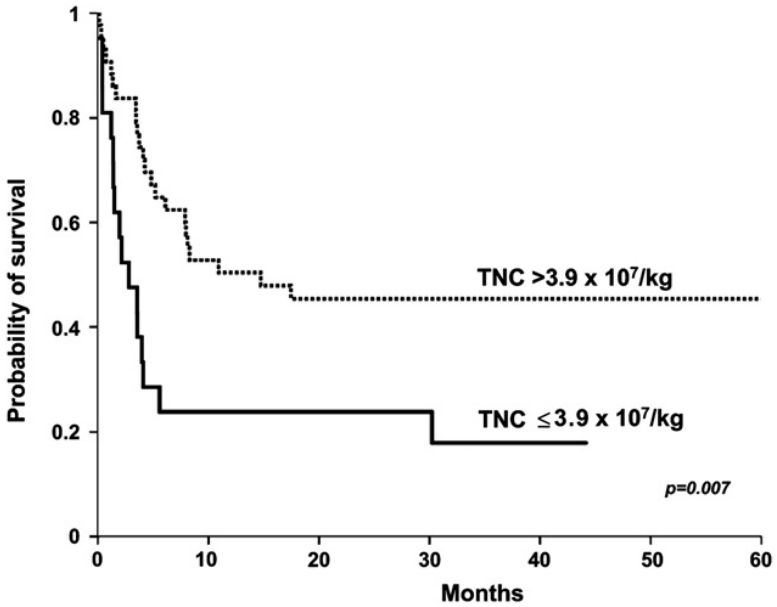
Jaing and Huang et al. 2011 (n=5)

This was a retrospective review of 5 children ages 3.8 to 16 years treated with UCB for relapsed or refractory SAA after failing one or more courses of IST. The TNC dose was at least 3.7 x 10^7 for four patients. All patients were alive and transfusion independent at a median follow-up of 25 months, but one received subsequent sibling UCB, 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 13years; 61% were under age 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 for all 71 patients was 38% ± 6% (SE). In a multivariate analysis, only prefreeze TNC dose > 3.9 x 10^7/kg was associated with improved survival (Figure 38). (The dose cut point was selected by the authors after analysis of the data.)

Figure 38: Survival in SAA Patients Following UCB Transplant – Eurocord Registry



Estimated 3-year OS according to TNC dose

Source: 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 treated in Japan 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. The estimated 3-year overall survival was 83%.

Severe Aplastic Anemia – Assessment

The evidence of efficacy of UCB transplantation in SAA has substantial limitations. 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, even in 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. Survival experience from a recent large series is not appreciably different from that contained in the docket. A recent publication concluded that prospective studies are needed before UCB can be recommended for SAA.

From an analysis of the docket datasets, survival appeared to be related to TNC dose, with patients who received a dose $< 2.5 \times 10^7$ TNC/kg experiencing worse survival, although those with doses above that level did not fare substantially better than the group as a whole.

4.10 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.

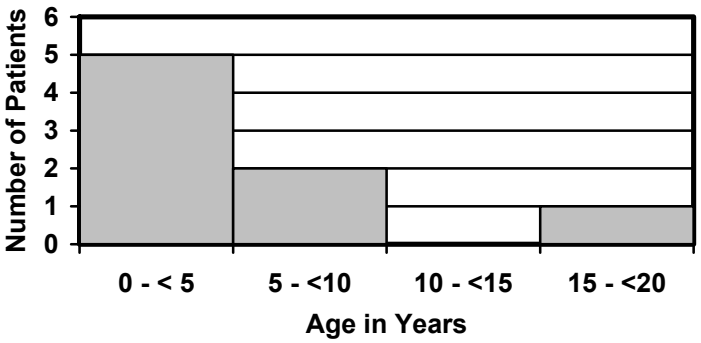
Baseline Data

Basic demographics for the beta-thalassemia patients in pooled datasets are shown in Table 18 below, together with basic treatment data. Demographic information other than age was not provided in one of the datasets.

Table 18: Demographics and Treatment Data for Beta-Thalassemia Patients – 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
10th, 25th, and 75th 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)

Figure 39: Age Distribution for Beta-Thalassemia Patients – Docket Data



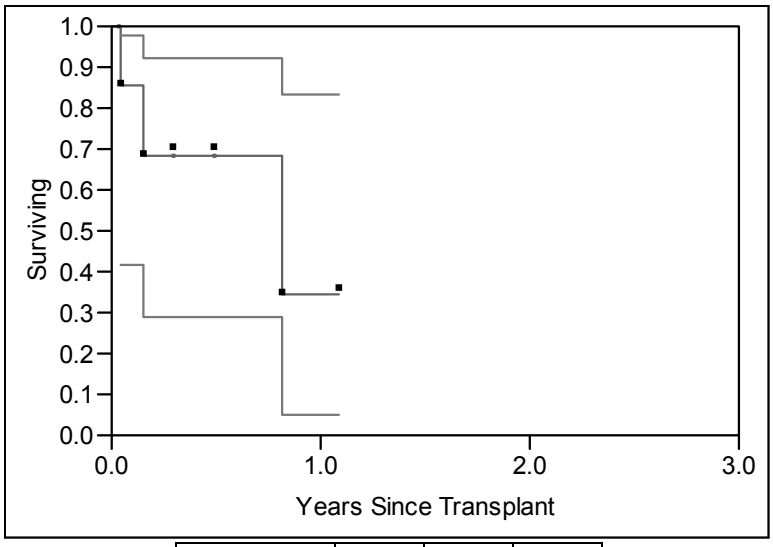
(Ages were: 2.0, 2.0, 3.7, 4.2, 4.2, 5.6, 8, and 20)

Analysis of Primary Endpoint

Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown in Figure 40 below for the 8 patients with beta-thalassemia from the pooled docket datasets. As estimated from the Kaplan-Meier curve, the mortality at 1 year is 66%. Median follow-up was 0.2 years.

Figure 40: Survival (± CI) 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

Relationship Between Dose and Survival

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 analyses of groups with dose above and below the median dose.

Case reports

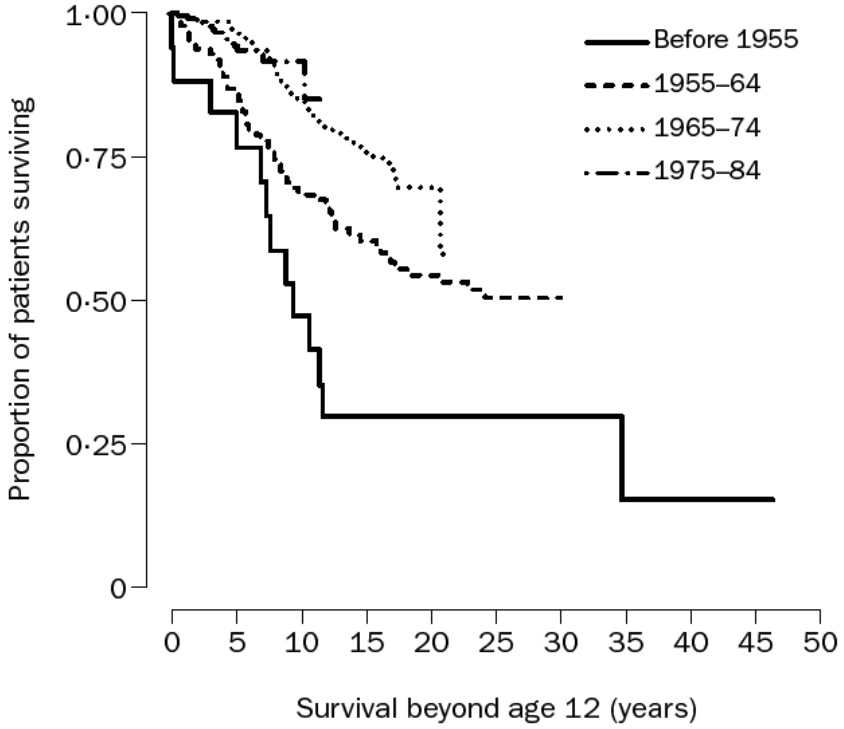
Case report information was provided in publications and related information submitted to the docket:

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.

Historical Control Data

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 noted that about 50% of patients die by the age of 35 years.

Figure 41: Survival Beyond Age 12 in Beta-Thalassemia by Birth Cohort – U.K.



Survival beyond 12 years of age by 10-year birth cohort

Source: Modell and Khan et al. 2000

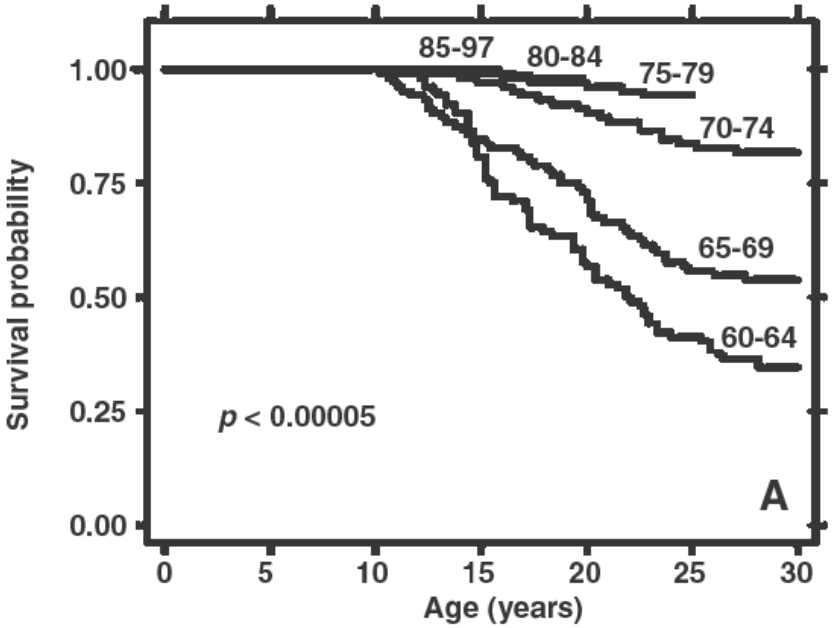
Similar analyses by Borgna-Pignatti also found a pattern of improving survival over time (Borgna-Pignatti and Rugolotto et al. 1998; Borgna-Pignatti and Rugolotto et al. 2004).

Table 19: Survival by Birth Cohort at Different Ages for Patents with Transfusion-Dependent Thalassemia

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 42: Survival Curves for Beta-Thalassemia in Italy Without Transplant – Borgna-Pignatti 2004



Survival after the first decade of life by birth year cohort (half decades from 1960 through 1984, then 1986 through 1997.

Source: Borgna-Pignatti and Rugolotto et al. 2004

Comparisons with Historical Control Data

With only 8 cases of beta-thalassemia represented in the docket datasets, it is difficult to make a meaningful comparison with the historical control data. However, the estimated 66% one-year mortality stands in contrast with the available historical data. Lack of information about the clinical status of the UCB transplanted patients makes it difficult to interpret this outcome. Much more substantial experience is found in the published experience reviewed below.

Analysis of Secondary Endpoints

The potential to substantiate claims for clinical benefits other than survival was not evaluated from the docket datasets because no disease-specific outcome data were included. The published case series submitted to the docket and described above provided some information about the effectiveness of UCB regarding hemoglobin expression and transfusion independence.

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). The AAP review did not provide references to specific data in support of its determination; the IOM report cited UCB case reports and a case series on use of related cord blood.

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. Ruggeri and Eapen et al. 2011 reported on a retrospective analysis of UCB experience in beta-thalassemia collected from a number of sources (as described further below). The authors drew the following conclusion:

> 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)

Published Experience with UCB in Beta-Thalassemia

As background, it is of some value also to note the published experience with HSCT experience other than UCB in beta-thalassemia. Lucarelli and Clift et al. 1999 reported on 87 adults who received related BMT; survival through 6 years was estimated to be 65% and rejection-free survival was 62%. Lucarelli and Gaziev 2008 reported on 515 pediatric patients with Pesaro class 1 or 2 who received BMT (relatedness not specified); survival through 20 years was estimated at 88% and thalassemia-free survival was 85%. An additional group of 73 patients who where class 3 had long-term survival of 87% and thalassemia-free survival of 82%. Experience with **related** cord blood appears to have generally similar results (Locatelli and Rocha et al. 2003; Lisini and Zecca et al. 2008)

The most relevant additional experience with UCB from the literature is summarized below:

<u>Jaing and Tan et al. 2008 (abstract, n=51)</u>

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, 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.

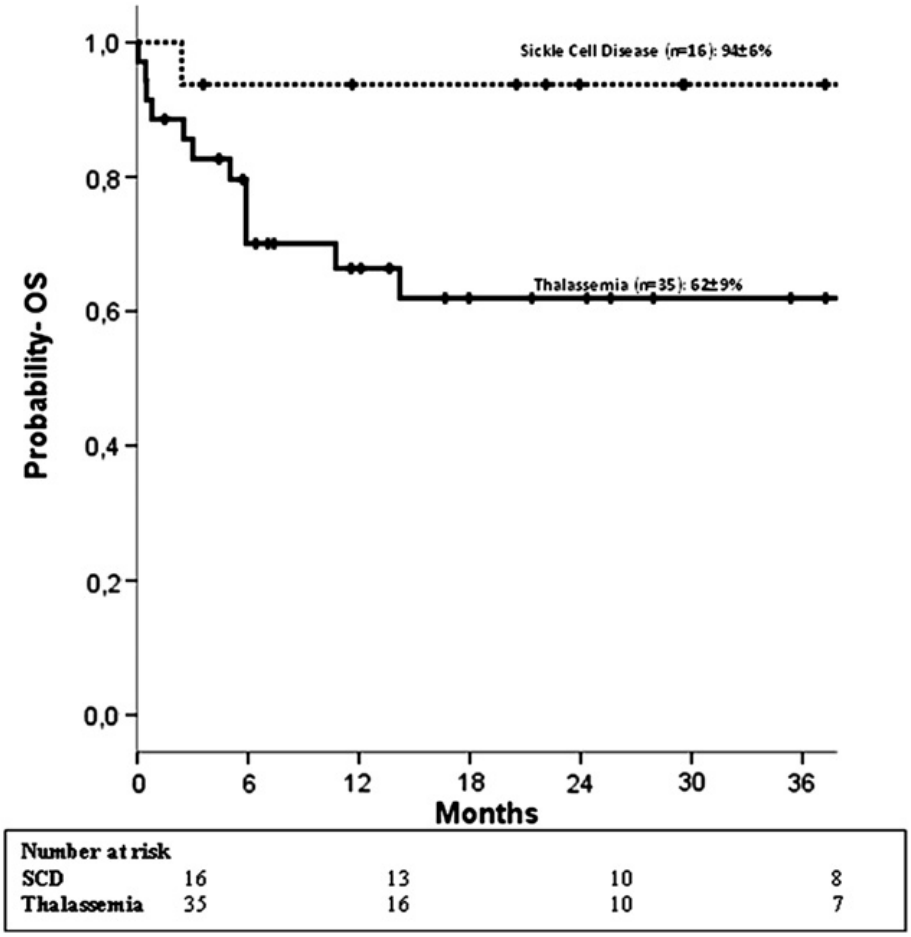
Jaing and Hung et al. 2011 (n=35)

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 a subsequent symposium proceedings (Laughlin and Kurtzberg et al. 2011), it was reported that 63% of patients were Pesaro class 1. All had conditioning regimen that involved busulfan, cyclophosphamide, and anti-thymocyte globulin. The GVHD prophylaxis used cyclosporine and methylprednisolone. HLA matching was full for 15%, one mismatch for 31%, two mismatches for 52%, and 3 mismatches 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 are not reported.

Ruggeri and Eapen et al. 2011 (n=35)

This presents an analysis of reports 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. 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 including anti-thymocyte globulin. HLA matching was full for 14%, one mismatch for 40%, two mismatches for 43%, and 3 mismatches for 3%. There were 12 deaths, of which 7 were 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.

Figure 43: Estimated Overall Survival Following UCB Transplant for Beta-Thalassemia (and Sickle Cell Disease) – Ruggeri 2011



Source: Ruggeri and Eapen et al. 2011

Beta-Thalassemia – Observations and Limitations

The evidence of efficacy of UCB transplantation in beta-thalassemia has substantial limitations. The estimated 66% 1-year mortality following UCB transplant exceeds the mortality in any available historical control group, but the docket experience is very limited. Published literature provided evidence of the ability of UCB to eliminate transfusion dependence, although that endpoint is not objective defined. The evidence from published literature regarding the effect of UCB on survival shows a range of results, but interpretation of reports is limited by the lack of controls and possibly selection bias or reporting bias. A recent review found that 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 should be discouraged outside of well-designed clinical trials. The number of patients with beta-thalassemia in the docket datasets was too small to permit evaluation of the relationship of dose to survival.

5. SUMMARY OF SAFETY INFORMATION

5.1 Nature and Scope of the Safety Review

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.

The key materials used in this safety review include:

- Datasets and summaries submitted by the applicant in BLA 125397
- Docket FDA-1997-N-0010 (Legacy Docket number 97N-0497)
- Docket FDA-2006-D-0157 (Legacy Docket number 06D-0514)
- Relevant literature
- Dataset for the COBLT Study – The Cord Blood Transplantation Study (COBLT) (NCT00000603) is a prospective safety and efficacy study of unrelated donor cord blood transplantation. It 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 (https://web.emmes.com/study/cord/). The main protocol is a prospective, single-arm trial of unrelated donor cord blood 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 x 10^7 TNC/kg. The expanded access protocol was open to subjects with a disease that warranted cord blood transplantation but who were not eligible for the main protocol. Treatment 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 cord blood transplantation.

The BLA was reviewed to characterize the safety profile of the product. Additional information used to develop the safety profile was obtained from the additional sources listed above. Submissions to the dockets were reviewed for reports and data pertinent to safety of cord blood. The results were supplemented with FDA's analyses of the COBLT dataset. Where sufficient detail is available, the safety outcomes were also assessed for each 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. The key issues addressed in this review include the safety experience of the applicant and the safety of the TNC dose $\geq$2.5 x 10^7 TNC/kg. The safety profile of the applicant's product was assessed on its own merit and in the context of the available relevant information from the additional sources.

5.2 Clinical Safety Data in BLA 125397

Umbilical cord blood units were provided to U.S. and foreign transplant centers under the New York Blood Center's IND 6637. No treatment protocol was conducted by the applicant; therefore, no data from prospective clinical trials or studies were available for the assessment of the safety of this applicant's product. The safety review was therefore based primarily on the serious adverse event reports and the outcomes dataset submitted by the applicant. Since much of the safety database is based on voluntary reporting, complete data are not available for all recipients.

From 1993 to 2007, data collection questionnaires were sent by the applicant directly to the transplant center. Outcomes information was received for over 90% of units transplanted during this time. If a serious, life-threatening infusion reaction was noted on the report, the applicant requested additional information from the transplant center.

From 2008 to current, data for units transplanted in the US are collected via the Stem Cell Therapeutic Outcomes Database (SCTOD) of the CW Bill Young Transplantation Program. The dataset is incomplete for the patients transplanted most recently due to the lack of time for follow-up. Data for units transplanted outside the US may be accrued via the SCTOD, but the applicant continues to send data collection questionnaires directly to non-US transplant centers which may choose to not utilize the SCTOD.

The applicant submitted a safety outcomes dataset of 3619 patients transplanted with 3946 NYBC units from August 1993 through January 2011. Of these, 409 patients requiring hematopoietic reconstitution received a cord blood unit manufactured using the process intended for licensure. A summary of the subsets of data available for analysis is shown in Table 20. Dataset 2 with demographic and allograft information was used for the analyses of infusion reactions. Dataset 3 was limited to recipients receiving a TNC dose > 2.5×10^7/kg and for whom outcomes information is available; it was used for safety outcomes analyses. Datasets 2 and 3 do not overlap with data in the docket.

Table 20: Development of Safety Data Subsets for Analysis

Data Set	Data file subset	Number
1	Submitted datafile	3619 patients transplanted with 3946 NYBC units
2	**Subset in this step are used for analysis of infusion reactions**	
	Step 1 file limited to records for units manufactured using the process intended for licensure , used for hematopoietic reconstitution, and that include demographics and allograft information	409 patients transplanted with 432 NYBC units
	2b. And limited to units with infusion reaction data	233 patients transplanted with 244 NYBC units
3	**Subset in this step are used for analysis of clinical outcomes**	
	Step 1 file limited to patients receiving units manufactured using the process intended for licensure, using a TNC dose $\geq 2.5 \times 10^7$/kg for hematopoietic reconstitution, and the record includes demographics, allograft and outcomes information	156 patients

The demographic characteristics of the 409 patients who received units manufactured using the process intended for licensure are summarized by FDA in Table 21.

Table 21: Demographics of Applicant's Safety Outcomes Dataset

Number of Patients		409	
Median Age (Range)		19.2 yrs (2 mos-73.3 yrs)	
Age Category	1 mo - <2 yr	40	(9.8%)
	2 – <13 yrs	119	(29.1%)
	13 - <17 yrs	31	(7.6%)
	17 - <65 yrs	203	(49.6%)
	≥65 yrs	13	(3.2%)
	Unknown	3	(0.7%)
Gender	Male	226	(55.3%)
	Female	183	(44.7%)
Ethnicity	White	89	(21.8%)
	African-American	32	(7.8%)
	Hispanic	44	(10.8%)
	Asian	18	(4.4%)
	Other	15	(3.7%)
	Unknown	211	(51.6%)
Diagnosis	Hematologic malignancies	324	(79.2%)
	Hurler Syndromes	4	(1.0%)
	Krabbe Disease	0	(0.0%)
	X-linked Adrenoleukodystrophy	5	(1.2%)
	Primary immunodeficiency diseases	17	(4.2%)
	Bone marrow failure	31	(7.6%)
	Beta thalassemia	4	(1.0%)
	Other	10	(2.4%)
	Unknown	14	(3.4%)
Number of Units Transplanted	1	234	(57.2%)
	>1	175	(42.8%)
Lowest HLA Match Level	4	194	(41.3%)
	5	186	(49.5%)
	6	29	(9.3%)
Median Dose (TNC x 10^7/kg) (Range)		4.2 (1.0-57.6)	

5.3 Supporting Safety Information

Each document submitted to the dockets was reviewed for relevant safety information. Raw datasets were submitted by the NMDP, NYBC and Duke University. The datasets from Duke had substantial overlap with those from COBLT, NMDP and NYBC, so the Duke dataset was not included in the pooled analyses. Cases were also excluded if the cord blood unit was reported to be expanded or otherwise manipulated prior to transplantation, if there was no cell dose, or if there was no outcome information. The final pooled dataset was limited to 356 patients from the COBLT Study main protocol, 577 patients from NMDP and 550 patients from NYBC. Demographics for the pooled dataset are listed in Table 22. Conclusions from analyses of this dataset must take into consideration that some of the data was submitted voluntarily and was not audited, and that the categorizations and definitions of events may not be the same for all sources. In addition, with the exception of the COBLT study, the minimum dose of cells to be administered was chosen by the treating physician.

Table 22: Demographics of Safety Outcomes Dataset – Pooled Data

		All Subjects Transplanted	Subjects with a TNC Dose >2.5 x 10^7/kg
Number of Subjects		1483	1212
Subject Characteristics			
Median Age (Range)		7 yrs (0-66yrs)	5 yrs (0-66 yrs)
Age Category	<2 yr	345 (23.3%)	344 (28.4%)
	2 – <17 yrs	863 (58.2%)	749 (61.8%)
	≥17 yrs	275 (18.5%)	119 (9.8%)
Gender	Male	537 (36.3%)	470 (38.8)
	Female	396 (26.7%)	356 (29.4%)
	Unknown	550 (37.0%)	386 (31.8%)
Ethnicity	White	571 (38.5%)	500 (41.3%)
	African-American	100 (6.7%)	86 (7.1%)
	Hispanic	136 (9.2%)	122 (10.1%)
	Asian	30 (2.0%)	27 (2.2%)
	Other	14 (0.9%)	12 (1.0%)
	Unknown	632 (42.5%)	465 (38.4%)
Diagnosis	Hematologic malignancies	1103 (74.4%)	862 (71.1%)
	Hurler Syndromes	55 (3.7%)	55 (4.5%)
	Krabbe Disease	4 (0.3%)	4 (0.3%)
	X-linked Adrenoleukodystrophy	18 (1.2%)	13 (1.1%)
	Primary immunodeficiency diseases,	97 (6.5%)	94 (7.8%)
	Bone marrow failure	110 (7.4%)	91 (7.5%)
	Beta thalassemia	8 (0.5%)	8 (0.7%)
	Other	88 (5.9%)	85 (7.0%)
Year of Transplantation	1993-2000	624 (42.1%)	450 (37.1%)
	2001-2006	859 (57.9%)	762 (62.9%)
Lowest HLA Match Level	<4	53 (3.6%)	38 (3.1%)
	4	679 (45.8%)	540 (44.6%)
	5	575 (38.8)	487 (40.2%)
	6	165 (11.1%)	138 (11.4%)
	Unknown	11 (0.7%)	9 (0.7%)
Median Dose (TNC x 10^7/kg) (Range)		5.0 (0.7-73.8)	6.2 (2.5-73.8)

The majority of the population was comprised of children with a diagnosis of a hematologic malignancy. There were 13 patients with hemoglobinopathy, including 8 identified as beta thalassemia, and there were a total of 146 patients with inherited metabolic disorders. Over 80% of the patients received a TNC dose ≥ 2.5 x 10^7/kg.

It was noted that there was a high correlation in the pooled dataset between the established prognostic factors (including age, gender, race, TNC dose, degree of HLA mismatch and primary disease). Consequently, direct comparisons of the safety outcomes for the applicant's dataset with those from the pooled dataset must take into consideration the differences between the populations in the proportions of patients with the various prognostic factors.

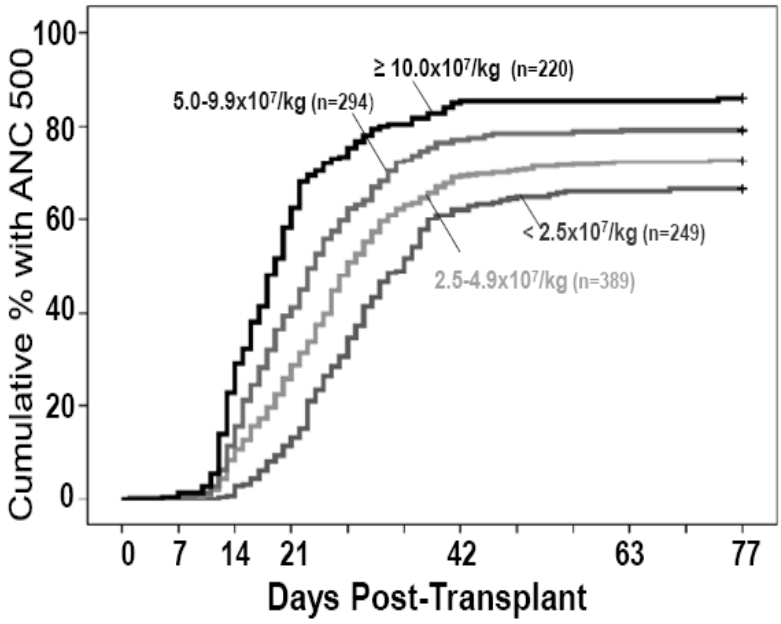
5.4 Hematopoietic Recovery

5.4.1 Applicant's Information

Applicant's Analysis of Hematopoietic Recovery

The applicant submitted four analyses of hematopoietic recovery on various subsets of patients in the safety dataset. The first analysis (Stevens and Carrier et al. 2011) evaluated the cumulative incidence of neutrophil recovery for 1202 patients with various diagnoses transplanted with a single unit. The applicant concluded that there was a step-wise decrease in the proportion with neutrophil recovery with decreasing TNC dose (Figure 44).

Figure 44: Time to ANC 500 by TNC Dose



Source: Stevens and Carrier et al. 2011

A second analysis (Barker and Scaradavou et al. 2010) evaluated the combined effects of TNC dose and HLA mismatch on neutrophil recovery in 1061 patients with various hematological malignancies transplanted 1993-2006 using a myeloablative preparative regimen and a single cord blood unit. The applicant concluded from this analysis that both TNC dose and the degree of HLA mismatch affect the time to neutrophil recovery.

A third analysis (van Rood and Stevens et al. 2009) evaluated the effect of mismatching for the noninherited maternal allele (NIMA) on neutrophil recovery in 1121 patients with various hematological malignancies transplanted 1993-2006 using a myeloablative preparative regimen and a single cord blood unit. The applicant concluded that patients who received 1-2 antigen mismatched transplants that were NIMA matched had faster engraftment than those with no NIMA match (RR 1.3, p=0.043).

A fourth analysis (Scaradavou and Stevens et al. 2007) evaluated the effect of duration of cryopreservation (< 2 yrs vs. >8 yrs) on neutrophil recovery in 343 patients with various diagnoses transplanted 2001-2006. The applicant concluded that there was no significant difference in time to neutrophil recovery between the two groups (RR 0.8, p=0.31), and no clinically meaningful difference in the rates of neutrophil recovery (80.5% vs. 73.3%, p=0.35).

FDA Analysis of Hematopoietic Recovery

FDA performed an analysis of hematopoietic recovery on the subset of patients who received a unit manufactured with the process intended for licensure and having a TNC dose >2.5 x 10^7/kg. Data for time to hematopoietic recovery was incomplete; the numbers of patients with evaluable data for each analysis are listed with the results of the analyses in Table 23.

Table 23: FDA Analysis of Hematopoietic Recovery

	Patients with a Suitable Allograft*	
	N	
Primary graft failure (%, 95% CI)+	156	14% (9-21%)
Secondary graft failure (%, 95%CI)	131	0%
Cumulative Incidence of ANC>500 by Day 42 (%, 95% CI)	156	83% (76-88%)
Cumulative Incidence of Platelets >20,000 by Day 100 (%, 95% CI)	124	78% (70-85%)
Median time to ANC>500 (range)	156	20 days
Median time to PLT >20,000 (range)	124	45 days

* Those who received a unit manufactured with the process intended for licensure and having a TNC dose ≥2.5 x 10^7/kg

\+ Includes death, 2nd transplantation or autologous recovery for patients surviving at least 14 days

The cumulative incidence of neutrophil recovery is 83%, and an additional 1% of patients had delayed neutrophil recovery. The primary graft failure rate was 14%. No patient was reported to have experienced rejection once neutrophil recovery occurred, although long-term follow-up in this subset may be incomplete.

5.4.2 Supporting Information

In a comprehensive review, Petropoulou and Rocha 2011 reported the cumulative incidence of graft failure after unrelated donor cord blood 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, colony forming units (CFU), or CD34), HLA matching, presence of noninherited maternal HLA antigens on the cord blood, use of fludarabine in the preparative regimen, and use of methotrexate for prevention of GVHD.

The risk of graft failure was especially high in patients with nonmalignant disorders, such as hemoglobinopathies. In comparison to patients with hematologic malignancies, patients with nonmalignant disorders were more likely to be alloimmunized from transfusion of nonlymphodepleted blood products and had not been exposed to immunosuppressive and

myelosuppressive chemotherapy prior to transplantation. Ruggeri and Eapen et al. 2011 reported that the increased risk of graft failure in these patients could in part be overcome by increasing the TNC dose to >5 x 10^7/kg.

Whether alloimmunization impacts the neutrophil recovery after unrelated donor cord blood transplantation is also a concern. The risk of graft rejection is higher in haploidentical and unrelated donor marrow or blood stem cell transplant recipients who have antibodies directed against donor HLA antigens, raising the concern that the same may be true for cord blood transplant recipients. Cutler and Kim et al. 2011 and Takanashi and Atsuta et al. 2010 have, in fact, reported that the presence of anti-donor HLA antibodies in cord blood 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 (odd ratio 16.3, p=0.0034). Brunstein and Noreen et al. 2011 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 hematologic recovery were similar (78% vs. 86%, respectively).

Gibbons 2005 provided to the Institute of Medicine (IOM) an analysis of 755 patients undergoing first unrelated donor cord blood transplantation 1993-2004 using data from the NMDP, NYBC and the COBLT study. Cell doses were categorized as low (<2.5 x 10^7/kg), intermediate (2.5-5.0 x 10^7/kg), or high (>5.0 x 10^7/kg). The main effects model showed a significant increase in graft failure with increased IBMTR risk group, TNC dose, degree of HLA mismatch, and source of data. An interaction between TNC dose and degree of HLA mismatch was apparent (Table 24); for those receiving a TNC dose <2.5 x 10^7/kg, graft failure rates were especially high unless there was no HLA mismatch. The subsequent recommendations of the IOM were based on its finding that an effective cord blood allograft was defined as having a TNC dose ≥2.5 x 10^7/kg and 2 or fewer HLA mismatches.

Table 24: Graft Failure – IOM Study (N=755)

	Estimated 3-Month Engraftment Failure Rates		
TNC x 10^7/kg	**HLA 4/6 Match**	**HLA 5/6 Match**	**HLA 6/6 Match**
<2.5	0.33	0.35	0.16
2.5-5.0	0.31	0.27	0.15
>5.0	0.21	0.16	0.09

The pooled dataset from the docket overlaps that used by Gibbons. The FDA analysis of hematopoietic recovery is summarized in Table 25. The graft failure rate was significantly lower in those who received a TNC dose ≥2.5 x 10^7/kg (17% vs. 31%, p<0.0001). In a multivariate analysis, graft failure was significantly associated with TNC dose, degree of HLA match and diagnosis. The cumulative incidence of neutrophil recovery by Day 42 was 74%, and an additional 5% had delayed recovery. The time to neutrophil recovery was significantly faster with a TNC dose ≥2.5 x 10^7/kg (median 26 vs. 36 days, p<0.001). In a multivariate analysis, time to neutrophil recovery was significantly associated with TNC dose and degree of HLA match.

Table 25: Hematopoietic Recovery – Pooled Dataset

	All Subjects Transplanted	Subjects with a TNC Dose $\geq 2.5 \times 10^7$/kg
Primary graft failure (N, %, 95%CI)*	19% (17-22%)	17% (15-19%)
Cumulative Incidence of ANC>500 by Day 42 (%, 95% CI)	74% (72-76%)	76% (74-79%)
Proportion with PLT >50,000 by Day 100 (%, 95%CI)	40% (37-42%)	45% (43-48%)
Median time to ANC>500	27 days	26 days
Median time to PLT >50,000	168 days	123 days

* Includes death, 2nd transplantation or autologous recovery for patients surviving at least 14 days without neutrophil recovery

Neutrophil recovery was also assessed by the individual indications for those receiving a TNC dose $\geq 2.5 \times 10^7$/kg (Table 26). Median times to ANC>500 vary from 19 to 31 days. Direct comparisons by indication are confounded by the differences in the cell dose administered and the small numbers of patients within each cohort.

Table 26: Hematopoietic Recovery by Indication – Pooled Dataset+

	Median TNC/kg (Range)	Median time to ANC>500	Primary graft failure* (%, 95%CI)
Primary immunodeficiency diseases	10.6 (2.7-73.8)	19 days	13 (7-22)
Krabbe Disease	12.8 (3.5-36.3)	21 days	50 (7-93)
Hurler Syndromes	10.3 (3.4-30.0)	22 days	11 (4-22)
Hematologic malignancies	5.4 (2.5-35.0)	26 days	16 (14-19)
X-linked Adrenoleukodystrophy	5.9 (2.8-14.2)	26 days	8 (0-39)
Bone marrow failure	5.5 (2.5-28.2)	30 days	31 (22-42)
Beta thalassemia	6.4 (2.5-18.2)	31 days	29 (4-71)

+ Subjects with a TNC Dose $\geq 2.5 \times 10^7$/kg
* Includes death, 2nd transplantation or autologous recovery for patients surviving at least 14 days without neutrophil recovery

5.4.3 Hematopoietic Recovery – Overall Assessment

FDA analysis of the pooled dataset confirmed that use of a TNC dose $\geq 2.5 \times 10^7$/kg correlated with a reduction in graft failure and a shorter time to neutrophil recovery. For patients in the applicant's dataset receiving a TNC dose $\geq 2.5 \times 10^7$/kg, the cumulative incidence of neutrophil recovery by Day 42 was 83%, the median time to neutrophil recovery was 20 days, and 14% had primary graft failure. Although these outcomes appear to be better than those from the pooled dataset, any comparison is confounded by the differences between the populations in factors (such as cell dose, degree of HLA mismatch, diagnosis, and age) that are prognostic for hematopoietic outcomes.

5.5 Infusion Reactions

5.5.1 Applicant's Information

Infusion Reaction Categorization

The applicant's data collection questionnaire requests only whether a "serious adverse reaction" occurred, and whether specific reactions (bradycardia, cardiopulmonary arrest, acute renal failure, hypertension, hypotension, hemolytic reactions, anaphylaxis or dyspnea) required intervention, such as oxygen administration, blood pressure support, bronchodilators or need for diuretics more than six hours after transplantation.

The SCTOD data collection form lists 17 potential events and allows for write-in of additional unspecified events to capture occurrence. Events of any degree of seriousness are reported. Whether the event required intervention and whether the event resolved are also requested.

Infusion Reactions Reported

On review of the application, the infusion reaction dataset was found to have information for infusions of 244 unique units administered to 233 patients. The FDA analysis of the infusion reactions is shown in Table 27. A subset of 150 patients received a unit with a TNC dose $\geq$2.5 x 10^7/kg. An adverse reaction was reported in association with the infusion for approximately 17% of the units infused; 11% had one symptom or sign reported, and 7% had multiple symptoms and/or signs. Adverse reactions reported for at least 1% of patients were hypertension, nausea, vomiting, hypoxemia requiring oxygen, dyspnea, tachycardia and cough. None of the patients were reported to have fever, headache, hives, hematuria, hypotension or rigors.

Table 27: Infusion Reactions for Process Intended for Licensure

	All Units Transplanted N (%)	Units with a TNC dose $\geq$2.5 x 10^7/kg N (%)
Number of infusions assessed	244	153
Number with any reaction	41 (16.8)	28 (18.3)
Hypertension	32 (13.1)	22 (14.4)
Nausea	10 (4.1)	7 (4.6)
Vomiting	9 (3.7)	6 (3.9)
Hypoxemia	4 (1.6)	4 (2.6)
Dyspnea	2 (0.8)	2 (1.3)
Tachycardia	2 (0.8)	2 (1.3)
Cough	2 (0.8)	2 (1.3)
Chest tightness/pain	4 (1.6)	1 (0.7)
Pain, abdominal	1 (0.4)	1 (0.7)
Pain, back	1 (0.4)	1 (0.7)
Diaphoresis	1 (0.4)	1 (0.7)
Agitation	1 (0.4)	1 (0.7)
Bradycardia	1 (0.4)	0 (0.0)
Hematuria	1 (0.4)	0 (0.0)

The median age was 15 yrs (5 mos-67 yrs) for those with an infusion reaction vs. 28 yrs (2 mos-73 yrs) for those without a reported reaction (p=0.29), and 6 yrs (5 mos-51 yrs) vs. 12 yrs (2

mos-66 yrs), respectively, for those with a TNC dose $\geq$ 2.5 x 10^7/kg (p=0.11). There were no univariate correlations between having a reaction and any of the demographic characteristics tested (age group, gender race/ethnicity, diagnosis).

The median TNC dose was 3.3 (1.4-57.6) x 10^7/kg for those with an infusion reaction vs. 2.8 (1.0-39.8) x 10^7/kg for those without a reported reaction (p=0.07), 4.7 (2.5-57.6) x 10^7/kg vs. 4.6 (2.5-39.8) x 10^7/kg, respectively, for those in the subgroup with a TNC dose $\geq$ 2.5 x 10^7/kg (p=0.11)). There were no univariate correlations between having a reaction and any of the product characteristics tested (single vs. multiple units, number of HLA mismatches, TNC dose). Correlations of infusion reactions with volume of the product could not be assessed as the dataset did not include the volume administered.

Infusion Reactions Reported as Serious Adverse Events

Six serious adverse events were reported to the applicant, and four of these were infusion-related (0.1% of all units transplanted). None of these was for a unit manufactured using the process intended for licensure. The four infusion-related events are summarized as follows:

- Case 1 is a patient with cardiopulmonary decompensation associated with pericardial tamponade beginning several hours after double cord transplantation. The patient expired the following day. The health care provider and applicant attributed the event to the chemotherapy administered to the patient prior to transplantation.

- Case 2 is a patient with chest pain and dyspnea that began at the end of infusion of the first of two units and worsened with infusion of the second unit. The event culminated with severe cardiomyopathy, pulmonary edema requiring intubation, and acute tubular necrosis requiring dialysis. The patient responded to supportive care, engrafted, and was discharged with mild renal insufficiency. The health care provider and applicant attributed the event to the chemotherapy administered to the patient prior to transplantation.

- Case 3 is a patient with dyspnea, chest tightness, wheezing, hypoxemia and tachycardia shortly after initiation of the infusion of the first cord blood unit. The infusion was discontinued. The patient responded to treatment of the anaphylactic reaction and went on to receive without problems two additional cord blood units that were washed prior to infusion. The patient developed a similar but less severe reaction when receiving a platelet transfusion 3 weeks later. The health care provider and applicant consider the event an allergic reaction, but the allergen was not identified specifically.

- Case 4 is a patient who developed hypertension, renal insufficiency, elevated LDH, and reduced hemoglobin without schistocytes several hours after completion of transplantation of two cord blood units. The patient responded to supportive care, engrafted, and was discharged. The applicant attributed the event to cyclosporine toxicity exacerbated by a hemolytic reaction and/or red blood cell debris infused with the cord blood unit.

In each of these cases, investigation at the NYBC revealed no manufacturing deviations, no shipping issues were identified, and all microbial cultures had no growth.

The applicant submitted a safety report from the NMDP dated 8/31/2009. This report describes four double cord transplant infusions (including NYBC Case 1 above) associated with hypertension, cardiomyopathy, acute respiratory distress, pulmonary edema, and acute tubular necrosis with acute renal failure. Three of the cases were associated with elevated troponins and two with hematuria. There were nine additional cases (total 13) with hypertension as a complication of the infusion, but these were lesser in severity. The NMDP concluded that the events were not related to manufacturing but resulted from improper preparation of the cord blood units for infusion at the transplant centers. Ma and Kwan et al. 2010 have published a complete summary of these cases of acute cardiopulmonary toxicity from the NMDP and two additional cases. They conclude that the events represent hypersensitivity reactions to dextran in the infusions.

5.5.2 Supporting Information

The adverse experiences related to infusion of cord blood include allergic reactions, immune-mediated events and toxic effects, the last of which may depend on how the cord blood unit is prepared for infusion. The most common methods of preparation 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 cord blood unit. Dextran-40 and DMSO are of particular concern.

Dextran-40 (reviewed in Data and Nies 1974) is a mixture of mainly α-1,6-glucan type polysaccharides with average molecular weight 40,000 daltons. 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 5% or 10% solutions for IV use, and the usual dosage is 5-10 mL/kg over 12 to 24 hours. 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. 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 (Zinderman and Landow et al. 2006).

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 (David 1972). Animal studies showed that DMSO and its metabolites are partially excreted through the kidneys, but the metabolite dimethyl sulfide is also excreted by exhalation. Dose-toxicity data for intravenous DMSO are limited. In a small phase 1 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 (Marshall and Camp et al. 1984). Other known side effects of intravenous DMSO include dysgeusia, nausea, vomiting, elevated liver enzymes, hemolysis and renal failure.

Encephalopathy occurs with very high doses (see Section 5.12 Overdosage). Anaphylaxis may occur, and it is not dose-dependent.

Removal of DMSO by washing the cord blood 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 would not eliminate the potential toxicities due to that agent (Nagamura-Inoue and Shioya et al. 2003; Prokopishyn and Lewis et al. 2008; Regan and Wofford et al. 2010; Ma and Kwan et al. 2010).

The specific cord blood infusion reactions reported in the literature 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. The reported incidence of cord blood 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 a life-threatening reaction (Ruiz-Delgado and Mancias-Guerra et al. 2009). It should be noted, however, that these published reports were largely analyses of data voluntarily submitted to banks or retrospective chart reviews, so the results may be incomplete.

The COBLT study provides the only dataset that includes prospective monitoring for infusion reactions. The dataset includes information for 511 patients who received 523 cord blood units. To prepare for infusion, cord blood units were washed and resuspended in 30-150 mL 8% dextran-40 with 4% albumin. Infusions were to be completed within 30 minutes. Premedications were administered for 98.5% of the infusions. A predefined list of infusion reactions were identified and graded according to the NCI CTC scale. The incidences of infusion reactions are listed in Table 28.

Table 28: COBLT Study - Infusion Reactions (N=523)

	Any grade	Grade 3-4
Any reaction	65.4%	26.6%
Hypertension	46.5%	19.9%
Vomiting	15.7%	0.2%
Nausea	15.0%	6.1%
Sinus bradycardia	10.3%	0.0%
Fever	5.5%	0.2%
Sinus tachycardia	5.2%	0.8%
Hypoxia	3.1%	2.8%
Allergy	3.1%	0.2%
Hypotension	2.9%	0.6%
Hemogloburia	1.9%	1.9%
Dyspnea	1.9%	1.1%
Infection	1.5%	1.5%
Chills	1.3%	0.0%

In this study, 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 had cited hypertension as an infusion reaction. Narratives are not available for the serious adverse events.

5.5.3 Infusion Reactions – Overall Assessment

The spectrum of infusion-related toxicities reported by the applicant is supported by the literature and the COBLT dataset. The incidence of each event, however, appears to be underestimated by the applicant's dataset in comparison to data from the COBLT study. A clear correlation between cell dose and the risk of infusion reaction was not seen.

Four fatal or life-threatening cardiopulmonary serious adverse events were reported to the applicant for an estimated incidence of 0.1%. These events were initially not considered related to the product by the healthcare provider. The report by NMDP suggests that there are more cases of cardiopulmonary decompensation, but the denominator was not provided, so an estimation of incidence is not available. In the COBLT study, 0.8% of infusions were associated with similar clinical findings, so again, the applicant's experience (0.1% incidence) may be an underestimate.

5.6 Deaths

5.6.1 Applicant's Information

There were 68 (44%) deaths amongst the 156 patients with follow-up information who received a suitable allograft. Death occurred by Day 100 for 39/156 (25%) patients. Results of the FDA analysis are shown in Table 29. The most common causes of death (≥5%) are organ failure, primary disease, infections, and GVHD. The majority of the deaths due to organ failure, infection, and graft failure occurred within 100 days after transplantation.

Table 29: Causes of Death After Transplantation*

Causes of Death	Total Reported N (%)	Through Day 100 N (%)
Graft Failure	6 (3.9%)	5 (3.2%)
Organ failure	20 (12.8%)	13 (8.3%)
Infection	12 (7.7%)	9 (5.8%)
GVHD	8 (5.1%)	3 (1.9%)
Primary disease	14 (9.0%)	4 (2.6%)
2nd Malignancy	1 (0.6%)	0 (0.0%)
Unknown	4 (2.6%)	3 (1.9%)
Other	3 (1.9%)	2 (1.3%)

*Of patients receiving a suitable allograft (N=156)

Since most of the deaths plausibly related to the cord blood unit occurred by 100 days after transplantation, additional exploratory analyses were conducted to determine if demographic or product parameters might be associated with such early deaths. There were no univariate

correlations between early death and any of the demographic (age group, gender race/ethnicity, diagnosis) or allograft characteristics tested (single vs. multiple units, degree of HLA match, TNC dose).

5.6.2 Supporting Information

The causes of death after cord blood transplantation include treatment-related complications and relapse of the primary disease. In the pooled dataset, there were 798 deaths reported (54% of the population); 457 deaths (31% of the population) occurred by 100 days after transplantation. Graft failure was the primary cause of death in almost 4% of the patients.

The most common causes of death by Day 100 were infection and organ failure (Table 30). The Day-100 mortality was significantly lower in those who received a TNC dose $\geq 2.5 \times 10^7$/kg vs. $<2.5 \times 10^7$ (26% vs. 52%, $p<0.0001$). In a multivariate analysis, Day-100 mortality was significantly associated with TNC dose, degree of HLA match, diagnosis and gender.

It is likely that the results of the multivariate analysis of the pooled dataset differ from that of the applicant's dataset due to major differences in the patient population. Specifically, the applicant's dataset does not include patients with low cell doses and with high degrees of HLA mismatches, both of which are associated with higher Day-100 mortality. The smaller number of patients in the applicant's dataset may also reduce the ability to detect a significant prognostic factor, but Cohen and Scaradavou et al. 2011 also reported that degree of HLA mismatch is not significant for Day-100 mortality in a cohort of 514 patients limited to those with 4/6 matches or better.

Table 30: Causes of Death After Transplantation – Pooled Dataset

Causes of Death	All Subjects Transplanted (N=1483)		Subjects with a TNC Dose $\geq 2.5 \times 10^7$/kg (N=1212)	
	Total	Through Day 100	Total	Through Day 100
Graft Failure	56 (3.8%)	42 (2.8%)	47 (3.9%)	33 (2.7%)
Organ failure	146 (9.8%)	108 (7.3%)	108 (8.9%)	80 (6.6%)
Infection	234 (15.8%)	164 (11.1%)	155 (12.8%)	97 (8.0%)
GVHD	95 (6.4%)	54 (3.6%)	69 (5.7%)	38 (3.1%)
Primary disease	192 (12.9%)	49 (3.3%)	158 (13.0%)	41 (3.4%)
2nd Malignancy	4 (0.3%)	0 (0.0%)	3 (0.2%)	0 (0.0%)
Unknown	40 (2.7%)	19 (1.3%)	36 (3.0%)	16 (1.3%)
Other*	29 (2.0%)	21 (1.4%)	17 (1.4%)	11 (0.9%)

*Other includes hemorrhage, pulmonary embolism, thrombocytopenic thrombotic purpura, myocardial infarction and drug reaction.

5.6.3 Deaths – Overall Assessment

The evaluation of the pooled dataset confirmed that Day-100 mortality was lower in those who received a TNC dose $\geq 2.5 \times 10^7$/kg. Using this dose as a guideline, the incidence of early deaths

due to graft failure in the applicant's dataset (2.7%) was similar to that in the pooled dataset (3.2%). Delayed engraftment raises the risk of life-threatening infection. The incidence of early death due to infection was slightly lower in the applicant's dataset than in the pooled dataset (5.8% vs. 8.0%). Overall, no safety issue related to the applicant's product was raised in the evaluation of early deaths.

5.7 Acute GVHD

5.7.1 Applicant's Information

Available data in the BLA included only the maximum grade of acute GVHD that occurred and the date of onset of any grade of acute GVHD. The data set included 141 evaluable patients with GVHD outcomes who had received a suitable graft, 89 (63%) of whom developed acute GVHD (grades are available for 85 patients). The results are shown in Table 31. The analysis showed that 44% developed grades 2-4 GVHD, and 20% developed grades 3-4 GVHD.

Table 31: FDA Analysis of GVHD

		Patients with a Suitable Allograft* N (%)
Maximum grade	0	32 (24%)
	1	26 (19%)
	2	32 (24%)
	3	19 (14%)
	4	8 (6%)
	Not evaluable	20 (15%)

* Of 137 patients with GVHD grades receiving a unit manufactured with the process intended for licensure and having a TNC dose >2.5 x 10^7/kg

5.7.2 Supporting Information

The reported rates of grades 2-4 acute GVHD after unrelated donor cord blood transplantation ranged from 14 to 52% in the literature and as reported in the dockets. The majority of the acute GVHD in the cord blood 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 (MacMillan and Weisdorf et al. 2009; Alsultan and Giller et al. 2011). Several risk factors for acute GVHD were identified, including CMV serostatus, pretransplant infection, gender, age, preparative regimen intensity, CD34 cell dose and HLA mismatch.

How HLA mismatching impacts the risk of GVHD is inconsistent, varying in the literature from no impact to increased rates with mismatch at specific combinations of loci or with increasing degree of mismatch (Kamani and Spellman et al. 2008). MacMillan and Weisdorf et al. 2009 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 that report, it was noted that the double unit transplant recipients had significantly higher TNC, CD34 and CD3 doses in comparison to the single unit transplant recipients.

In the pooled dataset, 88% of the patients had an assessment for acute GVHD reported. 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, 41.5% had grades 2-4 GVHD, and 20.1% had grades 3-4 GVHD (Table 32). When comparing patients who received a TNC dose $\geq 2.5 \times 10^7$/kg to those who received a lower TNC dose, the incidences of grades 2-4 GVHD (41.4% vs. 42.1%) and grades 3-4 GVHD (19.4% vs. 23.8%) were similar.

Table 32: Acute GVHD – Pooled Dataset

	All Subjects Transplanted (N=1307)	Subjects with a TNC Dose $\geq 2.5 \times 10^7$/kg (N=1110)
Number (%) with maximum grade 0	445 (34.0%)	363 (32.7%)
1	320 (24.5)	288 (25.9%)
2	280 (21.4%)	244 (22.0%)
3	171 (13.1%)	144 (13.0%)
4	91 (7.0%)	71 (6.4%)

The incidence of grades 2-4 and grades 3-4 acute GVHD by diagnosis are displayed in Table 33. Comparisons between diagnoses are limited by the small number of cases with a GVHD assessment reported in some of the groups, such as Krabbe disease (n=4), adrenoleukodystrophy (n=17), and beta thalassemia (n=6).

Table 33: Acute GVHD by Diagnosis – Pooled Dataset

	All Subjects Transplanted		Subjects with a TNC Dose $>2.5 \times 10^7$/kg	
	Gr 2-4	Gr 3-4	Gr 2-4	Gr 3-4
Hematologic malignancies	43%	22%	42%	21%
Hurler Syndromes	46%	19%	46%	18%
Krabbe Disease	50%	0%	50%	0%
X-linked Adrenoleukodystrophy	41%	24%	46%	23%
Primary immunodeficiency diseases	31%	13%	32%	13%
Bone marrow failure	51%	27%	53%	26%
Beta thalassemia	33%	0%	33%	0%

5.7.3 Acute GVHD – Overall Assessment

The assessment of acute GVHD by dose revealed no increase in the crude incidence of grades 2-4 or grades 3-4 acute GVHD at the higher dose, suggesting that the benefit of a TNC dose $\geq 2.5 \times 10^7$/kg for engraftment would not be outweighed by an increased risk of acute GVHD. Moreover, the rates of acute GVHD by grade within this dose range were similar in the

applicant's dataset and in the pooled dataset, raising no additional concern for the applicant's product with regard to acute GVHD.

5.8 Engraftment Syndrome

5.8.1 Applicant's Information

The applicant provided no information on the occurrence of engraftment syndrome. There were no instances of engraftment syndrome listed as cause of death in the applicant's dataset.

5.8.2 Supporting Information

Engraftment syndrome (ES) is a poorly characterized clinical entity that occurs in the pre- or peri-engraftment period in both autologous and allogeneic hematopoietic stem cell transplant recipients. Spitzer 2001 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 (Kishi and Kami et al. 2005), but this differentiation is not widely accepted. 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 cord blood transplant recipients (Kishi and Kami et al. 2005; Narimatsu and Terakura et al. 2007; Lee and Lim et al. 2008; Nishio and Yagasaki et al. 2009; Patel and Rice et al. 2010). Median onset is approximately 7-9 days after transplantation, potentially several weeks prior to neutrophil recovery. ES after unrelated donor cord blood transplantation resolved rapidly with a short course of high-dose steroid, and development of ES seems to have no impact on TRM or OS. The incidence of ES appears to be reduced by use of short-term methotrexate or corticosteroids in the GVHD prophylaxis regimen.

There were no submissions to the docket that addressed the risk of engraftment syndrome in cord blood transplant recipients. Of the datasets available for analysis, only the COBLT study included information applicable to engraftment syndrome. 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 was reported for 15% of the patients. Median time to onset of the event was 10 days after transplantation (range, 5-35 days).

5.8.3 Engraftment Syndrome – Overall Assessment

Although there are some reports in the literature of a high incidence of ES after cord blood transplantation, "cytokine storm" or "hyperacute GVHD" was reported for only 15% of patients in the COBLT study, and no cases of ES were reported by the applicant. The adequacy of the data to assess ES is likely compromised by the lack of a clear definition of the syndrome that is accepted and applied by all reporters, resulting in a wide variation in the reported incidence. Whether cell dose or treatment factors other than GVHD prophylaxis alter the risk is also unknown. This lack of clarity hinders firm conclusions about the risks and outcomes of ES after cord blood transplantation.

5.9 Malignancies of Donor Origin

5.9.1 Applicant's Information

The applicant reported that no leukemia of donor origin was reported to the bank. EBV lymphoproliferative disorder, presumed to be of donor origin, was reported as the cause of death for 0.6% of patients with follow-up information.

5.9.2 Supporting Information

Hematopoietic stem cell donor-derived malignancies are generally limited to leukemias and the opportunistic lymphoproliferative disorders (PTLD) resulting from EBV infection. There were no cases of donor cell leukemias reported to the docket. PTLD was not assessable in the pooled dataset. Further information was obtained by review of the literature.

Donor Cell Leukemia

Donor cell leukemia is a rare event in hematopoietic stem cell transplant recipients, estimated to occur in 124/100,000, although rates as high as 5% have been reported in single institution studies (Wiseman 2011). 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.

Nine cases of donor cell leukemia, myelodysplasia or myeloproliferative disorders in cord blood transplant recipients have been published (Table 34) for an estimated incidence of 90/100,000, an incidence slightly less than that estimated for all transplant recipients, as indicated in the paragraph above. A single institution has reported an incidence as high as 3% in cord blood transplant recipients (Ballen and Cutler et al. 2010). Amongst the reported cases in Table 34, 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 34: Donor Cell Leukemia and Myelodysplasia in Cord Blood Transplant Recipients

Reference	Original Diagnosis	Donor Cell Leukemia	Time from CBT to Diagnosis of Donor Cell Leukemia	Outcome
Fraser[1]	Histiocytosis	AML	40 mos	Died (10 mos)
Matsunaga[2]	Lymphoma	AML	(not reported)	(not reported)
Kusumoto[3]	AML	T cell LGL	(not reported)	(not reported)
Mitsui[4]	ALL	MPD	5 mos	(not reported)
Wang[5]	AML	AML	14.5 mos	Died (11 mos)
Wang[5]	CLL	MDS	6 mos	Alive (28 mos)
Wang[5]	ALL	MDS	5 mos	Alive (9 mos)
Ballen[6]	AML	MPD	26 mos	Died
Ballen[6]	Lymphoma	MDS-RAEB	21 mos	Died

[1] Fraser and Hirsch et al. 2005 [2] Matsunaga and Murase et al. 2005 [3] Kusumoto and Mori et al. 2007
[4] Mitsui and Nakazawa et al. 2007 [5] Wang and Hutchinson et al. 2011 [6] Ballen and Cutler et al. 2010

EBV-Related PTLD

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 hematopoietic stem cell transplant recipients, the cumulative incidence of PTLD was 1% at 10 years (Curtis and Travis et al. 1999). Risk factors for early onset PTLD (<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.

The reported incidence of EBV-related PTLD after unrelated donor cord blood transplantation varies from 2% to 16% overall (Ballen and Cutler et al. 2010; Barker and Martin et al. 2001; Brunstein and Weisdorf et al. 2006). The incidence is highest (>20%) in those who received a nonmyeloablative or reduced intensity preparative regimen with ATG. In EBV-related PTLD cases where donor cells were available, no evidence of infection by EBV was found (Gong and Bayerl et al. 2006; Heslop 2009) in the donor cells, although this is not always the case (see Section 5.10.2) (Haut and Kovarik et al. 2001). Therefore, the inciting EBV infection is thought to be a reactivation of prior infection in the recipient and is not transmitted from the cord blood donor to recipient. The reported response to rituximab is 33-55%. Many patients die from the fulminant lymphoma within weeks of diagnosis, 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 cord blood recipients than in other hematopoietic stem cell transplant patients.

5.9.3 Malignancies of Donor Origin – Overall Assessment

Donor cell leukemias after cord blood transplantation are relatively rare, and the lack of report of such a complication in the applicant's experience is likely due to the fact that the number of units

transplanted is too small to allow detection. PTLD, on the other hand, occurs more frequently than donor cell leukemia, but risk of PTLD appears to be associated with the treatment rather than the product.

5.10 Transmission of Serious Infection

5.10.1 Applicant's Information

In accordance with the Donor Eligibility Rule and related guidance document, NYBC screens the birth mother and the cord blood donor for communicable disease agents and diseases including HIV, hepatitis B (HBV), hepatitis C (HCV), human T-lymphotrophic virus (HTLV), human transmissible spongiform encephalopathy, West Nile virus (WNV), sepsis, vaccinia, syphilis, and communicable disease risks associated with xenotransplantation. The birth mother is tested for HIV, HBV, HCV, HTLV, Syphilis, CMV, WNV and Trypanosoma cruzi. Even in the face of negative screening and testing, infectious agents passed from mother to child in utero may be unknowingly transmitted to the cord blood recipient if the cord blood was collected during the prodrome period when neither mother nor child are symptomatic. However, the applicant reported that no case of transmission of infection was reported to the bank.

5.10.2 Supporting Information

Weinberg and Enomoto et al. 2005 assessed 362 cord blood 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 infection rate of 0.15%. The results indicate that even with the current testing, cord blood may harbor infectious agents that may be transmitted to the cord blood transplant recipient.

Haut and Kovarik et al. 2001 reported on a patient who died from EBV PTLD 6 months after cord blood transplantation. A DNA sample from the cord blood 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 rather than by infection, and that the EBV infection detected after transplantation was transmitted by the cord blood. 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 potential case of transmission of infection from a cord blood donor to the recipient was found on review of the literature.

5.10.3 Transmission of Serious Infection – Overall Assessment

Although the applicant has not received reports of transmitted infections, the data in the literature confirm that current screening and testing may miss infections due to either a false negative test result or due to collection during the prodrome. Moreover, cord blood may transmit other

agents, such as HHV-6, not currently tested for but which may cause fatal complications in transplant recipients.

5.11 Transmission of Rare Genetic Disorders

5.11.1 Applicant's Information

The applicant reported that no case of transmission of a genetic disease was reported to the bank. FDA review of the serious adverse event reports revealed one case of a cord blood unit from a donor with an inherited immunodeficiency disease being released and transplanted.

5.11.2 Supporting Information

There were no submissions to the docket that reported transmission of a genetic disease by cord blood transplantation, and there were no published cases of a genetic malady in a recipient that could be traced back to the cord blood donor.

5.11.3 Transmission of Rare Genetic Disorders – Overall Assessment

Several actions in the donor evaluation process mitigate transmission of rare genetic disorders from the cord blood donor to the recipient. The donor screening process excludes donors with a family history of an inheritable genetic disorder, review of the medical records excludes donors with any abnormalities at birth, and testing for hemoglobinopathies excludes donors with sickle cell disease and other detectable hemoglobin abnormalities. Still, the potential exists for transmission of a disorder that may not have been manifest in other family members or that may not be diagnosed until later in childhood.

5.12 Overdosage

5.12.1 Applicant's Information

The applicant reported that no case of overdosage was reported to the bank.

5.12.2 Supporting Information

The three major components of the cord blood product that may contribute to clinical overdosage include the cell content, dextran 40 and DMSO. The literature provides no reports of overdosage due to an excessive number of nucleated cells infused for cord blood; the upper limit of the tolerable cell dose range has not been established. Additionally, there no reports of overdosage from Dextran 40, although the recommended safe dose is 5-10 mL/kg over 12 to 24 hours. The current practice in the transplant community is to administer no more than 1 gm/kg/day of DMSO.

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 (Yellowlees and Greenfield et al. 1980). 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 and Goldberg et al. 1994 reported a toxic overdose in two patients with myeloma undergoing autologous blood stem cell transplantation. The first patient received approximately 225 mL DMSO (approximately 3.2 gm/kg) over 10 hours with infusion of the stem cells. 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 he 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 with supportive care alone.

There was one case of seizure and encephalopathy after infusion of a cord blood allograft reported to the docket. 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 in future patients. There were no reports in the literature of a DMSO overdose related to cord blood transplantation.

5.12.3 Overdosage – Overall Assessment

The applicant's product is cryopreserved in 25 mL containing 10% DMSO and 1% Dextran 40. The applicant recommends infusion of the cord blood unit following dilution to 170 mL with 5% Dextran 40 and 2.5% albumin. Even if two units are infused, the amount of DMSO (5 gm) would likely be toxic only for the very smallest of patients. On the other hand, one cord blood unit diluted according to instructions would provide 170 mL of 4.4% Dextran 40 (340 mL for two units) to be infused over 30 minutes. For double cord transplantation, 340 mL of 4.4% Dextran 40 infused over 1 hour could present a sizable increase in intravascular volume, especially if patients have been prehydrated to avoid renal failure from the free hemoglobin in the thawed unit. Consequently, some of the cardiopulmonary events reported by the applicant as infusion reactions could represent overdosage of Dextran 40.

5.13 Safety Summary

The IOM has concluded that an effective allograft would have a TNC dose $\geq$ 2.5 x 10^7/kg. Analysis of all available data shows that when comparing outcomes using a TNC dose <2.5 vs. $\geq$2.5 x 10^7/kg, the higher TNC dose was associated with a lower risk of graft failure, faster neutrophil recovery, and reduced Day-100 mortality without increasing the rates of infusion reactions or acute GVHD. The impact of TNC cell dose on chronic GVHD, engraftment syndrome, malignancies of donor origin, transmission of serious infections and transmission of rare genetic disorders from donor to recipient could not be ascertained from the data available.

The safety analysis for the applicant's product was limited to the 409 patients transplanted with 432 units manufactured with the process intended for licensure, and complete data for each analysis was available only for subsets of patients having received a TNC dose $\geq 2.5 \times 10^7$/kg. An adverse reaction was reported for 18% of the units infused. The most common adverse reactions were hypertension (14.4%), nausea (4.6%) and vomiting (3.9%), and hypoxemia (2.6%). Serious adverse events were reported for 0.1% of all infusions. The volume of Dextran-40 infused rapidly with the allograft was identified as a concern that might be related to the life-threatening cardiopulmonary events that were reported.

The primary graft failure rate for the applicant's product was 14%, the median time to neutrophil recovery was 20 days, and the cumulative incidence of neutrophil recovery by Day 42 after transplantation was 83%. The incidence of Grades 2-4 GVHD was 44%, and that for grades 3-4 GVHD was 20%. Day 100 mortality was 25%. The most common causes of death were organ failure (12.8%), primary disease (9.0%), infections (7.7%), and GVHD (5.1%). The majority of deaths due to organ failure, infection and graft failure occurred within 100 days after transplantation. The incidence of death due to graft failure was 3.9%.

The safety outcomes for the applicant's product appeared to be similar to, or at least no worse than, those estimated from the pooled dataset. Several demographic factors and product characteristics were identified as having an association with one or more of the safety outcomes. Development of a model, such as that reported by Gibbons, taking these prognostic factors into account might be of use as a benchmark for assessments of the safety outcomes. The value of such a benchmark, the safety outcome that would be assessed, and the acceptable target limit for the outcome is for consideration by the advisory committee.

6. ISSUES FOR DISCUSSION

DRAFT Questions for NYBC Advisory Committee

1) Hematologic malignancies:

   The submitted data and the briefing document contain information on efficacy of HPC-C transplantation in patients with hematologic malignancies that is largely derived from the use of HPC-C for hematopoietic reconstitution in patients with acute leukemia. Based on your knowledge of, and experience with, the treatment of hematologic malignancies and HPC-C transplantation, please discuss whether evidence of effectiveness in acute leukemias supports the use of HPC-C for hematopoietic reconstitution in patients with hematologic malignancies other than acute leukemia.

2) Hurler Syndrome (mucopolysaccharidosis I), Krabbe Disease, and X-linked Adrenoleukodystrophy

   Please discuss the evidence of effectiveness of HPC-C for hematopoietic reconstitution in patients with Hurler Syndrome, Krabbe disease, and X-linked adrenoleukodystrophy. Please comment on what you view as the strengths and weaknesses of the available data.

   Please discuss the overall benefit-risk profile of HPC-C for hematopoietic reconstitution in patients with Hurler Syndrome, Krabbe disease, and X-linked adrenoleukodystrophy. If the available data do not support a favorable overall benefit-risk profile for these indications, what additional information would be useful in the assessment of efficacy and/or safety for HPC-C transplantation in patients with these disorders?

3) Primary Immunodeficiency diseases

   Please discuss the evidence of effectiveness of HPC-C for hematopoietic reconstitution in patients with primary immunodeficiency diseases. Please comment on what you view as the strengths and weaknesses of the available data.

   Please discuss the overall benefit-risk profile of HPC-C for hematopoietic reconstitution in patients with primary immunodeficiency diseases.

   The submitted data and the briefing document contain information on efficacy in primary immunodeficiencies that is largely derived from use of HPC-C for hematopoietic reconstitution in patients with severe combined immunodeficiency (SCID).

   - If the overall benefit-risk profile in patients with SCID is favorable, please discuss whether the evidence of efficacy in SCID supports the use of HPC-C for hematopoietic reconstitution in patients with other primary immunodeficiencies (e.g., Wiskott-Aldrich syndrome)?

- If the available data do not support a favorable overall benefit-risk profile for patients with any of these primary immunodeficiency diseases, what additional information would be useful in the assessment of efficacy and/or safety for hematopoietic reconstitution in patients with these disorders?

4) Bone Marrow Failure

Please discuss the evidence of effectiveness of HPC-C for hematopoietic reconstitution in patients with bone marrow failure. Please comment on what you view as the strengths and weaknesses of the available data.

Please discuss the overall benefit-risk profile of HPC-C for hematopoietic reconstitution in patients with bone marrow failure.

The submitted data and the briefing document contain information on efficacy in bone marrow failure that is largely derived from use of HPC-C for hematopoietic reconstitution in patients with severe aplastic anemia (SAA) and/or Fanconi anemia.

- If the overall benefit-risk profile in patients with bone marrow failure is favorable, please discuss whether the evidence of efficacy in patients with SAA and/or Fanconi anemia supports the use of HPC-C for hematopoietic reconstitution in patients with other bone marrow failure conditions (e.g., osteopetrosis).

- If the available data do not support a favorable overall benefit-risk profile for patients with bone marrow failure, what additional information would be useful in the assessment of efficacy and/or safety for hematopoietic reconstitution in patients with bone marrow failure?

5) Please discuss the evidence of effectiveness of HPC-C for hematopoietic reconstitution in patients with beta-thalassemia. Please comment on what you view as the strengths and weaknesses of the available data.

Please discuss the overall benefit-risk profile of HPC-C for hematopoietic reconstitution in patients with beta-thalassemia. If the available data do not support a favorable overall benefit-risk profile for patients with beta-thalassemia, what additional information would be useful in the assessment of efficacy and/or safety for hematopoietic reconstitution in patients with beta-thalassemia?

6) Dose:

The available data suggests that safety and effectiveness of HPC-C may depend on cell dose per unit weight of the recipient. Please discuss the factors that you would consider in determining the appropriate dose, or minimum cell dose. Please consider this question both for hematologic malignancies and for the non-malignant indications specified above.

7) For the applicant's product, the safety outcomes included:

- 18% with infusion reactions
- 0.1% serious infusion reaction
- 14% primary graft failure
- median 20 days to neutrophil recovery
- 44% grades 2-4 GVHD
- 20% grades 3-4 GVHD
- 25% Day-100 mortality
- 3.9% death due to graft failure

a. What do you view as the primary safety concerns related to HPC-C transplantation that are applicable to all indications?

b. For each safety concern, please provide recommendations to mitigate the risk. In your recommendations, consider possible actions (e.g., by the referring physician (e.g., patient selection); by the transplant center (e.g., patient monitoring); by the FDA (e.g., instructions or warnings in the product label)) that may mitigate the risk.

c. Please discuss any safety concerns for which you recommend further investigation prior to, or as a condition of, marketing approval, for any (or all) indication.

d. Please discuss any additional significant safety concerns associated with HPC-C transplantation, for any or all indications.

8) Age, gender, race, diagnosis, degree of HLA mismatch and TNC dose have been identified as prognostic factors for some of the safety outcomes after cord blood transplantation. Differences in the distribution of these parameters within a cohort limits interpretation of the safety outcomes, Mathematical modeling, such as was performed for the IOM report, can be used to estimate expected safety outcomes for cord blood transplant recipients, and the expected outcomes can be used as a benchmark to assess safety risks.

a. Please discuss which of the safety outcomes would be reasonable to use in such a benchmarking process.

b. Please discuss whether the pooled dataset (patients transplanted 1993-2006) would be the appropriate dataset to use in developing the model for a benchmarking process for current era patients.

c. Please identify any limitations to the application of the proposed benchmarking approach to assess the safety experience for a cord blood bank.

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