CLINICAL AND STATISTICAL JOINT REVIEW

Application Type	Original
Application Number(s)	BLA 125397.0
Priority or Standard	Standard
Submit Date(s)	1/7/2011
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Office/Division	OCTGT/DCEPT/CEB
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Office/Division	OBE/DB/TEB
Team Leader	Boguang Zhen, PhD
Secondary Reviewer	Renee Rees, PhD
Established Name	Hematopoietic Progenitor Cells-Cord Blood
Trade Name	Hemacord
Therapeutic Class	Allogeneic cord blood hematopoietic progenitor cell therapy
Applicant	New York Blood Center, Inc.
Formulation(s)	Intravenous
Dosing Regimen	Recommended minimum dose is 2.5 x $10PP^{7}$ nucleated cells/kg cryopreserved
Indication(s)	Hematological malignancy, Hurler syndrome, Krabbe disease, X-linked adrenoleukodystrophy, Primary immunodeficiency disease, Bone marrow failure, Beta thalassemia

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ALD	(X-linked) Adrenoleukodystrophy
ALL	Acute lymphocytic leukemia
AML	Acute myelogenous leukemia
BMF	Bone marrow failure
BRMAC	Biological Response Modifiers Advisory Committee
CI	Confidence interval (95%, unless otherwise specified)
CML	Chronic myelogenous leukemia
CMV	Cytomegalovirus
COBLT	The Cord Blood Transplantation Study
CTGTAC	Cellular, Tissue and Gene Therapies Advisory Committee
DLCL	Diffuse large cell lymphoma
DMSO	Dimethyl sulfoxide
EBV	Epstein Barr virus
ES	Engraftment syndrome
FA	Fanconi anemia
GAG	Glycosaminoglycan
GALC	Galactocerebrosidase
GVHD	Graft versus host disease
HHV	Human herpes virus
HLA	Human leukocyte antigen
HPC-A	Hematopoietic progenitor cells-apheresis
HPC-C	Hematopoietic progenitor cells-cord blood
HPC-M	Hematopoietic progenitor cells-marrow
HR	Hazard ratio
HSA	Human serum albumin
IST	Immunosuppressive therapy
IUDA	Iduronidase
MDS	Myelodysplastic syndrome
MPD	Myeloproliferative disorder
MPS	Mucopolysaccharidosis
MRI	Magnetic resonance imaging
NCBP	National Cord Blood Program
NCI CTC	National Cancer Institute Common Toxicity Criteria
NHLBI	National Heart, Lung and Blood Institute
NIMA	Noninherited maternal allele
NMDP	National Marrow Donor Program
NYBC	New York Blood Center
PTLD	Posttransplant lymphoproliferative disorder
SAA	Severe aplastic anemia
SCID	Severe combine immunodeficiency disorder
SCTOD	Stem Cell Therapeutic Outcomes Database
TNC	Total nucleated cells
TREC	T cell receptor excision circle
WAS	Wiskott Aldrich Syndrome

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends full approval of Hemacord [Hematopoietic Progenitor Cells-Cord Blood (HPC-C)] for patients with any of the following conditions undergoing unrelated donor HPC transplantation when used in conjunction with an appropriate preparative regimen and graft-versus-host disease prophylaxis.

- For treating patients with hematologic malignancy.
- For treating children with absence or severe deficiency of the lysosomal enzyme alpha-L-iduronidase due to Hurler syndrome (mucopolysaccharidosis type IH, MPS IH).
- For treating children with absence or severe deficiency of the lysosomal enzyme galactocerebroside beta-galactosidase (galactosylceramidase) due to Krabbe disease (globoid leukodystrophy).
- For treating patients with absence or severe deficiency of peroxisomal beta-oxidation activity due to X-linked adrenoleukodystrophy (ALD) and MRI abnormalities characteristic of progressive disease.
- For improving immunologic function in children with a primary immunodeficiency disease who have failed conventional therapy if available.
- For improving bone marrow function in patients with bone marrow failure who have failed conventional therapy if available.
- For treating children with anemia due to beta thalassemia major who have failed or are intolerant of conventional therapy.

1.2 Risk Benefit Assessment

The risk benefit analysis to support the recommendations listed in Section 1.1 is based on data submitted by the applicant in the BLA, data submitted to Dockets FDA-1997-N-0010 and FDA-2006-D-0157 as cross-referenced by the applicant, the relevant literature, and other information in the public domain, including The COBLT Study dataset. Throughout this review, total nucleated cell dose (TNC) dose refers to the dose at cryopreservation.

Hematological Malignancies

The current standard of care based on disease-free survival or overall survival outcomes reserves HPC transplantation for patients with hematological malignancies failing conventional therapy or

for those with a high risk of relapse with conventional therapy. Early mortality after HPC-C in the docket dataset was 26.6%, and the primary graft failure rate was 16.3% (95% CI, 13.8-18.9%), both of which were inversely correlated with TNC dose. Recent literature reports comparable outcomes using HPC-C and other types of HPC for patients with high risk acute leukemias, and where data are available, this is confirmed by the results from the Stem Cell Therapeutic Outcomes Database (SCTOD). Overall, the totality of the data available support a favorable risk benefit for HPC-C transplantation for the treatment of hematological malignancies.

Hurler Syndrome

The data available show that patients with Hurler syndrome undergoing HPC transplantation have a survival greater than that expected for those who are untreated or treated with enzyme replacement alone. Survival with HPC-C transplantation plateaus at 70% using the docket data and 58% using the applicant's dataset, both of which are considerably higher than for the reported natural history with or without enzyme replacement therapy. Transplantation has also been associated with neurocognitive and some physical improvements that are clinically meaningful. The biological plausibility of the therapy is supported by the increase in α-L-iduronidase levels after transplantation. Early mortality was reported for 17.6% of the patients, but there was a trend for a reduction in graft failure and early mortality by use of TNC doses $\geq 5 \times 10^7$/kg. Overall, the totality of the data available support a favorable risk benefit for HPC-C transplantation for the treatment of Hurler Syndrome IH without extensive neurologic abnormalities.

Krabbe Disease

Since the majority of the patients with Krabbe Disease have the infantile form, expected long-term survival is near 0% and not more than the 30% experienced by those with the less fatal late onset form. Survival data available show that patients with Krabbe Disease undergoing HPC transplantation have a survival greater than that expected, which was confirmed in a retrospective cohort comparison. Survival with HPC-C transplantation plateaus at 80% for asymptomatic patients in the docket dataset and 62% using the applicant's dataset. Transplanted patients, though alive, continue to experience neurocognitive and motor abnormalities. The biological plausibility of the therapy is supported by the increase in galactocerebrosidase levels after transplantation. Early mortality after HPC-C transplantation was reported for 9.8% of the patients and graft failure in 10.3%. There was no correlation between TNC and graft failure or early mortality. Overall, the totality of the data available support a favorable risk benefit for HPC-C transplantation for the treatment of infantile onset Krabbe Disease.

Adrenoleukodystrophy

Although the reported survival of patients with cerebral ALD without transplantation has varied over time, there is no plateau. By contrast, their survival after HPC transplantation plateaus at 54-75% in the datasets analyzed, and at more than 80% for patients transplanted at less than 14 years of age. Moreover, a retrospective cohort comparison showed a significant survival benefit

for patients with early stage cerebral ALD who undergo HPC transplantation (p=0.006). Transplanted patients who survive are reported to track normally in cognitive and motor development. The biological plausibility of the therapy is supported by the detection of ABCD1 expression in neurological tissue from autopsy specimens of transplanted patients. Early mortality and graft failure after HPC-C were relatively low, 4.0% and 10.5%, respectively. There was no correlation between TNC and graft failure or early mortality. Overall, the totality of the data available support a favorable risk benefit for HPC-C transplantation for the treatment of childhood ALD with early cerebral involvement.

Primary Immunodeficiency Disorders

The data support a clear survival benefit for patients with severe combined immunodeficiency disorder (SCID). The calculated survival rates in the two datasets were 65% and 60% for these patients. Moreover, the SCTOD reveal similar survival using unrelated donor HPC-C or haploidentical HPC-A transplantation. The SCTOD data also show similar survivals for patients with WAS and other immunodeficiencies using unrelated donor HPC-M vs HPC-C, but the true clinical benefit for these patients requires correction of the immunodeficiency, which is born out by the literature. Overall, the totality of the data available support a favorable risk benefit for HPC-C transplantation for the treatment of SCID and for treatment of patients with other immunodeficiency disorders who are failing conventional supportive therapies

Bone Marrow Failure

Patients with marrow failure and transfusion dependence due to severely low blood counts are at risk for life-threatening sequelae. The SCTOD data support the use of allogeneic HPC transplantation for treatment of marrow failure, although this modality is clearly reserved for those with transfusion dependence who have failed conventional therapies rather than for those with mild cytopenias. The early survivals for patients with severe aplastic anemia (SAA) transplanted using HPC-C are clearly inferior to those for transplantation of unrelated donor HPC-M or HPC-A, but in the absence of a suitably matched adult donor, the survival using HPC-C is acceptable for patients who are otherwise suffering from the morbidities of the severe cytopenias. The early survivals reported for the patients transplanted for Fanconi Anemia (FA) are also inferior using HPC-C, although less so than for patients with SAA. The results of HPC-C transplantation for SAA or FA reported by the SCTOD are also somewhat better than those in the docket (28-29%) or in the applicant's dataset (27-32%); this may be due to the shorter follow-up or to the use of more modern transplant supportive care in the more recent SCTOD cohort. The safety review also highlights a high early mortality and high graft failure rate for these patients, which may in part be due to alloimmunization from multiple transfusions. However both the literature and the safety review suggest that the outcomes can be improved by use of higher TNC doses. Additional benefit is derived from the correction of the marrow failure and cessation of transfusion independence. Overall, the totality of the data available support a favorable risk benefit for HPC-C transplantation for the treatment of patients with marrow failure with severe cytopenias and transfusion dependence who have failed conventional therapies, and the TNC dose used should be in the higher range to maximize outcomes.

Beta Thalassemia Major

Given the proven efficacy of transfusion and chelation therapy for thalassemia major, it is a very small minority of patients who fail such therapy and undergo HPC transplantation. Reports from the early literature support HPC transplantation from related donors for beta thalassemia, but there was a high rate of graft failure with unrelated donor HPC-C transplantation. The high graft failure rate and limited survival are reflected in the analyses of the docket data from that era. Analyses of more recent data suggested that higher TNC doses might overcome the risk of graft failure. Indeed, survival plateaus at 60% for the patients in the applicant's dataset who received a TNC dose >5 x 10^7/kg. The published literature also shows that survivors can achieve complete amelioration of their disease with resolution of anemia and transfusion-independence. Thus, although there are no comparative studies with supportive care as the control, the thalassemia-free survivals reported after HPC transplantation (60-83%) would still be substantially better than without transplantation (0%) for those without other treatment options. Overall, the totality of the data available support a favorable risk benefit for HPC-C transplantation for the treatment of beta thalassemia major failing conventional therapy and when using a TNC dose >5 x $10^{7/}$kg.

Efficacy Across Diagnoses

The ability of HPC-C to reconstitute hematopoiesis after transplantation is demonstrated in The COBLT Study. This study included 324 subjects transplanted with a TNC dose $\geq$2.5 x 10^7/kg for various disorders affecting the hematopoietic system. In this cohort, recovery of all three major lineages were reported. The cumulative incidence of neutrophil recovery by day 42 was 76%, similar to that seen in the pooled docket dataset (77%) and in the applicant's dataset for Hemacord (83%). The time to neutrophil and platelet recovery after HPC-C transplantation is longer than after HPC-M or HPC-A transplantation, but this is due to the much lower number of progenitors in HPC-C.

The data also demonstrate that immune reconstitution appears to be complete by 2 years after HPC-C transplantation for patients transplanted for primary immunodeficiencies as well as for other malignant and nonmalignant disorders. Reconstitution includes lymphoid cell numbers as well as function as measured by in vitro proliferative responses to antigens from infectious agents, serum immunoglobulin levels, responses to vaccines in vivo, and control of infections. In vitro studies show that the lymphoid cells are of donor origin and originate from precursors in the HPC-C as demonstrated by detection of T cell receptor excision circles (TRECs) rather than just being mature lymphocytes infused with the allograft. It should be noted that the immune system is a complex organ, and only the cells of hematopoietic origin are donor-derived after HPC-C transplantation.

Additional support for the functional value of the transplanted cells comes from studies of donor-derived enzyme production in patients transplanted for inherited metabolic storage disorders. For Hurler Syndrome there was a clear correlation between the degree of chimerism, the enzyme level in peripheral blood leukocytes, and measurement of urinary glycosaminoglycans (GAGs) after transplantation. A potential additional benefit is that the cells of hematopoietic origin home throughout the tissues of the body, including the central nervous system as microglia, areas not

exposed to systemically administered enzyme replacement therapies. There are no clear data, however, that any affected cells other than those of hematopoietic origin are donor-derived after HPC-C transplantation.

Overall, the totality of the data support the use of Hemacord in conjunction with an appropriate preparative regimen for treatment of disorders affecting the hematopoietic system. The degree of success, however, appears to depend on the TNC dose and HLA match, and the data on time to hematopoietic recovery do not support use of HPC-C when HPC-M or HPC-A from a suitably matched donor is available.

Safety

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

Deaths: Day-100 mortality for patients transplanted with Hemacord is 25%. The most common causes of death (>5%) by day 100 are organ failure and infection for patients treated with the recommended cell dose. Day-100 mortality due to graft failure is 3.2%. There were no demographic or product characteristics that correlated with early mortality for patients transplanted with Hemacord.

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

Graft Failure: The primary graft failure rate was 15% (95% CI 9-21%) for patients transplanted with Hemacord. When assessed by TNC dose and degree of HLA mismatch, there was no apparent increase in the graft failure rate over that expected. Further analyses revealed no additional safety issues regarding engraftment for Hemacord other than those established for HPC-C in general.

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

The graft failure rate in the pooled docket dataset varied with diagnosis and ranged from 9.5% to 31.1%. When assessed by individual diagnosis, there was a significant inverse correlation

between TNC dose group and graft failure for the subjects transplanted with hematological malignancies, bone marrow failure and immunodeficiency disorders. For Hurler syndrome and bone marrow failure, a substantial decrease in graft failure especially occurs with a TNC dose $\geq 5 \times 10^7$/kg. The literature review suggests that the higher TNC dose may also be required to optimize engraftment rates in patients transplanted for thalassemia.

Infusion Reactions: Information on infusion reactions was available from voluntary reports for 244 patients transplanted with Hemacord. The reactions were not graded. Any type of reaction was reported for 18% of the patients. The most common infusion reactions noted were hypertension (14%), nausea (5%), vomiting (4%), hypoxemia (3%), dyspnea (1%), tachycardia (1%), cough (1%), and chest tightness or pain (1%). The rate of serious adverse cardiopulmonary reactions was 0.1%.

The COBLT dataset included information on 442 infusions at a TNC dose $\geq 2.5 \times 10^7$/kg. This dataset was used for the detailed assessment of infusion reactions. Infusion reactions were predefined events usually associated with HPC infusions that occurred within 24 hours of transplantation. These events were graded by the National Cancer Institute Common Toxicity Criteria (NCI CTC). An infusion reaction was reported for 65% of these subjects. The most common Grade 3-4 infusion reactions noted were hypertension (21%), nausea (6%) and hypoxia (2%). The rate of serious adverse cardiopulmonary events was 0.8%. On multivariate analysis, younger age and higher volumes of infusate were significantly associated with development of a grades 3-4 adverse event and with development of any grade of hypertension.

Review of the literature suggests the adverse infusion reactions may in part be due to Dextran 40. The volume of Dextran 40 in Hemacord prepared for infusion may be greater than tolerated for individuals of lower weight, possibly accounting for the higher incidence of infusion reactions in children. Dimethyl sulfoxide (DMSO) can also cause significant toxicity. Severe DMSO toxicity can also be prevented by limiting DMSO administration to less than 1 gm/kg/day. Allergic reactions to Dextran 40 and DMSO are rare and not dose-dependent.

Acute GVHD: For the patients who received Hemacord, 43% developed grades 2-4 GVHD, and 20% developed grades 3-4 GVHD. Similar rates of GVHD were reported for subjects in the pooled docket dataset who received a TNC dose $\geq 2.5 \times 10^7$/kg (42.1% and 18.8%, respectively). In addition, there was no significant difference in the rates of acute GVHD when comparing TNC doses above vs below 2.5×10^7/kg.

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

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

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

Transmission of Rare Genetic Disorders: The applicant reported one case of transplantation of HPC-C from a donor with an inheritable genetic disorder. Since starting manufacture of Hemacord, there are no reports of transmission of genetic disorders from the donor. Procedures are in place to assess additional risk information from the donor up to 6 months after donation.
Conclusion: The review of the docket data and public information support that HPC transplantation has clinical benefit in terms of survival and/or quality of life. It is acknowledged that there is a substantial rate of early mortality associated with the transplantation procedure, but the long-term benefits, including the potential for cure, outweigh the risks for the specified populations in the seven indications. For Hurler Syndrome, Krabbe Disease, X-linked adrenoleukodystrophy, primary immunodeficiency disorders and marrow failure syndromes, supporting data comes from the experience using HPC-C specifically, while for thalassemia major and most hematological malignancies, efficacy is extrapolated from the experience using other HPC types. Where a sufficiently broad dose range is available for analysis, outcomes were frequently improved with a TNC dose $\geq 2.5 \times 10^7$/kg.

Efficacy across diagnoses was demonstrated in The COBLT Study, a prospective, single-arm trial of HPC-C transplantation for patients with hematological malignancies, inherited metabolic disorders, primary immunodeficiencies and marrow failure syndromes. Hematopoietic recovery of all three lineages was seen, and immunological reconstitution was acceptable within 2 years of transplantation. Hematopoietic recovery across diagnoses was also established by analysis of the 155 patients transplanted with Hemacord.

The mechanism of action of HPC-C is shown in vivo not only by recovery of the blood counts and immune function but also by the expression of the cognate enzyme after transplantation for patients with inherited metabolic storage disorders. There are no data to suggest, however, that HPC-C reconstitutes any cell type other than those of hematopoietic origin.

Infusion reactions were reported for 18% of patients treated with Hemacord. This rate may reflect under-reporting, since responses from the transplant centers were voluntary. In The COBLT Study, 65% of patients had an infusion reaction, and 28% had a grade 3-4 reaction. The most common grade 3-4 infusion reactions were hypertension (21%), nausea (6%) and hypoxia (2%). Hypertension and any grade 3-4 reaction were more common in younger patients and when the total volume infused was more than 150 mL. Serious cardiopulmonary reactions were reported for 0.1% of patients transplanted with Hemacord and 0.8% in The COBLT Study. The spectrum of signs and symptoms for the serious cardiopulmonary reactions are similar to those seen with overinfusion of Dextran 40, raising a concern about the concentration and volume of Dextran 40 in the final preparation for infusion.

For the patients who received Hemacord, the day-100 mortality was 25%, mortality due to graft failure was 3.2%, the primary graft failure rate was 15%, and acute GVHD occurred in 43% at grades 2-4 and in 20% at grades 3-4. There was an inverse correlation between TNC dose and

early mortality and with primary graft failure, but there was no relation between TNC dose and GVHD, suggesting that increasing the TNC dose to improve efficacy outcomes and reduce mortality or graft failure will not be associated with worsening GVHD within the range of TNC doses used in the analysis population.

The safety review also revealed that engraftment syndrome occurred in 15% or more of patients after HPC-C transplantation. The estimated risks of donor cell leukemia, transmission of infection and transmission of a genetic disorder were small, but the seriousness of these events warrants highlighting them in the label.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no Risk Evaluation and Mitigation Strategies recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

The results of the safety review suggest that the concentration and volume of Dextran 40 in the final preparation for infusion may be a contributory factor for infusion reactions. In vitro study to determine the lowest concentration of Dextran 40 that can be used without impairing the product function is recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Hematopoietic Progenitor Cells-Cord

Proposed Trade Name: HemaCord

Therapeutic Class: Somatic Cell

Applicant: New York Blood Center, Inc
310 East 67th Street
New York, NY 10065

Applicant's Proposed Indication and Intended Use: [From the proposed prescribing information] "HemaCord™ HPC-C is intended for use for allogeneic HPC 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."

Dose and Regimen: Not provided.

Product Description: [Provided by the applicant] Hematopoietic Progenitor Cells, Cord (HPC-C) manufactured and issued by the National Cord Blood Program (NCBP) of the New York Blood Center (NYBC) are minimally manipulated cellular biologic products that contain live human cord blood cells after volume reduction and partial Red Cell and Plasma depletion. The final cell suspension (20 mL) is cryopreserved 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 controlled rate, and stored in liquid nitrogen (-196°C) to preserve the cell viability.

The label of each individual HPC-C unit provides information about the total nucleated cell content, post-processing viability and viable CD34+ cells contained. The minimum nucleated cell content is 5.0 $x10^8$ total nucleated cells, with post-processing viability of at least 85%, and the minimum CD34+ cell content is 1.25$x10^6$ viable CD34+ cells.

2.2 Currently Available Treatments for Proposed Indications

Alternative stem cell sources for allogeneic HPC transplantation for the indications listed include hematopoietic progenitor cells – marrow (HPC-M) or hematopoietic progenitor cells – apheresis (HPC-A) from related or unrelated donors. Minimally manipulated HPC-A from related donors and minimally manipulated HPC-M from related or unrelated donors are not regulated. Minimally manipulated HPC-A from unrelated donors are regulated, and there are currently none licensed. The choice of HPC source for allogeneic transplantation is individualized for each recipient as it will depend on donor availability, HLA-matching and the risk benefit assessment.

2.3 Availability of Proposed Active Ingredient in the United States

There are no HPC-C products licensed in the US at this time.

2.4 Summary of Presubmission Regulatory Activity Related to Submission

4/26/1996	IND 6637 submitted; allowed to proceed 5/29/1996
1/8/2002	Type C meeting
1/18/2005	Pre-BLA meeting
10/13/2006	Pre-BLA meeting

2.5 Other Relevant Background Information

On January 20, 1998 (63 FR 2985), FDA issued a notice in the Federal Register entitled "Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Blood Hematopoietic Stem/Progenitor Cell Products; Request for Comments" that FDA proposed to determine if it would be possible to develop product standards and establishment and processing controls of minimally manipulated unrelated allogeneic hematopoietic stem/progenitor cell products intended for hematopoietic reconstitution, based on existing clinical trial data, or data developed shortly thereafter, demonstrating the safety and effectiveness of such cells. In this notice, FDA requested the submission of comments proposing establishment controls, process controls, and product standards designed to ensure the safety and effectiveness of minimally manipulated unrelated allogeneic hematopoietic stem/progenitor cell products derived from peripheral and cord blood for hematopoietic reconstitution. Submitted comments were to include supporting clinical and nonclinical laboratory data and other relevant information. A period of two years was provided, until January 20, 2000, for interested persons to submit proposed product standards and establishment and processing controls with supporting clinical and nonclinical data. At the request of industry, the comment period was reopened for 90 days until July 17, 2000 (65 FR 20825, April 18, 2000).

The Biological Response Modifiers Advisory Committee (BRMAC) met 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 FDA as well as information provided by guest experts regarding the safety and effectiveness of cord blood for hematopoietic reconstitution. On the basis of the assessment of submitted information, discussion of the BRMAC, and review of published literature on this subject, 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 the Federal Register notice of January 17, 2007 (72 FR 1999), FDA announced the availability of the draft guidance for licensure of minimally manipulated cord blood entitled "Guidance for Industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies" dated

December 2006. Additional discussion was held with the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) on March 30, 2007.

FDA received comments on the December 2006 draft guidance with additional data, this new information along with the recommendations of the CTGTAC were considered, and the guidance was finalized. In the Federal Register notice of October 20, 2009 (74 FR 53753), FDA announced the availability of the finalized guidance entitled "Guidance for Industry: Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Specified Indications" dated October 2009 ("HPC-C licensure guidance"). The HPC-C licensure guidance provides recommendations to cord blood manufacturers applying for licensure of their HPC-Cs for the indications hematologic malignancies, Hurler Syndrome, Krabbe Disease, X-linked adrenoleukodystrophy, primary immunodeficiency diseases, bone marrow failure and beta thalassemia.

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 in part to establish efficacy in the specified indications.

2.6 Pediatric Issues

Partial waivers are recommended for the indications and age groups listed below. The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in those age groups and/or is not likely to be used in a substantial number of pediatric patients in the groups identified. Therefore, conduct of studies would be impracticable.

- Hematologic malignancies – Partial waiver for neonates
- Hurler Syndrome (MPS I) – Partial waiver for neonates and those ≥13 years of age
- X-linked Adrenoleukodystrophy – Partial waiver for neonates
- Bone marrow failure – Partial waiver for neonates
- Beta thalassemia – Partial waiver for neonates

Reviewer Comment: Although there are sufficient data to assess engraftment across the entire pediatric age range, additional supporting evidence of clinical benefit for some of the indications is not available for the neonatal subgroup. In most cases, the reason for the lack of information is that HPC-C transplantation would not be considered as the first line of therapy for neonates with those disorders in general, so no data have been generated. For the cases in which early HPC-C transplantation might be considered, the number of patients is so small as to make a clinical trial impracticable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

BLA 125397 was an electronic submission received 1/10/2011. Although the format for the original CMC section was in accordance with the structure requested by FDA in the guidance, much additional material was needed for the clinical review. With the submission of amendment 1, the application was deemed complete and filed on 3/9/2011. The original submission and amendments had numerous errors in format and completeness, but the issues identified were resolved in subsequent submissions. Related amendments for the BLA are listed in Table 1.

Table 1: BLA 125397 Submission and Amendments

Date	Item or Communication
1/7/2011	**Original** BLA submission
2/11/2011	**A.1**-Revised 356h, CMC information, adverse event experience, outcome dataset, outcome analyses, SOPs for outcomes analyses and adverse event reporting.
3/9/2011	***BLA Filed***
5/13/2011	**A.2**-Responses to letter 3/9/2011 and telecon 4/11/2011; CMC information including collection SOPs, revised outcomes dataset
5/18/2011	**A.3**-Response to 483 Observations, CMC information
5/27/2011	**A.4**-Response to PLI queries, CMC information
6/20/2011	**A.5**-Response to 5/31/2011 telecon request for information
7/8/2011	**A.6**-Response to 5/16/2011 telecon request for information
7/15/2011	**A.7**- Response to 6/15/2011 and 6/17/2011 telecon request for information
8/11/2011	**A.8**-Response to 6/15/2011, 6/17/2011 and 7/13/2011 telecon requests for information; response to data queries, updated data key and SOPs
8/26/2011	**A.9**-Response to 483 Observations, response to 7/27/2011 telecon request for clinical information
8/31/2011	**A.10**-Response to 8/24/2011 telecon request for information
9/27/2011	**A.11**-Response to 483 Observations, CMC information
9/29/2011	**A.12**-Collection site list revision
10/3/2011	**A.13**-Updated labels and accompanying records
10/28/2011	**A.14**-Response to 483 Observations, CMC information

3.2 Compliance with Good Clinical Practices

No clinical trials were conducted or submitted by the applicant.

3.3 Financial Disclosures

No financial disclosures were submitted by the applicant.

Reviewer Comment: The applicant cited the data in the docket to support this application, so no clinical trials are needed. Consequently, no financial disclosures were expected.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

4.1.1 Collection Procedures

Collections are performed at eight fixed sites. NYBC staff at each site are responsible for the ex utero collection of the cord blood, obtaining maternal consent, reviewing medical records, and coordinating transportation of the cord blood and associated documents and blood samples. No in utero collections are performed by the attending physician. As such, no training materials for the attending physician are required. The SOPs listed in Table 2 were reviewed, and no clinical issues were identified in the versions cited.

Table 2: Collection SOPs reviewed

SOP Number.Version	Title
Maternal consent	
CB37.0002.1	Obtaining Permission To Collect Cord Blood and Maternal Informed Consent
CB37.0003.1	Maternal Refusal of Cord Blood Collection or Cord Blood Donation
CB37.0016.1	Review of Maternal Consent
Maternal screening	
CB37.0005.1	Collection Form, Maternal Interview and Hospital Record Review
Family history screening	
CB37.0005.1	Collection Form, Maternal Interview and Hospital Record Review
Donor eligibility determination	
CB37.0023.4	Donor Eligibility – Infectious Disease Testing, Maternal and Infant Risk Factors
CB37.0001.2	Collection of Cord Blood
CB37.0006.2	Obtaining Maternal Blood Specimens
Notification of mothers or their responsible physicians of positive or indeterminate test results	
CB37.0021.1	Reporting Results of Infectious Disease Tests
In utero collection	
Not applicable	Not applicable
Elicitation and handling of post donation information	
CB37.0032.1	Follow-Up of Cord Blood Donors

4.1.2 Product Information

4.1.2.1 Manufacturing Procedures

Four manufacturing methods have been used by the applicant for manufacturing HPC-C units. The applicant has requested licensure only for the units manufactured using manufacturing "Method #4."

4.1.2.2 Preparation for Infusion

The HPC-C unit is cryopreserved in 1% Dextran 40 with DMSO. The instructions for use provide (b)(4) methods for thaw and preparation. ----(b)(4)---- the product is diluted to 170 mL in 5% Dextran 40 with 2.5% Human Serum Albumin (HSA). ----------(b)(4)----------.

Reviewer Comment: The presence of DMSO and Dextran 40 need to be taken into account when assessing the safety of the product.

4.2 Preclinical Pharmacology/Toxicology

The device components used in manufacturing and storage are cleared by FDA for cord blood processing, and the anticoagulant and diluents are approved by FDA. No additional studies of biocompatibility or of leachables were required.

No preclinical studies of Hemacord were performed by the applicant. DMSO represents a potentially toxic component of Hemacord. Published studies report teratogenic responses were caused by intraperitoneal administration of DMSO to rodents, and intravenous administration of DMSO to rodents caused hemolysis.

Reviewer Comment: The published preclinical data underscore the need to determine how DMSO contributes to the clinical toxicity of Hemacord. The potential teratogenicity of DMSO is a concern. There are no data available on use of HPC-C or DMSO systemically in pregnant subjects, so the uncertainly regarding the safety of Hemacord in pregnant patients should be reflected in the label.

4.3 Pharmacovigilance

4.3.1 Outcomes Analysis

The "NCBP Outcomes Analysis Plan" adequately describes the personnel responsible and the procedures in place for periodic analysis of safety outcomes.

Reviewer Comment: The recommendations that the plan include an analysis of aggregate SAE data, that benchmarks be established, and that the plan specify what will happen if a benchmark is reached for a safety event should be conveyed to the applicant.

4.3.2 Adverse Event Reporting

SOP CB42.004.01 "Reporting of Infusion-Related Reactions" describes the plan for adverse event elicitation and reporting. The plan adequately describes the personnel responsible and the procedures in place. The plan for reporting is consistent with 21 CFR 600.80.

Reviewer Comment: The recommendations that that the title be broadened to reporting all adverse experiences related to the product, not just infusion-related reactions, should be conveyed to the applicant.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

No clinical trials were conducted or submitted by the applicant. Several retrospective analyses of subsets of subjects in the outcomes dataset were submitted with the BLA, but there were no protocols describing patient selection or the analysis plan for any of the studies.

The key materials used in the review include:

- Submitted BLA
- Docket FDA-1997-N-0010 (Legacy Docket number 97N-0497)
- Docket FDA-2006-D-0157 (Legacy Docket number 06D-0514)
- Relevant literature and datasets available in the public domain
- The COBLT Study dataset
- Responses to review queries

The dockets and public information are reviewed in detail in the FDA documents provided in Appendices 9.4-9.6.

5.2 Review Strategy

5.2.1. Efficacy

Each indication was reviewed separately. The literature was assessed to determine when unrelated donor HPC-C transplantation had a demonstrated clinical benefit. In the absence of data using unrelated donor HPC-C, if extant data that showed HPC transplantation using HPC-M or HPC-A had demonstrated a clinical benefit for the indication and data were available to show that use of unrelated donor HPC-C provided appropriate hematopoietic reconstitution without a

safety concern, the clinical benefit of HPC-M or HPC-A was extrapolated to HPC-C. Confirmation of the benefit from use of HPC-C was derived by analysis of data in both the pooled docket data and the entire dataset submitted by the applicant. The SCTOD was interrogated to provide additional supporting data for transplantations performed 2003-2008.

Since the dockets and public information have been reviewed for this BLA and described in the Efficacy Review (Oncology) – Docket and Public Information (Appendix 9.4) and Efficacy Review (Non-Oncology) – Docket and Public Information (Appendix 9.5), information from those reviews will be only summarized here. Only new information and any relevant data submitted by the applicant will be provided in detail within this review.

5.2.2 Safety

Since no protocols were submitted with the BLA, it was not possible to confirm the analysis reports provided by the applicant. Consequently, the safety review was based primarily on the serious adverse event reports and outcomes dataset submitted by the applicant. Review of the data in the docket and in the public domain were use to augment the assessment of safety (Safety Review – Docket and Public Information, Appendix 9.6). Due to the lack of a standardized plan for safety monitoring and event categorization, the review concentrated on a subset of events of concern for this product class.

5.2.3 Statistical Considerations

Methodologies used in this review are described within each section as used. p-Values <0.05 were considered to be significant. However, p-values presented in the following sections should be interpreted with caution due to the exploratory nature of the analyses.

5.3 Discussion of Individual Studies/Clinical Trials

The dataset submitted by the applicant is described in Section 7.2 of this review. The pooled dataset from the Docket, and the dataset for the COBLT Study are described in Section 7.2.3 of the Safety Review – Docket and Public Information (Appendix 9.6). The design of The COBLT Study is provided in Section 9.3.1 of the Safety Review – Docket and Public Information (Appendix 9.6).

6 Review of Efficacy

6.1 Efficacy Summary

The applicant has cited Docket 1997N-0497 for the efficacy data to support this application for the indications HPC transplantation for the treatment of patients with hematologic malignancies, Hurler Syndrome, Krabbe Disease, X-linked Adrenoleukodystrophy, primary immunodeficiency diseases, bone marrow failure and beta thalassemia. This information was supplemented with published reports.

Hematological Malignancies

The current standard of care based on disease-free survival or overall survival outcomes reserves HPC transplantation for patients with hematological malignancies failing conventional therapy or for those with a high risk of relapse with conventional therapy. Early mortality after HPC-C in the docket dataset was 26.6%, and the primary graft failure rate was 16.3% (95% CI, 13.8-18.9%), both of which were inversely correlated with TNC dose. Recent literature reports comparable outcomes using HPC-C and other types of HPC for patients with high risk acute leukemias, and where data are available, this is confirmed by the results from the SCTOD. Overall, the totality of the data available supports a favorable risk benefit for HPC-C transplantation for the treatment of hematological malignancies.

Hurler Syndrome

The data available show that patients with Hurler syndrome undergoing HPC transplantation have a survival greater than that expected for those who are untreated or treated with enzyme replacement alone. Survival with HPC-C transplantation plateaus at 70% using the docket data and 58% using the applicant's dataset, both of which are considerably higher than for the reported natural history with or without enzyme replacement therapy. Transplantation has also been associated with neurocognitive and some physical improvements that are clinically meaningful. The biological plausibility of the therapy is supported by the increase in α-L-iduronidase levels after transplantation. Early mortality was reported for 17.6% of the patients, but there was a trend for a reduction in graft failure and early mortality by use of TNC doses $\geq 5 \times 10^7$/kg. Overall, the totality of the data available supports a favorable risk benefit for HPC-C transplantation for the treatment of Hurler Syndrome IH without extensive neurologic abnormalities.

Krabbe Disease

Since the majority of the patients with Krabbe Disease have the infantile form, expected long-term survival is near 0% and not more than the 30% experienced by those with the less fatal late onset form. Survival data available show that patients with Krabbe Disease undergoing HPC transplantation have a survival greater than that expected, which was confirmed in a retrospective cohort comparison. Survival with HPC-C transplantation plateaus at 80% for asymptomatic patients in the docket dataset and 63% using the applicant's dataset. Transplanted

patients, though alive, continue to experience neurocognitive and motor abnormalities. The biological plausibility of the therapy is supported by the increase in galactocerebrosidase levels after transplantation. Early mortality after HPC-C transplantation was reported for 9.8% of the patients and graft failure in 10.3%. There was no correlation between TNC and graft failure or early mortality. Overall, the totality of the data available supports a favorable risk benefit for HPC-C transplantation for the treatment of infantile onset Krabbe Disease.

Adrenoleukodystrophy

Although the reported survival of patients with cerebral ALD without transplantation has varied over time, there is no plateau. By contrast, the survival after HPC transplantation plateaus at 54-75% in the datasets analyzed, and at more than 80% for patients transplanted at less than 14 years of age. Moreover, a retrospective cohort comparison showed a significant survival benefit for patients with early stage cerebral ALD who undergo HPC transplantation (p=0.006). Transplanted patients who survive are reported to track normally in cognitive and motor development. The biological plausibility of the therapy is supported by the detection of ABCD1 expression in neurological tissue from autopsy specimens of transplanted patients. Early mortality and graft failure after HPC-C were relatively low, 4.0% and 10.5%, respectively. There was no correlation between TNC and graft failure or early mortality. Overall, the totality of the data available supports a favorable risk benefit for HPC-C transplantation for the treatment of childhood ALD with early cerebral involvement.

Primary Immunodeficiency Disorders

The data support a clear survival benefit for patients with SCID. The calculated survival rates in the two dataset were 65% and 60% for these patients. Moreover, the SCTOD reveal similar survival using unrelated donor HPC-C or haploidentical HPC-A transplantation. The SCTOD data also show similar survivals for patients with WAS and other immunodeficiencies using unrelated donor HPC-M vs HPC-C, but the true clinical benefit for these patients requires correction of the immunodeficiency, which is born out by the literature. Overall, the totality of the data available supports a favorable risk benefit for HPC-C transplantation for the treatment of SCID and for treatment of patients with other immunodeficiency disorders who are failing conventional supportive therapies

Bone Marrow Failure

Patients with marrow failure and transfusion dependence due to severely low blood counts are at risk for life-threatening sequelae. The SCTOD data support the use of allogeneic HPC transplantation for treatment of marrow failure, although this modality is clearly reserved for those with transfusion dependence who have failed conventional therapies rather than for those with mild cytopenias. The early survivals for patients with SAA transplanted using HPC-C are clearly inferior to those for transplantation of unrelated donor HPC-M or HPC-A, but in the absence of a suitably matched adult donor, the survival using HPC-C is acceptable for patients who are otherwise suffering from the morbidities of the severe cytopenias. The early survivals reported for the patients transplanted for Fanconi Anemia are also inferior using HPC-C,

although less so than for patients with SAA. The results of HPC-C transplantation for SAA or Fanconi Anemia reported by the SCTOD are also somewhat better than those in the docket (28-29%) or in the applicant's dataset (27-32%); this may be due to the shorter follow-up or to the use of more modern transplant supportive care in the more recent SCTOD cohort. The safety review also highlights a high early mortality and high graft failure rate for these patients, which may in part be due to alloimmunization from multiple transfusions. However both the literature and the safety review suggest that the outcomes can be improved by use of higher TNC doses. Additional benefit is derived from the correction of the marrow failure and cessation of transfusion independence. Overall, the totality of the data available supports a favorable risk benefit for HPC-C transplantation for the treatment of patients with marrow failure with severe cytopenias and transfusion dependence who have failed conventional therapies, and the TNC dose used should be in the higher range to maximize outcomes.

Beta Thalassemia Major

Given the proven efficacy of transfusion and chelation therapy for thalassemia major, it is a very small minority of patients who fail such therapy and undergo HPC transplantation. Reports from the early literature support HPC transplantation from related donors for beta thalassemia, but there was a high rate of graft failure with unrelated donor HPC-C transplantation. The high graft failure rate and limited survival is reflected in the analyses of the docket data from that era. Analyses of more recent data suggested that higher TNC doses might overcome the risk of graft failure. Indeed, survival plateaus at 60% for the patients in the applicant's dataset who received a TNC dose $>5 \times 10^7$/kg. The published literature also shows that survivors can achieve complete amelioration of their disease with resolution of anemia and transfusion-independence. Thus, although there are no comparative studies with supportive care as the control, the thalassemia-free survivals reported (60-83%) would still be substantially better than no transplantation (0%) for those without other treatment options. Overall, the totality of the data available supports a favorable risk benefit for HPC-C transplantation for the treatment of beta thalassemia major failing conventional therapy and when using a TNC dose $>5 \times 10^{7/}$kg.

Efficacy Across Diagnoses

The ability of HPC-C to reconstitute hematopoiesis after transplantation is demonstrated in The COBLT Study of 324 subjects transplanted with a TNC dose $\geq 2.5 \times 10^7$/kg for various disorders affecting the hematopoietic system. In this study, recovery of all three major lineages was reported. The cumulative incidence of neutrophil recovery by day 42 was 76%, similar to that seen in the pooled docket dataset (77%) and in the applicant's dataset for Hemacord (83%). The time to neutrophil and platelet recovery after HPC-C transplantation is longer than after HPC-M or HPC-A transplantation, but this is due to the much lower number of progenitors in HPC-C.

The data also demonstrate that immune reconstitution appears to be complete by 2 years after HPC-C transplantation for patients transplanted for primary immunodeficiencies as well as for other malignant and nonmalignant disorders. Reconstitution includes lymphoid cell numbers as well as function as measured by in vitro proliferative responses to antigens from infectious agents, serum immunoglobulin levels, responses to vaccines in vivo, and control of infections.

In vitro studies show that the lymphoid cells are of donor origin and originate from precursors in the HPC-C as demonstrated by detection of TRECs rather than just being mature lymphocytes infused with the allograft. It should be noted that the immune system is a complex organ, and only the cells of hematopoietic origin are donor-derived after HPC-C transplantation.

Additional support for the functional value of the transplanted cells comes from studies of donor-derived enzyme production in patients transplanted for inherited genetic disorders. For Hurler Syndrome there was a clear correlation between the degree of chimerism, the enzyme level in peripheral blood leukocytes, and measurement of urinary GAGs. A potential additional benefit is that the cells of hematopoietic origin home throughout the tissues of the body, including the central nervous system as microglia, areas not exposed to systemically administered enzyme replacement therapies. There are no clear data, however, that any affected cells other than those of hematopoietic origin are donor-derived after HPC-C transplantation.

Overall, the totality of the data supports the use of Hemacord in conjunction with an appropriate preparative regimen for treatment of disorders affecting the hematopoietic system. The degree of success, however, appears to depend on the TNC dose and HLA match, and the data on time to hematopoietic recovery do not support use of HPC-C when HPC-M or HPC-A from a suitably matched donor is available.

6.2 Hematologic Malignancies

6.2.1 Background

HPC transplantation is not indicated as primary therapy for almost all hematologic malignancy and related neoplastic disorders. Primary therapy generally consists of conventional chemotherapy with or without additional radiation, depending on the specific disorder. A risk-based approach is used for the application of HPC transplantation, depending on the disease, disease status (stage, refractoriness to treatment, poor prognostic markers), and donor type available. HPC transplantation from unrelated donors and patient-donor pairs with HLA mismatches (alternative donors) are known to carry higher treatment-related mortality and poorer outcomes than for HPC transplantation using a matched sibling donor. HPC transplantation is indicated only for those patients with hematological malignancies who have failed initial therapy or who are at high risk of relapse with initial therapy, and alternative donor HPC transplantation is usually reserved for those with the poorest prognoses using conventional therapy.

6.2.2 Stem Cell Transplantation

The Docket Efficacy Review (Oncology) (Appendix 9.4) included the following:

- The literature review revealed that leukemia-free survival and/or overall survival after transplantation using HPC-C are comparable to those for other HPC types for patients with acute leukemias and chronic myeloid leukemia.
- Comparative outcomes studies are not available for the other hematological malignancies. Single arm studies and registry data, however, indicate that hematopoietic reconstitution after

transplantation of HPC-C for the other hematological malignancies is adequate for use of HPC-C as alternative to HPC-M or HPC-A from unrelated donors.
- The studies that evaluated the effect of HLA disparity and TNC doses on long-term outcomes for hematological malignancies did not conclusively support a specific dose.
- The use of UCB for treatment of hematological malignancies in older subjects may provide comparable long-term outcomes when reduced intensity conditioning regimens are used.

The Docket Safety Review (Appendix 9.6) included the following:

- Day-100 mortality was 26.6% after HPC-C transplantation for hematological malignancies. There was a significant reduction in early mortality with increasing TNC doses.
- The median time to neutrophil recovery was 26 days. The primary graft failure rate was 16.3% (95% CI, 13.8-18.9%). There was a significant reduction in graft failure with increasing TNC doses.
- Acute GVHD grades 2-4 occurred in 42.5% and grades 3-4 in 21.0%, which are not substantially different from the rates for the entire population in the pooled dataset.

6.2.3 SCTOD

Survival rates after unrelated donor HPC transplantation for various hematological malignancies and other neoplastic hematological disorders is shown in Table 3. HPC-C is used in the minority of transplantations, and for several of the diseases the numbers of patients transplanted is too small for a meaningful analysis.

Table 3: SCTOD Data for Unrelated Donor Hematopoietic Stem Cell Transplantations for Hematological Malignancies and Neoplastic Hematological Disorders 2003-2008

Disease and Status at Transplantation[+]	Survival Assessed at	Survival (95%CI), N		
		HPC-M	HPC-A	HPC-C
AML CR1	3 years	44.8% (39.3 - 50.4%) (n=385)	42.6% (39.4 - 45.8%) (n=1217)	38.5% (31.2 - 45.7%) (n=242)
AML CR2	3 years	47.1% (41.2 - 53.0%) (n=321)	41.7% (37.6 - 45.8%) (n=663)	38.8% (32.1 - 45.6%) (n=262
AML in relapse	1 year	34.9% (29.7 - 40.0%) (n=335)	36.4% (33.1 - 39.6%) (n=857)	27.7% (21.3 - 34.0%) (n=210)
ALL CR1	3 years	55.2% (48.4 - 62.1%) (n=234)	42.4% (37.0 - 47.8%) (n=404)	53.6% (44.5 - 62.7%) (n=146)
ALL CR2	3 years	48.9% (43.6 - 54.3%) (n=387)	36.1% (30.9 - 41.3%) (n=393)	40.5% (34.7 - 46.3%) (n=364)
ALL in relapse	1 year	37.4% (27.4 - 47.3%) (n=91)	30.9% (24.6 - 37.3%) (n=210)	32.9% (20.5 - 45.3%) (n=59)
CML chronic phase	1 year	77.4% (71.5 - 83.4%)	71.0% (64.9 - 77.1%)	70.3% (54.1 - 86.6%)

Table 3: SCTOD Data for Unrelated Donor Hematopoietic Stem Cell Transplantations for Hematological Malignancies and Neoplastic Hematological Disorders 2003-2008

Disease and Status at Transplantation+	Survival Assessed at	Survival (95%CI), N		
		HPC-M	HPC-A	HPC-C
		(n=194)	(n=216)	(n=31)
CML not in chronic phase	1 year	* (n=11)	* (n=47)	* (n=6)
Other MPD	1 year	* (n=16)	49.4% (34.8 - 64.0%) (n=46)	* (n=5)
MDS Refractory Anemia	1 year	64.3% (52.8 - 75.8%) (n=68)	65.3% (57.6 - 73.1%) (n=146)	66.5% (49.6 - 83.5%) (n=31)
MDS Refractory Cytopenia Multilineage Dysplasia	1 year	* (n=8)	* (n=29)	* (n=2)
MDS Refractory Anemia with Excess Blasts	1 year	* (n=16)	48.1% (33.8 - 62.3%) (n=50)	* (n=10)
Chronic Lymphocytic Leukemia	1 year	58.2% (48.1 - 68.4%) (n=91)	62.2% (57.6 - 66.7%) (n=450)	48.9% (34.6 - 63.2%) (n=52)
Hodgkin Disease CR	1 year	* (n=1)	* (n=14)	* (n=4)
Hodgkin Disease in relapse	1 year	* (n=9)	56.5% (42.2 - 70.8%) (n=46)	* (n=12)
Diffuse Large Cell Lymphoma	1 year	* (n=31)	51.7% (42.3 - 61.0%) (n=110)	* (n=15)
Ki-1+ Lymphoma	1 year	* (n=8)	* (n=22)	* (n=8)
Peripheral T Cell Lymphoma	1 year	* (n=12)	57.3% (44.6 - 70.0%) (n=60)	* (n=10)
Myeloma	1 year	* (n=5)	* (n=27)	* (n=1)
Familial erythrophagocytic lymphohistiocytosis	3 years	65.0% (51.2 - 78.9%) (n=52)	* (n=7)	73.8% (61.1 - 86.4%) (n=53)
Other Hemophagocytoses	1 year	* (n=4)	* (n=6)	* (n=13)

* Too few patients with follow-up for analysis
+AML, acute myelogenous leukemia; ALL, acute lymphocytic leukemia; CML. chronic myelogenous leukemia; CR, complete response; MPD, myeloproliferative disorder; MDS, myelodysplastic syndrome;

6.2.4 Analysis of Applicant's Dataset

Survival data were available for 2155 patients with hematological malignancies in the applicant's dataset. Five-year survivals for diseases with enough patients to evaluate are shown in Table 4. It should be noted that disease status at the time of transplantation was not available for all

patients, so the disease categories in Table 4 include subjects in any remission together with those in relapse.

Table 4: Patients with Hematological Malignancies – Applicant's Dataset

Diagnosis	N	5-year Survival (95% CI)
ALL	569	36% (32-41%)
AML	409	26% (21-32%)
CML	148	23% (16-34%)
MDS	85	30% (20-45%)

Reviewer Comment: The current standard of care based on disease-free survival or overall survival outcomes reserves HPC transplantation for patients with hematological malignancies failing conventional therapy or for those with a high risk of relapse with conventional therapy. Early mortality after HPC-C in the docket dataset was 26.6%, and the primary graft failure rate was 16.3% (95% CI, 13.8-18.9%), both of which were inversely correlated with TNC dose. Recent literature reports comparable outcomes using HPC-C and other types of HPC for patients with high risk acute leukemias, and where data are available, this is confirmed by the results from the SCTOD. Overall, the totality of the data available support a favorable risk benefit for HPC-C transplantation for the treatment of hematological malignancies.

6.3 Hurler Syndrome

6.3.1 Background

Hurler Syndrome (MPS IH) is a lysosomal storage disorder caused by a deficiency in α-L-iduronidase (IUDA). Diagnosis is by testing for enzyme expression and the genetic mutation. Over 100 mutations in the IDUA gene have been identified in patients with the Hurler Syndrome spectrum. The severe phenotype (IH) is identified by a combination of age at presentation, rate of progression of clinical features, and the individual's genotype. Genotype alone is not usually sufficient to identify the phenotype, as only a few specific mutations are clearly correlated with the IH or other phenotypes of the disease, while the remainder have a more heterogeneous expression of the clinical features. Hurler syndrome has an age-adjusted incidence of 1/100,000.

Patients generally appear normal at birth but manifest a progressive developmental delay and physical abnormalities thereafter, usually being diagnosed by age 2 (or younger if there is an affected proband). Enzyme replacement therapy with laronidase is available, but its efficacy with regard to CNS complications of the disease is minimal. Most patients with the IH phenotype die by age 10 due to the cardiopulmonary or neurologic complications of the disease.

6.3.2 Stem Cell Transplantation

The Docket Efficacy Review (Appendix 9.5) included the following:

- Survival was 70% at 2 yrs for the 71 patients transplanted for Hurler Syndrome for whom data were available using HPC-C, and the curve plateaued through 10 years.
- There was no clear correlation between TNC dose and survival, although it should be noted that all patients received a TNC dose $\geq 2.5 \times 10^7$/kg.
- One retrospective comparison of transplanted patients vs patients who were not transplanted reported a survival benefit with transplantation (HR 0.58, $p<0.001$).
- Data in the docket showed that there is an increase in α-L-iduronidase levels after transplantation, and this was supported by one publication.
- Eight additional publications were reviewed. In summary, these publications reported that transplantation was associated with reversal of organomegaly, arrest in the decline of cognitive function, improvement in growth rates, and at least partial amelioration of cardiac abnormalities. In one series, all children were attending school, with 81% in age-appropriate classes. Neurologic complications that were extensive could not be reversed, and ocular and orthopedic sequelae required further intervention.

The Docket Safety Review (Appendix 9.6) included the following:

- Day-100 mortality was 17.6% for patients transplanted for Hurler Syndrome, less than the proportion for all patients in the analysis. There was a trend for a reduction in early mortality using TNC doses $\geq 5 \times 10^7$/kg.
- The median time to neutrophil recovery was 21 days. The primary graft failure rate was 9.5% (95% CI, 3.9-18.5%) which is lower than the median for all patients in the analysis. There was a trend for a reduction in graft failure using TNC doses $\geq 5 \times 10^7$/kg.
- Acute GVHD grades 2-4 occurred in 47.9% and grades 3-4 in 15.5%, which are not substantially different from the rates for the entire population.

In its 2009 report,[1] the International Consensus Panel on the Management and Treatment of Mucopolysaccharidosis I recommended HPC transplantation for patients with Hurler Syndrome IH who are <2 years of age, have a developmental quotient ≥ 70, and are at risk for progression of disease as assessed by clinical findings, neurodevelopmental testing and genotype.

6.3.3 SCTOD

The SCTOD reports 105 patients transplanted for Hurler Syndrome 2003-2008 (Table 5). Almost 70% of these patients were transplanted using HPC-C from an unrelated donor. Survival for the HPC-C recipients is 70.2% at 3 years.

Table 5: SCTOD Data for Allogeneic Transplantations for Hurler Syndrome (MPS-IH) 2003-2008

Donor Type	Cell Source	Number	Survival (95%CI)		
			100 Days	1 Year	3 Years
HLA-matched sibling	Bone marrow	11	*	*	*
	Peripheral blood	1	*	*	*
	Cord blood	1	*	*	*
Other related	Bone marrow	1	*	*	*
Unrelated	Bone marrow	15	*	*	*
	Peripheral blood	3	*	*	*
	Cord blood	73	86.3% (78.4 - 94.2%)	75.0% (65.0 - 85.0%)	70.2% (59.4 - 81.0%)

* Too few patients for analysis

6.3.4 Analysis of Applicant's Dataset

The applicant's dataset for analysis includes 44 children with Hurler Syndrome of median age 1.4 yrs (range, 0.2-8.0 yrs). Neonates are not represented in the dataset. Median follow-up of survivors is 6 months, and the longest follow-up is 10 years. Overall survival plateaus at 2 years after transplantation at 58.5% (95% CI, 41.2-75.4%).

Reviewer Comment: The data available show that patients with Hurler syndrome undergoing HPC transplantation have a survival greater than that expected for those who are untreated or treated with enzyme replacement alone. Survival with HPC-C transplantation plateaus at 70% using the docket data and 58% using the applicant's dataset, both of which are considerably higher than for the reported natural history with or without enzyme replacement therapy. Transplantation has also been associated with neurocognitive and some physical improvements that are clinically meaningful. The biological plausibility of the therapy is supported by the increase in α-L-iduronidase levels after transplantation. Early mortality was reported for 17.6% of the patients, but there was a trend for a reduction in graft failure and early mortality by use of TNC doses $\geq 5 \times 10^7$/kg. Overall, the totality of the data available support a favorable risk benefit for HPC-C transplantation for the treatment of Hurler Syndrome IH without extensive neurologic abnormalities.

6.4 Krabbe Disease

6.4.1 Background

Krabbe Disease (globoid cell leukodystrophy) is a lysosomal storage disorder caused by a deficiency of galactocerebrosidase (GALC). Diagnosis is by testing for enzyme expression. Genetic testing is also available, and over 60 mutations in the GALC gene have been identified. Krabbe Disease has an age-adjusted incidence of approximately 1/140,000.

There are four types of Krabbe Disease categorized by age at presentation and clinical course. These include early infantile (presents by 6 months of age), late infantile (presents by 24 months of age), juvenile (presents in early to mid childhood), and adult. Approximately 70-90% of the

patients have the early infantile form. The early infantile form is rapidly fatal, with a median survival of 17 months, and nearly all patients have died by 5 years of age. Patients with the late infantile form have a median survival of 7 years, and approximately 30% survive long-term. There is no approved treatment for Krabbe Disease.

6.4.2 Stem Cell Transplantation

The Docket Efficacy Review (Appendix 9.5) included the following:

- Survival was 60% at 3 yrs and 44% at the plateau out to 10 years for the 38 patients undergoing HPC-C transplantation for Krabbe Disease for whom data were available. Those with a Lansky score >80 at transplantation had a survival ≥80% through 8 years.
- There was a trend for improved survival using TNC doses $\geq 16.5 \times 10^7$/kg.
- One retrospective comparison of transplanted patients vs patients who were not transplanted reported a survival benefit with transplantation for those who were asymptomatic vs those who were symptomatic (p=0.01) and vs. those who were not transplanted (p=0.001).
- Data in the docket showed that there is an increase in galactocerebrosidase levels after transplantation.
- Four additional publications were reviewed. In summary, these publications reported that outcomes were better for patients transplanted early in the course of their disease, and that even with transplantation some patients still had some expressive language delay, growth delay, and mild to severe impairment of gross motor function.

The Docket Safety Review (Appendix 9.6) included the following:

- Day-100 mortality was 9.8% after HPC-C transplantation for Krabbe Disease, less than the proportion for all patients in the analysis. There was no correlation between early mortality and TNC dose.
- The median time to neutrophil recovery was 22 days. The primary graft failure rate was 10.3% (2.9-24.2%), which is lower than the median for all patients in the analysis. There was no correlation between graft failure and TNC dose.
- Acute GVHD grades 2-4 occurred in 45.0% and grades 3-4 in 10.0% which are not substantially different from the rates for the entire population.

New York State employs a rating scale based on neurological exam, magnetic resonance imaging (MRI), cerebrospinal fluid protein, neurophysiological testing and genotyping to determine which patients are at high risk and should be considered for transplantation.[2]

6.4.3 SCTOD

The SCTOD reports 31 patients transplanted for Krabbe Disease 2003-2008 (Table 6). Over 90% of these patients were transplanted using HPC-C from an unrelated donor. Survival for the HPC-C recipients is 63.9% at 3 years.

Table 6: SCTOD Data for Allogeneic Transplantations for Krabbe Disease 2003-2008

			Survival (95%CI)

			100 Days	*1 Year*	3 Years
HLA-matched sibling	Bone marrow	1	*	*	*
Unrelated	Bone marrow	2	*	*	*
	Cord blood	28	78.6% ----- (63.4 - 93.8%)	71.4% ----- (54.7 - 88.2%)	63.9% ----- (46.0 - 81.8%)

* Too few patients for analysis

6.4.4 Analysis of Applicant's Dataset

The applicant's dataset for analysis includes 23 children with Krabbe Disease of median age 0.7 yrs (range, 0.08-16.7 yrs). Median follow-up of survivors is 1 year, and the longest follow-up is 9 years. Overall survival plateaus at 3 year after HPC-C transplantation at 62.5% (95% CI, 40.0-85.2%).

Reviewer Comment: Since the majority of the patients with Krabbe Disease have the infantile form, expected long-term survival is near 0% and not more than the 30% experienced by those with the less- fatal, late-onset form. Survival data available show that patients with Krabbe Disease undergoing HPC transplantation have a survival greater than that expected, and this was confirmed in a retrospective cohort comparison. Survival with HPC-C transplantation plateaus at 80% for asymptomatic patients in the docket dataset and 62% using the applicant's dataset. Transplanted patients, though alive, continue to experience some neurocognitive and motor abnormalities. The biological plausibility of the therapy is supported by the increase in galactocerebrosidase levels after transplantation. Early mortality after HPC-C transplantation was reported for 9.8% of the patients and graft failure in 10.3%. There was no correlation between TNC and graft failure or early mortality. Overall, the totality of the data available support a favorable risk benefit for HPC-C transplantation for the treatment of infantile onset Krabbe Disease.

6.5 X-linked adrenoleukodystrophy (ALD)

6.5.1 Background

ALD is a peroxisomal storage disorder caused by an abnormality in the ABCD1 protein, a member of the ATP-binding cassette family. Diagnosis is by testing for protein expression. Genetic testing is also available, and numerous mutations in the ABCD1 gene have been identified. There is no correlation between genotype and phenotype. ALD has an age-adjusted incidence of approximately 1/42,000.

There are several phenotypes characterized by age at onset, organs involved, and the time course of neurologic deterioration. Prognosis varies by phenotype. Time to onset is highly variable. Median age at diagnosis for the childhood form is 7 years. The major clinical manifestations include adrenal insufficiency and an inflammatory demyelinating encephalopathy. Reported 5-year survival from onset of cerebral disease has ranged from 30 to 66%, although survival curves

for all cerebral forms have an unrelenting downward trend in all reports. There is no FDA-approved replacement therapy available.

6.5.2 Stem Cell Transplantation

The Docket Efficacy Review (Appendix 9.5) included the following:

- Survival plateaued at 75% by 2 years through 10 years after transplantation for the 21 patients transplanted for ALD for whom data were available. For the 18 patients transplanted at less than 14 years of age, long-term survival plateaued at >80%.
- There was no correlation between survival and TNC dose.
- One retrospective cohort comparison reported a significant survival benefit for patients undergoing HPC transplantation for early stage cerebral ALD vs no transplantation (p=0.006).
- Three additional publications were reviewed. In summary, these publications reported that posttransplant cognitive and motor development tracked normally if the patient had a pretransplant MRI Loes score ≤10.

The Docket Safety Review (Appendix 9.6) included the following:

- Day-100 mortality was 4.0% after HPC-C transplantation for ALD, less than the proportion for all patients in the analysis. There was no correlation between early mortality and TNC dose.
- The median time to neutrophil recovery was 22 days. The primary graft failure rate was 10.5% (1.3-33.1%) which is lower than the median for all patients in the analysis. There was a trend for correlation between graft failure and TNC dose.
- Acute GVHD grades 2-4 occurred in 47.8% and grades 3-4 in 26.1%, which are not substantially different from the rates for the entire population.

The mechanism of action of HPC-C transplantation is supported by the finding of ABCD1 expression in autopsy specimens from the central nervous system of patients with ALD who died after transplantation.[3]

In an international collaborative report, HPC transplantation was recommended for boys with ALD who have early but definitive evidence of cerebral disease.[4]

6.5.3 SCTOD

The SCTOD reports 71 patients transplanted for ALD 2003-2008 (Table 7). Over 50% of these patients were transplanted using HPC-C from an unrelated donor, but long-term survival from transplantation is not reported for the cohort.

TTTable 7: SCTOD Data for Allogeneic Transplantations for Adrenoleukodystrophy 2003-2008

			Survival (95%CI)		
Donor Type	***Cell Source***	***Number***	***100 Days***	***1 Year***	3 Years

TTTable 7: SCTOD Data for Allogeneic Transplantations for Adrenoleukodystrophy 2003-2008

Donor Type	*Cell Source*	*Number*	Survival (95%CI)		
			100 Days	***1 Year***	3 Years
HLA-matched sibling	Bone marrow	13	*	*	*
	Peripheral blood	1	*	*	*
	Cord blood	1	*	*	*
Other related	Bone marrow	3	*	*	*
	Peripheral blood	1	*	*	*
Unrelated	Bone marrow	11	*	*	*
	Peripheral blood	5	*	*	*
	Cord blood	36	91.7% ----- (82.6 - 100.0%)	73.9% ----- (59.2 - 88.6%)	*

* Too few patients for analysis

6.5.4 Analysis of Applicant's Dataset

The applicant's dataset for analysis includes 32 children with ALD of median age 8.5 yrs (range, 1.7-26.3 yrs). Median follow-up of survivors is 1 year, and the longest follow-up is 12 years. Overall survival plateaus at 3 years after transplantation at 54.4% (95% CI, 32.8-76.0%).

Reviewer Comment: Although the reported survival of patients with cerebral ALD without transplantation has varied over time, there is no plateau. By contrast, the survival after HPC transplantation plateaus at 54-75% in the datasets analyzed, and at more than 80% for patients transplanted at less than 14 years of age. Moreover, a retrospective cohort comparison showed a significant survival benefit for patients with early stage cerebral ALD who undergo HPC transplantation (p=0.006). Transplanted patients who survive are reported to track normally in cognitive and motor development. The biological plausibility of the therapy is supported by the detection of ABCD1 expression in neurological tissue from autopsy specimens of transplanted patients. Early mortality and graft failure after HPC-C were relatively low, 4.0% and 10.5%, respectively. There was no correlation between TNC and graft failure or early mortality. Overall, the totality of the data available support a favorable risk benefit for HPC-C transplantation for the treatment of childhood ALD with early cerebral involvement.

6.6 Primary Immunodeficiency Disease

6.6.1 Background

The primary immunodeficiencies are comprised of more than 100 genetically defined inheritable disorders of lymphocytes, phagocytes and other cells of the immune system. The age-adjusted incidence varies by the specific disorder from 1/1,000,000 for Wiskott-Aldrich syndrome (WAS) and some phagocyte disorders to 1/50,000 for all types of severe combined immunodeficiency disorder (SCID) combined.

Patients with SCID are generally diagnosed by 3-8 months of age (or earlier with newborn screening or if there is an affected proband). Treatment is supportive, and patients generally do not survive early childhood. The exception is SCID due to adenosine deaminase deficiency for which pegademase is an approved therapy. Patients with WAS can generally be treated with supportive care, but prognosis and morbidity vary with the levels of WAS protein expression; those with very low levels of WAS protein have severe disease manifestations. The remaining immunodeficiency disorders have varied natural histories, but most are treated initially with supportive measure, using antibiotics, cytokines and/or immunoglobulin replacement.

6.6.2 Stem Cell Transplantation

The Docket Efficacy Review (Appendix 9.5) included the following:

- Survival plateaued at 65% by 2 years through 5 years after HPC-C transplantation for the 47 patients with SCID for whom data were available.
- There was no correlation between survival and TNC dose, although no patients received <2.5 x 10^7 TNC/kg.
- One retrospective cohort comparison reported a substantial improvement in survival by HPC transplantation using haploidentical or matched related donors.

The Docket Safety Review (Appendix 9.6) included the following:

- Day-100 mortality was 17.7% after HPC-C for primary immunodeficiency disorders, less than the proportion for all patients in the analysis. There was no correlation between early mortality and TNC dose.
- The median time to neutrophil recovery was 19 days. The primary graft failure rate was 12.8% (6.6-21.7%) which is lower than the median for all patients in the analysis. There was trend for a correlation between graft failure and TNC dose.
- Acute GVHD grades 2-4 occurred in 30.1% and grades 3-4 in 12.9%, which are somewhat lower than the rates for the entire population.

Follow-up of patients transplanted for SCID shows restoration of immune function in surviving patients.[5] Allogeneic HPC transplantation also corrects both the platelet and lymphoid abnormalities in patients with WAS if full chimerism can be achieved, but late autoimmune disorders may still occur.[6] Case reports and series substantiate the correct of the immunodeficiencies in SCID, WAS and other rare immunodeficiencies following unrelated donor HPC-C transplantation.[7,8,9] In these series, long-term survivors had complete immune reconstitution by 2 years after transplantation, did not require immunoglobulin replacement therapy, and were responding to vaccinations against infectious agents.

6.6.3 SCTOD

The SCTOD reports 100 patients with SCID, 90 patients with WAS and 67 patients with other immunodeficiency disorders transplanted 2003-2008 (Tables 8-10). Within these diagnoses, 24-40% of the patients were transplanted using HPC-C from an unrelated donor.

Table 8: SCTOD Data for Allogeneic Transplantations for SCID 2003-2008

Donor Type	Cell Source	Number	Survival (95%CI)		
			100 Days	1 Year	3 Years
HLA-matched sibling	Bone marrow	17	*	*	*
	Peripheral blood	1	*	*	*
Other related	Bone marrow	4	*	*	*
	Peripheral blood	29	93.1% TT(83.9 - 100.0%)	71.1% (54.1 - 88.1%)	*
Unrelated	Bone marrow	16	100.0% (100.0 - 100.0%)	*	*
	Peripheral blood	3	*	*	*
	Cord blood	30	73.3% (57.5 - 89.2%	69.8% (53.4 - 86.3%)	*

* Too few patients for analysis

Table 9: SCTOD Data for Allogeneic Transplantations for Wiskott Aldrich Syndrome 2003-2008

Donor Type	Cell Source	Number	Survival (95%CI)		
			100 Days	1 Year	3 Years
HLA-matched sibling	Bone marrow	11	*	*	*
	Peripheral blood	1	*	*	*
	Cord blood	2	*	*	*
Other related	Bone marrow	2	*	*	*
	Peripheral blood	2	*	*	*
Unrelated	Bone marrow	32	93.8% (85.4 - 100.0%)	90.6% (80.5 - 100.0%)	86.5% (74.0 - 99.0%)
	Peripheral blood	4	*	*	*
	Cord blood	36	97.2% (91.9 - 100.0%)	94.4% (86.8 - 100.0%)	*

* Too few patients for analysis

Table 10: SCTOD Data for Allogeneic Transplantations for Other CID 2003-2008

Donor Type	Cell Source	Number	Survival (95%CI)		
			100 Days	1 Year	3 Years
HLA-matched sibling	Bone marrow	9	*	*	*
	Peripheral blood	3	*	*	*
	Cord blood	2	*	*	*
Other related	Bone marrow	2	*	*	*
Unrelated	Bone marrow	30	83.3%	80.0%	*

Table 10: SCTOD Data for Allogeneic Transplantations for Other CID 2003-2008

Donor Type	Cell Source	Number	Survival (95%CI)		
			100 Days	1 Year	3 Years
			(70.0 - 96.7%)	(65.7 - 94.3%)	
	Peripheral blood	5	*	*	*
	Cord blood	16	100.0% (100.0 - 100.0%)	*	*

* Too few patients for analysis

6.6.4 Analysis of Applicant's Dataset

The applicant's dataset for analysis includes 184 children with primary immunodeficiency disorders. The patients were categorized as SCID, WAS or other immunodeficiency disorders. Ages, follow-up times and survivals are shown in Table 11. In all subgroups, the survival shown represents the plateau.

Table 11: Patients with Primary Immunodeficiency Disorders – Applicant's Dataset

	SCID	WAS	Other
Number	90	46	48
Median Age (range)	0.9 yrs (0.07-17.0 yrs)	1.5 yrs (0.2-10.5 yrs)	1.6 yrs (0.2-20.8 yrs)
Median Follow-Up	6 mos	11 mos	5 mos
Longest Follow-Up	10 yrs	9 yrs	9 yrs
Survival (95% CI)	59.8% (48.3-71.25%)	67.7% (53.1-82.3%)	55.8% (40.5-71.1%)

Reviewer Comment: The data support a clear survival benefit for patients with SCID. The calculated survival rates in the two dataset were 65% and 60% for these patients. Moreover, the SCTOD reveal similar survival using unrelated donor HPC-C or haploidentical HPC-A for transplantation for SCID. The SCTOD data also show similar survivals for patients with WAS and other immunodeficiencies using unrelated donor HPC-M vs HPC-C, but the true clinical benefit for these patients requires correction of the immunodeficiency, which is born out by the literature. Overall, the totality of the data available support a favorable risk benefit for HPC-C transplantation for the treatment of SCID and for treatment of patients with other immunodeficiency disorders who are failing conventional supportive therapies.

6.7 Bone Marrow Failure

6.7.1 Background

The bone marrow failure syndromes include numerous inheritable and acquired disorders of marrow production. The estimated age-adjusted incidence is approximately 1/350,000. The natural history and age at diagnosis varies by disease.

Severe aplastic anemia (SAA) is defined by laboratory parameters reflecting marrow cellularity and peripheral blood counts. Potential etiologies include direct damage by petrochemicals or radiation, congenital disorders of the marrow, or immunologic causes. Patients with less severe cytopenias are generally observed. Once blood counts reach the severe level, treatment with immunosuppressive drugs (IST), such as antithymocyte globulin, is administered. Patients who remain transfusion-dependent despite IST are at risk of life-threatening and fatal bleeding or infection.

Fanconi Anemia (FA) is a genetically and phenotypically heterogeneous group of disorders arising from mutations in several genes involved in DNA repair and cell cycling. Diagnosis is by clinical examination, genotyping and testing for chromosomal fragility. Clinical manifestations include congenital malformations and progressive marrow failure with a predisposition to malignancies. Progression of the clinical manifestations is highly variable; most patients are observed or treated with supportive care until they are transfusion-dependent or develop malignant transformation.

6.7.2 The Docket Efficacy Review (Appendix 9.5) included the following:

Severe Aplastic Anemia

- Survival plateaued at 29% by 2 years through 7 years after transplantation for the 37 patients with SAA for whom data were available.
- There was a correlation between survival and TNC dose.
- Two comparative studies showed a survival advantage for HPC transplantation over supportive care.
- Eight additional publications were reviewed in detail. The reported survivals after HPC-C transplantation for patients with SAA who failed IST ranged from 38% to 83%. The major additional information in these publications is that survival is significantly improved with use of a TNC dose $\geq 3.9 \times 10^7$/kg (p=0.007).

Fanconi Anemia

- Survival plateaued at 28% by 2 years through 7 years after transplantation for the 39 FA patients for whom data were available.
- There was a correlation between survival and TNC dose $\geq 2.5 \times 10^7$/kg and a trend for improved survival with TNC doses $>4.5 \times 10^7$/kg.
- No comparative studies were identified.
- Four additional publications were reviewed in detail. The major additional information in these publications is that factors which significantly correlate with survival are CMV serostatus, use of fludarabine in the preparative regimen, and use of a TNC dose $\geq 4.9 \times 10^7$/kg.

The Docket Safety Review (Appendix 9.6) included the following:

- Day-100 mortality was 46.5% after HPC-C transplantation for marrow failure. There was a trend for a correlation between early mortality and TNC dose.
- The median time to neutrophil recovery was 30 days. The primary graft failure rate was 31.1% (95% CI, 21.8-41.7%). There was a significant correlation between graft failure and TNC dose (p=0.001) with a striking reduction in the rate of graft failure at TNC doses $\geq$5 x 10^7/kg.
- Acute GVHD grades 2-4 occurred in 51.3% and grades 3-4 in 25.6%, which somewhat higher than the rates for the entire population.

Patients who survive HPC-C transplantation have correction of the marrow deficiencies and become transfusion-independent.[10,11] Patients with FA who are transplanted successfully still have nonhematological clinical manifestations, including malignancies, which require additional intervention.[12]

6.7.3 SCTOD

The SCTOD reports 935 patients with SAA and 174 patients with Fanconi Anemia transplanted 2003-2008 (Tables 12-13). HPC-C from an unrelated donor was used for 7% of the patients with SAA and 22% of those with Fanconi Anemia.

Table 12: SCTOD Data for Transplantations for Severe Aplastic Anemia 2003-2008

Donor Type	Cell Source	Number	Survival (95%CI)		
			100 Days	1 Year	3 Years
HLA-matched sibling	Bone marrow	325	96.3% (94.3 - 98.4%)	93.0% (90.2 - 95.8%)	91.0% (87.6 - 94.4%)
	Peripheral blood	102	87.3% (80.8 - 93.7%)	73.6% (64.9 - 82.4%)	63.5% (52.7 - 74.3%)
	Cord blood	4	*	*	*
Other related	Bone marrow	23	86.4% (72.0 - 100.0%)	81.6% (65.2 - 97.9%)	*
	Peripheral blood	23	73.9% (56.0 - 91.9%)	*	*
	Cord blood	1	*	*	*
Unrelated	Bone marrow	278	88.5% (84.7 - 92.2%)	77.1% (72.2 - 82.1%)	69.1% (63.2 - 75.0%)
	Peripheral blood	110	84.5% (77.8 - 91.3%)	73.3% (64.9 - 81.6%)	60.9% (51.1 - 70.8%)
	Cord blood	69	70.6% (59.8 - 81.5%)	45.9% (33.8 - 57.9%)	*

* Too few patients for analysis

Table 13: SCTOD Data for Transplantations for Fanconi Anemia 2003-2008

Donor Type	Cell Source	Number	Survival (95%CI)		
			100 Days	1 Year	3 Years
HLA-matched sibling	Bone marrow	25	100.0% (100.0 - 100.0%)	95.8% (87.8 - 100.0%)	95.8% (87.8 - 100.0%)
	Peripheral blood	2	*	*	*
	Cord blood	7	*	*	*
Other related	Bone marrow	6	*	*	*
	Peripheral blood	3	*	*	*
	Cord blood	1	*	*	*
Unrelated	Bone marrow	51	86.3% (76.8 - 95.7%)	72.5% (60.3 - 84.8%)	*
	Peripheral blood	41	87.8% (77.8 - 97.8%)	70.7% (56.8 - 84.7%)	*
	Cord blood	38	68.4% (53.6 - 83.2%)	62.9% (47.5 - 78.4%)	*

* Too few patients for analysis

6.7.4 Analysis of Applicant's Dataset

The applicant's dataset for analysis includes 255 patients with marrow failure disorders. The patients were categorized as SAA, FA or other bone marrow failures. Ages, follow-up times and survivals are shown in Table 14. In all subgroups, the survival shown represents the plateau.

Table 14: Patients with Marrow Failure – Applicant's Dataset

	SAA	FA	Other
Number	76	84	95
Median Age (range)	9.5 yrs (0.3-62.5 yrs)	8.0 yrs (1.0-45.4 yrs)	1.8 yrs (0.2- 24.0 yrs)
Median Follow-Up	4 mos	2 mos	5 mos
Longest Follow-Up	8 yrs	12 yrs	12 yrs
3-yr Survival (95% CI)	32.3% (15.2-49.4%)	22.4% (10.8-34.1%)	37.5% (23.9-51.1%)

Reviewer Comment: Patients with marrow failure and transfusion dependence due to severely low blood counts are at risk for life-threatening sequelae. The SCTOD data support the use of allogeneic HPC transplantation for treatment of marrow failure, although this modality is clearly reserved for those with transfusion dependence who have failed conventional therapies rather than for those with mild cytopenias.

The early survivals for patients with SAA transplanted using HPC-C are clearly inferior to those for transplantation of unrelated donor HPC-M or HPC-A, but in the absence of a suitably-matched adult donor, the survival using HPC-C is acceptable for patients who are otherwise suffering from the morbidities of the severe cytopenias. The early survivals reported for the patients transplanted for Fanconi Anemia are also inferior using HPC-C, although less so than for patients with SAA. The results of HPC-C transplantation for SAA or Fanconi Anemia reported by the SCTOD are also somewhat better than those in the docket (28-29%) or in the applicant's dataset (22-32%); this may be due to the shorter follow-up or to the use of more modern transplant supportive care in the more recent SCTOD cohort.

The safety review also highlights a high early mortality and a high graft failure rate for these patients, which may in part be due to alloimmunization from multiple transfusions. However both the literature and the safety review suggest that the outcomes can be improved by use of higher TNC doses. Additional benefit is derived from the correction of the marrow failure and cessation of transfusion independence. Overall, the totality of the data available support a favorable risk benefit for HPC-C transplantation for the treatment of patients with marrow failure with severe cytopenias and transfusion dependence who have failed conventional therapies, and the TNC dose used should be in the higher range to maximize beneficial outcomes.

6.8 Beta Thalassemia Major

6.8.1 Background

Beta thalassemia is characterized by decreased expression of beta globin, leading to anemia, bone disease and a prothrombotic state. The level of expression of beta globin varies with the specific mutation in the gene, and the clinical course varies with the level of beta globin expression. Beta thalassemia has an age-adjusted incidence in the US of approximately 1/100,000. The current standard of care for thalassemia major is transfusion therapy combined with chelation therapy to prevent the complications of iron overload. This treatment is supportive only, but it has led to long-term survival in those who are compliant.

6.8.2 Stem Cell Transplantation

The Docket Efficacy Review (Appendix 9.5) included the following:

- The actuarial 1-year survival was 34% for the 8 patients transplanted for beta thalassemia major for whom data were available.
- There were too few patients to evaluate the correlation between survival and TNC dose.
- There was one comparative study that reported 5-yr disease-free survival of 83% with HPC-C transplantation vs 87% with HPC-M transplantation.
- Eleven additional publications were reviewed in detail. In summary, these publications reported that there is a high rate of graft rejection in these multiply transfused patients, that surviving patients can achieve transfusion-independence and resolution of the anemia (thalassemia-free survivals 60-83% with high TNC dose), and that outcomes are better for patients transplanted while in Pesaro class I or with a high TNC dose.

The Docket Safety Review (Appendix 9.6) included the following:

- Day-100 mortality was 25.0% after HPC-C transplantation for beta thalassemia major. There was no correlation between early mortality and TNC dose.
- The median time to neutrophil recovery was 31 days. The primary graft failure rate was 28.6% (3.7-71.0%), which is higher than the median for all patients in the analysis. There was no correlation between graft failure and TNC dose, although the small number of patients may have limited the sensitivity of the analysis.
- Acute GVHD grades 2-4 occurred in 33.3% and grades 3-4 in 0.0%, which are somewhat better than the rates for the entire population.

6.8.3 SCTOD

The SCTOD reports 110 patients transplanted for thalassemia not otherwise specified 2003-2008 (Table 15). Approximately 15% of these patients were transplanted using HPC-C from an unrelated donor. Long-term survival from transplantation is not reported for the cohort.

Table 15: SCTOD Data for Allogeneic Transplantations for Thalassemia 2003-2008

			Survival (95%CI)		
Donor Type	***Cell Source***	***Number***	***100 Days***	***1 Year***	3 Years
HLA-matched sibling	Bone marrow	30	96.7% (90.2 - 100.0%)	89.2% (77.7 - 100.0%)	*
	Peripheral blood	3	*	*	*
	Cord blood	13	*	*	*
Other related	Bone marrow	1	*	*	*
	Cord blood	1	*	*	*
Unrelated	Bone marrow	10	*	*	*
	Peripheral blood	4	*	*	*
	Cord blood	17	*	*	
Unrelated (any stem cells)	0-10 yrs old	28	85.7% (72.8 - 98.7%)	82.0% (67.7 - 96.3%)	*
	11-20 yrs old	3	*	*	*

* Too few patients for analysis

6.8.4 Analysis of Applicant's Dataset

The applicant's dataset for analysis includes 21 children with beta thalassemia of median age 5.0 yrs (range, 0.2-15.1 yrs). The median TNC dose was 8.1 (range 3.6-31.8) x 10^7/kg. Median follow-up of survivors is 7 mos, and the longest follow-up is 11 years. Overall survival plateaus at 2 year after transplantation at 53.3% (95% CI, 30.1-76.6%). For the 15 patients who received a TNC dose $\geq$5 x 10^7/kg, survival plateaued at 60% (95% CI, 35.2-84.8).

Reviewer Comment: Given the proven efficacy of transfusion and chelation therapy for thalassemia major, it is a very small minority of patients who fail such therapy and undergo HPC transplantation. Reports from the early literature support HPC transplantation from related donors for beta thalassemia, but there was a high rate of graft failure with unrelated donor HPC-C transplantation. The high graft failure rate and limited survival are reflected in the analyses of the docket data from that era. Analyses of more recent data suggested that higher TNC doses might overcome the risk of graft failure. Indeed, survival plateaus at 60% for the patients in the applicant's dataset who received a TNC dose $\geq$5 x 10^7/kg. The published literature also shows that survivors can achieve complete amelioration of their disease with resolution of anemia and transfusion-independence. Thus, although there are no comparative studies with supportive care as the control, the thalassemia-free survivals reported would still be substantially better than no transplantation (0%) for those without other treatment options. Overall, the totality of the data available support a favorable risk benefit for HPC-C transplantation for the treatment of beta thalassemia major failing conventional therapy and when using a TNC dose $\geq$5 x 10^7/kg.

6.9 Efficacy Across Diagnoses

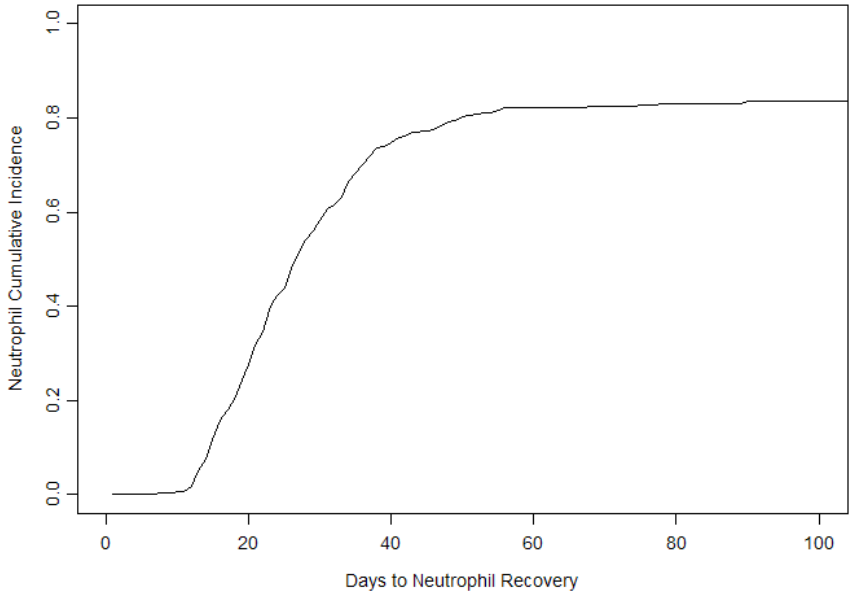
6.9.1 The COBLT Study

The COBLT Study is reviewed in detail in the Safety Review – Dockets and Public Information (Appendix 9.6). The COBLT Study is the only available prospective trial of unrelated donor

HPC-C transplantation with data for analysis. Efficacy data were available for 324 subjects enrolled in the main protocol who received a total nucleated cell dose ≥ 2.5 x 10^7/kg. The population was 59% male and 41% female of median age 4.6 years (range 0.07–52.2 years).

The median time to neutrophil recovery to greater than 500/uL was 27 days (Figure 1), and the cumulative incidence by day 42 was 76.1% (95% CI 70.7 - 80.5%). The median time to platelet recovery to greater than 20,000/uL was 90 days, and the cumulative incidence by day 100 was 57.2% (50.8-62.7%). The median time to platelet recovery to greater than 50,000/uL was 113 days and the cumulative incidence by day 100 was 45.5% (39.2-51.1%). The median time to erythrocyte recovery to a reticulocyte count greater than 30,000/uL was 64 days, and the cumulative incidence by day 100 was 65% (58-71%).

TTFigure 1: Neutrophil Recovery After HPC-C Transplantation in The COBLT Study.



The results of evaluation of immune reconstitution in 153 subjects from The COBLT Study was published by Cohen et al.[13] The authors reported that absolute number of lymphocytes expressing CD3, CD4, CD8 or CD19 remained low until 6-12 months after transplantation and rose thereafter through more than 2 years of sampling. Proliferative responses to a Herpes virus were demonstrated for 66 of 153 evaluable patients. These responses were thought to result from infection after transplantation. Such responses were considered effective in that infection-related mortality was significantly lower in subjects with a measurable response than in those who showed no response (2% vs 13%, p=0.02).

6.9.2 Docket Reviews and Supporting Literature (Appendix 9.6)

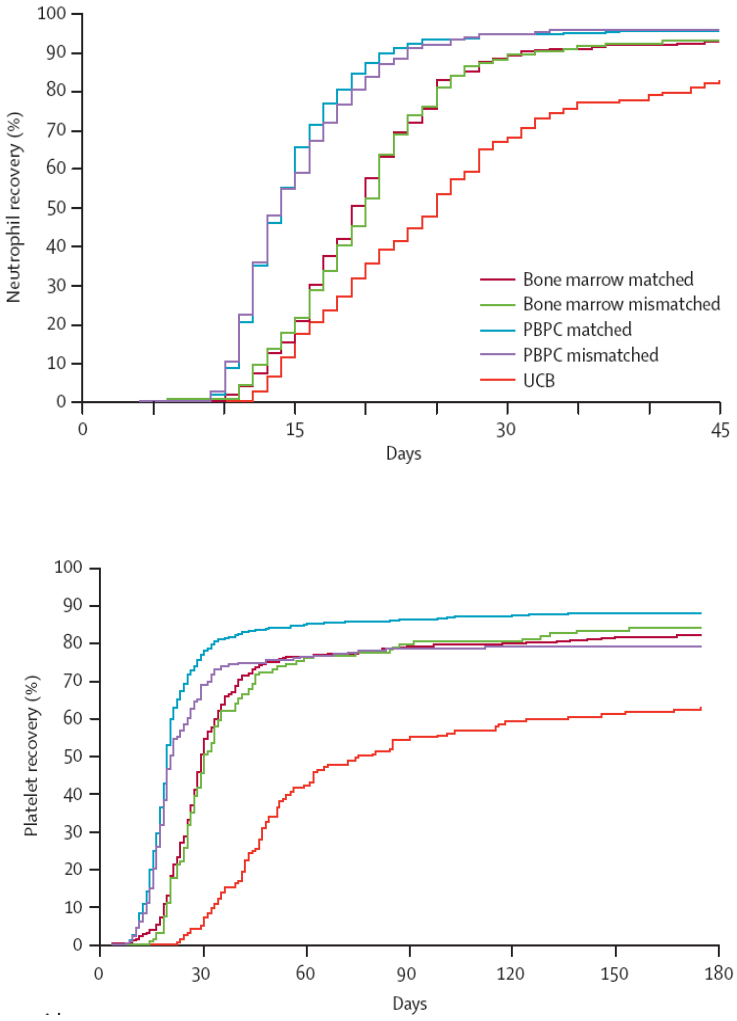
6.9.2.1 Hematopoietic Recovery

In the pooled docket dataset (described in Appendix 9.6), the time to neutrophil recovery was significantly faster with a TNC dose ≥2.5 x 10^7/kg than with a lower dose (p<0.001). For

subjects receiving a TNC dose ≥2.5 x 10^7/kg, the cumulative incidence of neutrophil recovery by day 42 was 77% (75-79%), and the median time to neutrophil recovery was 25 days. The median time to neutrophil recovery varied by diagnosis and ranged from 19 days to 31 days. This variation was due in part to differences in the TNC doses administered within each subgroup.

For all subjects in the pooled docket dataset, the degree of HLA mismatch and TNC dose were significantly associated with the time to neutrophil recovery on multivariate analysis. The time to neutrophil recovery was clearly delayed with TNC doses <2 x 10^7/kg, but even with TNC doses as high as 20 x 10^7/kg, the time to neutrophil recovery still exceeded 30 days for 10% of the subjects, a much higher rate of delayed recovery than with unrelated donor HPC-M or HPC-A (Figure 2).[14,15]

Figure 2: Neutrophil and Platelet Recovery After Unrelated Donor HPC Transplantation
Adapted from Reference 14.



There are no in vitro data to suggest that the leukocyte, erythrocyte and platelet progeny of the engrafted HPC-C function differently from those after HPC-M or HPC-A transplantation. Successfully engrafted patients are not reported to have impaired oxygenation in the absence of pulmonary disease, nor have there been reports of bleeding disorders once the platelet count has recovered. In a comparison of outcomes after unrelated donor HPC-C vs unrelated donor HPC-M or HPC-A, Hamza et al[16] reported a higher rate of bacterial infections using HPC-C in the first 50 days after transplantation, but this was thought to result from the longer time to neutrophil recovery rather than neutrophil dysfunction in these patients; after day 50, there were no differences in the rates of bacterial, fungal or viral infections.

6.9.2.2 Immune Reconstitution

Jacobson et al[17] compared immune reconstitution in adults after unrelated donor HPC-C (n=42) or HPC-A (n=102) transplantation for hematological malignancies. HPC-C recipients received multiple units to achieve a median TNC dose of 4.2 x 10^7/kg. The median absolute numbers of lymphoid subsets and median IgG levels are shown in Figure 3 below. For the HPC-C recipients, recoveries of CD3+, naive and memory cells were delayed and recoveries of CD19+ and CD56/16+ cells were accelerated in comparison to those for HPC-A recipients, but all were in the normal range by 24 months after transplantation. Only the T-NK subset recovery still lagged after HPC-C transplantation at that time. Serum IgG levels did not differ significantly between the two groups. Additional examples of successful immune reconstitution are provided in Section 6.6.2 above for patients transplanted for primary immunodeficiency disorders.

The initial delay in recovery of T cells after HPC-C transplantation for hematological disorders has been confirmed by others for both adult and pediatric patients.[18,19,20] The initial T cells recovered are predominantly effector memory donor T cells with limited expansion as revealed by their oligoclonality. Late-appearing T cells are derived from precursors in the HPC-C as evidenced by TREC formation that is classic for naive T cells. This population is clonally diverse and provides for long-term durable immune reconstitution after HPC-C transplantation.

Reconstitution of the immune system after HPC transplantation appears to be limited to cells of hematopoietic origin. There are no reports, for example, of donor-derived thymic epithelium or donor-derived reticular cells in the lymph nodes.

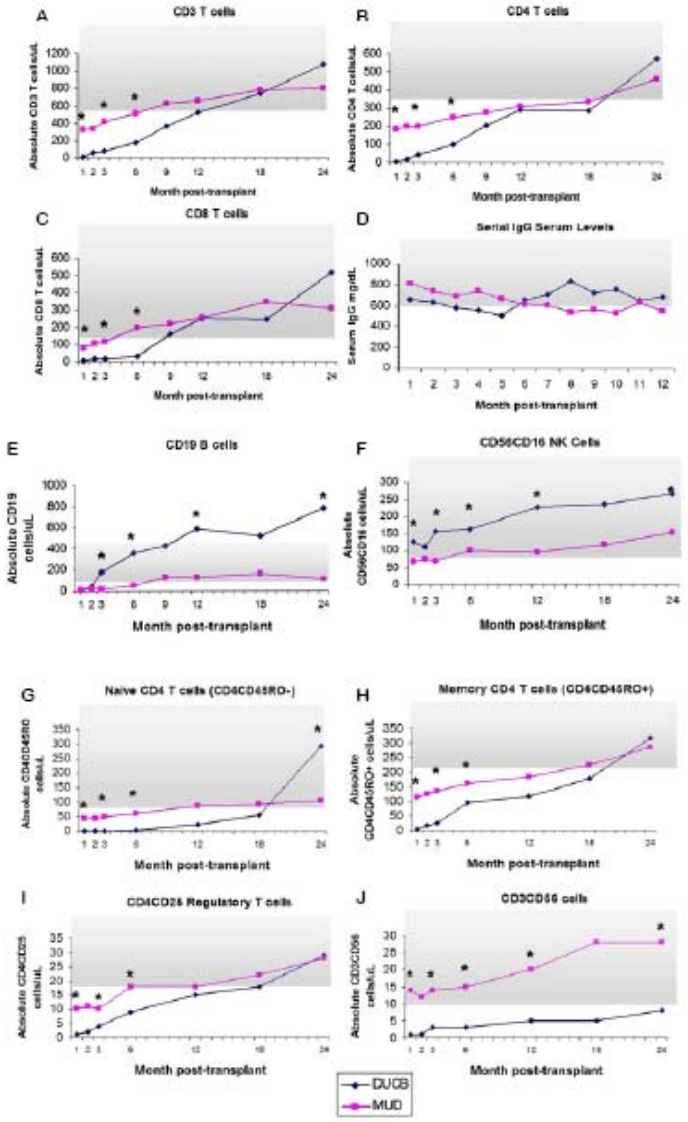


Figure 3: Comparison of Immune Reconstitution after Unrelated Donor HPC-C vs HPC-A Transplantation.

Median absolute numbers per microliter of CD3 (A), CD4 (B), CD8 (C), CD19 (E), CD56/16 (F), naive CD4 (G), memory CD4 (H), regulatory T (I) and T-NK (J) cells, and serum IgG level (D) after double HPC-C (blue line) or HPC-A (pink line) transplantation. The range of normal is represented by the gray shaded area. *p<0.05. Adapted from reference 17.

6.9.2.3 Other Cellular Functions

Expression of missing enzymes is the major assessment used for cellular function after HPC-C transplantation. Docket submission FDA-2006-D-0157-DRAFT-0054 included enzyme data for 81 evaluable subjects transplanted for inheritable metabolic disorders. The data showed

increases in enzyme levels for 4/5 subjects transplanted for Hunter Syndrome, 32/34 subjects with Hurler Syndrome, 31/32 subjects with Krabbe Disease, 2/2 subjects with Sandhoff Disease, and 7/8 subjects with Tay Sach Disease. Although the data are consistent with published reports of enzyme reconstitution after HPC-C transplantation for these diseases,[21,22,23] interpretation of the data in the docket is limited by the lack of information regarding what assay was performed, what tissue was assayed, when after transplantation the tissue was sampled, and whether there was a corresponding clinical effect.

Church et al[22] observed a correlation between donor-derived enzyme levels and function in patients transplanted for Hurler Syndrome. In their series of 39 patients, leukocyte α-L-iduronidase levels rose within 6 months after transplantation. The levels achieved varied with the degree of chimerism and whether the donor was homozygous normal or heterozygous. Urinary glycosaminoglycans (GAGs), a surrogate for the total body burden, was inversely correlated with the α-L-iduronidase levels at 12 and 24 months after transplantation.

Of concern is the observation that patients with Hurler syndrome treated with laronidase develop antibodies to the enzyme, although the clinical consequences are not clear. Such antibodies have not been reported in HPC-C transplant recipients successfully engrafted with α-L-iduronidase-expressing normal hematopoietic cells.[24]

Coccia et al[25] also reported significant bone remodeling by donor-derived osteoclasts in patients transplanted for infantile malignant osteopetrosis. The beneficial effect of the osteoclast function, however, is frequently accompanied by complications of severe hypercalcemia resulting from the sudden bone resorption.[26]

6.9.3 Analysis of Applicant's Dataset

FDA performed an analysis of hematopoietic recovery on the entire safety population in the applicant's dataset (described in Appendix 9.6) and on the subset of subjects who received a unit manufactured with Method #4 and having a TNC dose $\geq 2.5 \times 10^7$/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 16.

Table 16: Hematopoietic Recovery – Applicant's Dataset

	All Subjects Transplanted		**Subjects with a Suitable Allograft***	
	N		N	
Cumulative Incidence of ANC>500 by Day 42 (95% CI)	2460	74% (72-76%)	155	83% (76-88%)
Cumulative Incidence of Platelets >20,000 by Day 100 (95% CI)	1855	62% (60-64%)	124	77% (69-84%)
Median time to ANC>500 (range)	2458	25 days	155	20 days
Median time to PLT >20,000 (range)	1855	65 days	124	45 days

* Those who received a unit manufactured with Method #4 and having a TNC dose $>2.5 \times 10^7$/kg

For the subset of patients who received a suitable allograft, the cumulative incidence of neutrophil recovery is 83% at day 42, and the cumulative incidence of platelet recovery is 77% at

day 100. After transplantation with Hemacord, no patient was reported to have experienced rejection once neutrophil recovery occurred, although long-term follow-up in this subset may be incomplete.

Reviewer Comment: The ability of HPC-C to reconstitute hematopoiesis after transplantation is demonstrated in The COBLT Study of 324 subjects transplanted with a TNC dose ≥2.5 x 10^7/kg for various disorders affecting the hematopoietic system. In this study, recovery of all three major lineages were reported. The cumulative incidence of neutrophil recovery by day 42 was 76%, similar to that seen in the pooled docket dataset (77%) and in the applicant's dataset for Hemacord (83%). The time to neutrophil and platelet recovery after HPC-C transplantation is longer than after HPC-M or HPC-A transplantation, but this is most likely due to the much lower number of progenitors in HPC-C.

The data also demonstrate that immune reconstitution appears to be complete by 2 years after HPC-C transplantation for patients transplanted for primary immunodeficiencies as well as for other malignant and nonmalignant disorders. Reconstitution includes lymphoid cell numbers as well as function as measured by in vitro proliferative responses to antigens from infectious agents, serum immunoglobulin levels, responses to vaccines in vivo, and control of infections. In vitro studies show that the lymphoid cells are of donor origin and originate from precursors in the HPC-C as demonstrated by detection of TRECs rather than just being mature lymphocytes infused with the allograft. It should be noted that the immune system is a complex organ, and only the cells of hematopoietic origin are donor-derived after HPC-C transplantation.

Additional support for the functional value of the transplanted cells comes from studies of donor-derived enzyme production in patients transplanted for inherited genetic disorders. For Hurler Syndrome there was a clear correlation between the degree of chimerism, the enzyme level in peripheral blood leukocytes, and measurement of urinary GAGs. A potential additional benefit is that the cells of hematopoietic origin home throughout the tissues of the body, including the central nervous system as microglia, areas not exposed to systemically administered enzyme replacement therapies. There are no clear data, however, that any affected cells other than those of hematopoietic origin are donor-derived after HPC-C transplantation.

Overall, the totality of the data support the use of Hemacord in conjunction with an appropriate preparative regimen for treatment of disorders affecting the hematopoietic system. The degree of success, however, appears to depend on the TNC dose and HLA match, and the data on time to hematopoietic recovery do not support use of HPC-C when HPC-M or HPC-A from a suitably matched donor is available.

7 Review of Safety

7.1 Safety Summary

The safety of Hemacord was based on a review of a dataset of 409 patients transplanted with 432 NYBC units manufactured using the manufacturing method intended for licensure. Additional supporting information included data submitted by the applicant for all 3619 patients transplanted with 3946 NYBC units and the Safety Review of HPC-C (Appendix 9.6). The information reviewed pertained to HPC-C from various manufacturers, but due to the lack of clear identification of manufacturer for individual subject data, no comparisons between manufacturers were made.

Raw datasets in the docket were submitted from the National Marrow Donor Program (NMDP), NYBC and Duke University, and the COBLT dataset was obtained from the National Heart, Lung and Blood Institute (NHLBI). Cases that were not overlapping between these sources were pooled for statistical analyses. The pooled docket dataset included 1572 subjects of median age 6 years (range <1-66 yrs) transplanted from 1993 - 2006. The male:female ratio was 1.4:1. Over 70% of the subjects were being treated for a hematological malignancy. The donor was HLA matched with the subject at 6/6 antigens for 10.8% of the pairs, 5/6 for 39%, 4/6 for 46.0% and <4/6 for the remainder. The median cryopreserved TNC dose was 5.3 (range, 0.7-73.8) x 10^7/kg. A TNC dose $\geq$2.5 x 10^7/kg was administered to 1299 (81.6%) of the subjects.

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

Deaths: Day-100 mortality for patients transplanted with Hemacord is 25%. The most common causes of death (>5%) by day 100 are organ failure and infection. Day-100 mortality due to graft failure is 3.2%. There were no demographic or product characteristics that correlated with early mortality for these patients transplanted with Hemacord.

For the pooled docket dataset, the incidence of early mortality and the causes of death were similar to those reported for Hemacord. When comparing those who received a TNC $\geq$2.5 x 10^7/kg vs <2.5 x 10^7/kg, patients with the higher TNC dose had fewer deaths by day 100 (25% vs 52%, p<0.001). There was a continuous downward trend in early mortality with increasing increments of TNC dose by 1 x 10^7/kg with an apparent inflection point in the curve between 2 and 3 x 10^7 TNC/kg. Other factors that correlated with day-100 death were age, gender, diagnosis and degree of HLA mismatch.

Graft Failure: The primary graft failure rate was 15% (95% CI 9-21%) for patients transplanted with Hemacord. When assessed by TNC dose and degree of HLA mismatch, there was no apparent increase in the graft failure rate over that expected. Further, two subjects had an actual time to neutrophil recovery that exceeded the expected upper 95% confidence interval, suggesting that there were no additional safety issues regarding engraftment for Hemacord other than those established for HPC-C in general.

In the pooled docket dataset, the primary graft failure rate was 16.4% (14.4-18.6%) for subjects receiving a TNC dose $\geq$2.5 x 10^7/kg. The graft failure rates fell below 20% only for incremental TNC doses $\geq$4 x 10^7/kg and remained at approximately 5-20% until falling further at TNC doses $\geq$17 x 10^7/kg. On multivariate analysis, there was a significant association between graft failure and diagnosis (p=0.006), degree of HLA mismatch (p<0.001), and TNC dose group (P<0.001). The literature review also suggests that alloimmunization may increase the risk of graft failure.

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

Infusion Reactions: Information on infusion reactions was available from voluntary reports for 244 patients transplanted with Hemacord. The reactions were not graded. Any type of reaction was reported for 18% of the patients. The most common infusion reactions noted were hypertension (14%), nausea (5%), vomiting (4%), hypoxemia (3%), dyspnea (1%), tachycardia (1%), cough (1%), and chest tightness or pain (1%). The rate of serious adverse cardiopulmonary reactions was 0.1%.

The COBLT dataset included information on 442 infusions at a TNC dose $\geq$2.5 x 10^7/kg that was used for the detailed assessment of infusion reactions. Infusion reactions were defined as events usually associated with HPC infusions and occurring within 24 hours of transplantation and graded by NCI CTC. An infusion reaction was reported for 65% of these subjects. The most common Grade 3-4 infusion reactions noted were hypertension (21%), nausea (6%) and hypoxia (2%). The rate of serious adverse cardiopulmonary events was 0.8%. On multivariate analysis, younger age and higher volumes of infusate were significantly associated with development of a grades 3-4 adverse event and with development of any grade of hypertension.

Review of the literature suggests the adverse infusion reactions may in part be due to Dextran 40. The volume of Dextran 40 in Hemacord prepared for infusion may be greater than tolerated for individuals of lower weight, accounting for the higher incidence of infusion reactions in children. DMSO can also cause significant toxicity. Severe DMSO toxicity can also be prevented by limiting DMSO administration to less than 1 gm/kg/day.

Acute GVHD: For the patients who received Hemacord, 43% developed grades 2-4 GVHD, and 20% developed grades 3-4 GVHD. Similar rates of GVHD were reported for subjects in the pooled docket dataset who received a TNC dose $\geq$2.5 x 10^7/kg, the incidence of grades 2-4 GVHD was 42.1%, and for grades 3-4 GVHD it was 18.8%. In addition, there was no significant difference in the rates of acute GVHD when comparing TNC doses above vs below 2.5 x 10^7/kg or by diagnosis.

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

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

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

Transmission of Rare Genetic Disorders: The applicant reported one case of transplantation of HPC-C from a donor with an inheritable genetic disorder. Since starting manufacture of Hemacord, there are no reports of transmission of genetic disorders from the donor.

7.2 Methods

7.2.1 Studies/Clinical Trials Used to Evaluate Safety

No clinical trials or studies were available for an assessment of the safety of this applicant's product. This safety review was based primarily on the serious adverse event reports and the outcomes dataset submitted by the applicant.

From 1993 to 2007, data collection questionnaires were sent 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, additional information was requested.

From 2008 to present, data for units transplanted in the US is collected via the Stem Cell Therapeutic Outcomes Database (SCTOD) of the CW Bill Young Transplantation Program. The dataset is incomplete in the most recent records.

From 2008 to present, 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 choose to not utilize the SCTOD.

7.2.2 Categorization of Adverse Events

7.2.2.1 Infusion Reactions

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 (specified as oxygen administration, blood pressure support, bronchodilators or need for diuretics more that 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 at any degree of seriousness. Whether the event required intervention and whether the event resolved are also requested.

7.2.2.2 Other Events of Interest

Other events of interest include graft versus host disease (GVHD), engraftment syndrome, time to neutrophil recovery, graft failure, transplant-related mortality, malignancies of donor origin, transmission of serious infection, and transmission of rare genetic disease. The SCTOD has standardized definitions of these events and grading criteria for GVHD. The applicant has provided no criteria for assessing seriousness of events collected directly from the transplant center. Definitions of events as provided verbatim by the applicant include:

Engraftment: Time to myeloid engraftment is defined as the first of three consecutive days of absolute neutrophil cell count ≥500/μl (ANC>500). Note: for the evaluation of engraftment the cytoreduction regimen needs to be taken under consideration. The myeloablative cytoreduction regimen "empties" the patient's bone marrow, so all peripheral blood cells after the transplant are derived from the graft. In cases on non-myeloablative conditioning, some of the peripheral blood cells initially derive from the patients' own residual marrow and donor cell engraftment must be verified by chimerism studies.

Primary graft failure was defined as either: a) never having achieved ANC>500 within the time interval defined according to the transplant center procedures, or
b) ANC>500 with no donor engraftment by chimerism studies (autologous recovery).

Survival: Overall survival and the exact opposite variable,

Transplant-Related Mortality (TRM) have been evaluated in all studies. For patients with hematologic malignancies, TRM is defined as death from any cause, while the patient was in remission. Among patients without hematological malignancies all deaths are considered transplant-related. Surviving patients are censored at the time of last follow up.

Relapse: In patients with hematologic malignancies, diagnosis of relapse is based on clinical or cytogenetic relapse. In patients with non-hematologic malignancies, disease "recurrence" is defined in cases of autologous recovery.

Graft-versus- Host Disease: Acute Graft-versus-Host Disease is diagnosed by the transplant centers; grades of acute GvHD (I-IV) and chronic (limited or extensive) are used as assigned by the transplant centers.

7.2.3 Pooling of Data Across Studies/Clinical Trials

For the analysis of time to engraftment, data from both the periods 1993 to 2007 and 2008 to present have been pooled. This dataset includes information submitted directly to the applicant and via the SCTOD. The safety database includes minimally manipulated units transplanted,

units expanded ex vivo prior to transplantation, and units used to prepare cellular immunotherapies such as antiviral lymphocytes or natural killer cells.

Reviewer Comment: This dataset has several major limitations. These include a) submission of data was largely voluntary, so the dataset may be incomplete, b) the data are unaudited, so the dataset may be inaccurate, c) the dataset is pooled from two different sources with potential differences in the definitions of the events and grading of seriousness, and d) for several events, grading of seriousness was not performed at all. The degree to which these limitations call into question the integrity of the dataset is unclear.

7.3 Adequacy of Safety Assessments

7.3.1 Overall Exposure at Appropriate Doses

The applicant submitted a safety outcomes dataset of 3619 patients transplanted August, 1993 through January, 2011. Data on patient demographics, allograft characteristics, hematopoietic recovery and outcomes were not complete for all patients. A summary of the subsets of data available for analysis is shown in Table 17.

Table 17: Development of Safety Data Subsets for Analyses

Step	Data file subset	Number
1	Submitted datafile	3619 patients transplanted with 3946 NYBC units
2	**Subsets in this step are used for analysis of infusion reactions**	
	Step 1 file limited to records for units used for hematopoietic reconstitution and that include demographics and allograft information	3587 patients transplanted with 3908 NYBC units
	2a. And limited to units manufactured using Method #4	409 patients transplanted with 432 NYBC units
	2b. And limited to units with infusion reaction data	233 patients transplanted with 244 NYBC units
	2c. And limited to a TNC dose $\geq$ 2.5 x 10^7/kg	150 patients transplanted with 153 NYBC units
3	**Subsets in this step are used for analyses of deaths and GVHD**	
	Step 1 file limited to patients receiving the allograft for hematopoietic reconstitution and the record includes demographics, allograft and outcomes information	2691 patients
	3a. And limited to patients who received a TNC dose $\geq$ 2.5 x 10^7/kg and units manufactured using Method #4	155 patients
4	**Subsets in this step are used for analysis of hematopoietic recovery**	
	Step 1 file limited to patients receiving the allograft for hematopoietic reconstitution and the record includes demographics, allograft, hematopoietic recovery and outcomes information	2460 patients
	4a. And limited to patients who received a TNC dose $\geq$ 2.5 x 10^7/kg and units manufactured using Method #4	155 patients

Of these, 409 patients requiring hematopoietic reconstitution received a HPC-C unit manufactured using Method #4. Demographics of these patients are shown in Table 18.

Table 18: Safety Outcomes Dataset – Subject Demographics

		All Subjects Transplanted N (%)		Unit Manufactured Using Method #4 N (%)	
Number of Patients		3587		409	
Median Age (Range)		10.4 yrs (27 days-79.2 yrs)		19.2 yrs (2 mos-73.3 yrs)	
Age Category	< 1 month	4	(0.1%)	0	(0.0%)
	1 mo - <2 yr	613	(17.1%)	40	(9.8%)
	2 – <13 yrs	1377	(38.4%)	119	(29.1%)
	13 - <17 yrs	277	(7.7%)	31	(7.6%)
	17 - <65 yrs	1252	(34.9%)	203	(49.6%)
	≥65 yrs	50	(1.4%)	13	(3.2%)
	Unknown	14	(0.4%)	3	(0.7%)
Gender	Male	2068	(57.7%)	226	(55.3%)
	Female	1481	(41.3%)	183	(44.7%)
	Unknown	38	(1.1%)	0	(0.0%)
Ethnicity	White	1431	(39.9%)	89	(21.8%)
	African-American	383	(10.7%)	32	(7.8%)
	Hispanic	466	(13.0%)	44	(10.8%)
	Asian	121	(3.4%)	18	(4.4%)
	Other	168	(4.7%)	15	(3.7%)
	Unknown	1018	(28.4%)	211	(51.6%)
Diagnosis	Hematologic malignancies	2722	(75.9%)	324	(79.2%)
	Hurler Syndromes	54	(1.5%)	4	(1.0%)
	Krabbe Disease	23	(0.6%)	0	(0.0%)
	X-linked Adrenoleukodystrophy	40	(1.1%)	5	(1.2%)
	Primary immunodeficiency diseases	254	(7.1%)	17	(4.2%)
	Bone marrow failure	265	(7.4%)	31	(7.6%)
	Beta thalassemia	33	(0.9%)	4	(1.0%)
	Other	158	(4.4%)	10	(2.4%)
	Unknown	38	(1.1%)	14	(3.4%)
Year of Transplantation	1993-2000	1074	(29.9%)	0	(0.0%)
	2001-2005	918	(25.6%)	0	(0.0%)
	2006-2010	1595	(44.5%)	317	(100.0%)

7.3.2 Explorations for Dose Response

Characteristics of the allografts transplanted are summarized in Table 19. The dose of cells to be administered was chosen by the treating physician and not stipulated by the manufacturer. Throughout this review, TNC dose refers to the dose at cryopreservation. The dose range listed

in the Table 19 refers to the total cell dose administered in the case of multiple unit allografts. The dose range is sufficiently wide to allow an assessment of safety outcomes by dose. It should be noted, however, that reactions related to volume of the product will not be detectable as the dataset does not include the volume administered.

Table 19: Safety Outcomes Dataset – HPC-C Unit Characteristics

		All Subjects Transplanted N (%)	Unit Manufactured Using Method #4 N (%)
Number of Units Transplanted	1	2871 (80.0%)	199 (62.8%)
	>1	716 (20.0%)	118 (37.2%)
Lowest HLA Match Level	2-3	104 (1.9%)	0 (0.0%)
	4	1849 (45.9%)	151 (41.5%)
	5	1395 (43.3%)	146 (50.2%)
	6	239 (8.9%)	20 (8.3%)
Median Dose (TNC x 10^7/kg) (Range)		4.5 (0.7-71.1)	4.9 (2.5-57.6)
Manufacturing Method	1	463 (4.9%)	
	2	884 (18.9%)	
	3	1831 (58.7%)	
	4	409 (17.5%)	317 (100%)

* Those who received a unit manufactured with Method #4 and having a TNC dose $\geq$2.5 x 10^7/kg

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

The assessment of safety for HPC-C units from other manufacturers is provided in the Safety Review – Dockets and Public Information (Appendix 9.6). The pertinent information is summarized within this BLA review, and the detailed report is provided in the appendix.

7.4 Major Safety Results

7.4.1 Deaths

7.4.1.1 Docket Review (Appendix 9.6)

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

When comparing those who received a TNC $\geq$2.5 x 10^7/kg vs <2.5 x 10^7/kg, patients with the higher TNC dose had fewer deaths overall (49% vs 74%, p<0.001) and fewer deaths by day 100 (25% vs 52%, p<0.001). There was a continuous downward trend in early mortality with

increasing increments of TNC dose by 1 x 10^7/kg with an apparent inflection point in the curve between 2 and 3 x 10^7 TNC/kg. Other factors that correlated with day-100 death were age, gender, diagnosis and degree of HLA mismatch.

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

7.4.1.2 Deaths reported

The applicant provided no assessment of the causes of death. There were 1499 (56%) deaths amongst 2691 patients with follow-up information; 68 (44%) deaths occurred in the 155 patients who received a suitable allograft. Deaths through day 100 are 932/2691 (35%) and 39/155 (25%), respectively. Results of the FDA analysis of causes of death are shown in Table 20.

Table 20: Causes of Death After Transplantation

	All Subjects Transplanted N (%)		Subjects with a Suitable Allograft* N (%)	
Causes of Death	**Total Reported**	**Through Day 100**	**Total Reported**	**Through Day 100**
Graft Failure	296 (11.0)	234 (8.7)	6 (3.8)	5 (3.2)
Organ failure	260 (9.7)	183 (6.8)	20 (12.9)	13 (8.4)
Infection	369 (13.7)	260 (9.7)	12 (7.7)	9 (5.8)
GVHD	132 (4.9)	82 (3.0)	8 (5.2)	3 (1.9)
Primary disease	352 (13.1)	130 (4.8)	14 (9.0)	4 (2.6)
2nd Malignancy	20 (0.7)	5 (0.2)	1 (0.6)	0 (0.0)
Prior malignancy	1 (0.04)	0 (0.0)	0 (0.0)	0 (0.0)
Accident	2 (0.07)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	55 (2.0)	31 (1.2)	4 (2.6)	3 (1.9)
Other	12 (0.4)	7 (0.3)	3 (1.9)	2 (1.3)

* Those who received a unit manufactured with Method #4 and having a TNC dose $\geq$2.5 x 10^7/kg

The most common causes of death ($\geq$5%) for patients who received a suitable allograft 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. There was a slight increase in the frequency of death due to organ failure amongst the patients who received a suitable allograft as compared to the whole group, and the rates of death due to graft failure or infection appeared to be lower when a suitable allograft was used.

Reviewer Comment: The evaluation of the pooled dataset confirmed that day-100 mortality was lower in those who received a TNC dose $\geq$2.5 x 10^7/kg. Using this dose as a guideline, the incidence of early deaths due to graft failure in the applicant's dataset (3.2%) was similar to

that in the pooled dataset (2.5%). 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. 7.8%). Overall, no safety issue related to the applicant's product was raised in the evaluation of early deaths.

7.4.1.3 Early Mortality Interactions with Demographic and Allograft Characteristics

Since most of the deaths plausibly related to the HPC-C unit occurred by 100 days after transplantation, additional exploratory analyses were conducted to assess patient or treatment parameters that might be associated with such early deaths. The applicant provided no assessment of the rate of early deaths by demographic characteristics. There were 2691 patients for whom follow-up information and some demographic information were available; 155 of the patients received a suitable allograft. Results of the FDA analysis are shown in Table 21.

Table 21: Early Mortality Interactions with Demographic Characteristics

	All Subjects Transplanted N (%)			Subjects with a Suitable Allograft* N (%)		
Demographic	**Patients**	**Deaths ≤ Day100**	**p**	**Patients**	**Deaths ≤ Day100**	**p**
Age Group						
< 1 mo	4	1 (25)	<0.001	0	0 (0)	0.36
1 mo - 2 yrs	488	127 (26)		24	4 (17)	
2 yrs – 12 yrs	1061	349 (33)		49	15 (31)	
13 yrs – 16 yrs	221	88 (40)		11	2 (18)	
17 yrs – 64 yrs	872	349 (40)		65	15 (23)	
> 65 yr	38	15 (40)		5	2 (40)	
Unknown	7	3 (43)		1	1 (100)	
Gender						
Male	1552	513 (33)	0.10	84	20 (24)	0.67
Female	1107	405 (37)		71	19 (27)	
Unknown	32	14 (44)		0	0 (0)	
Race/Ethnicity						
African American	322	127 (39)	0.06	20	4 (20)	0.13
Asian	90	24 (27)		5	0 (0)	
Caucasian	1176	418 (36)		37	7 (19)	
Hispanic	349	124 (36)		10	7 (41)	
Other	132	36 (27)		10	1 (10)	
Unknown	622	203 (33)		66	20 (30)	
Diagnosis Group						
Marrow Failure	203	86 (42)	<0.001	13	6 (46)	0.27
Hemoglobinopathy	38	5 (13)		2	0 (0)	
Heme Malignancy	2043	747 (37)		122	31 (25)	
Immunodeficiency	196	45 (23)		10	1 (10)	
Metabolic Disorder	202	45 (22)		7	1 (14)	
Other	2	1 (50)		0	0 (0)	
Unknown	7	3 (43)		1	0 (0)	

* Those who received a unit manufactured with Method #4 and having a TNC dose $\geq 2.5 \times 10^7$/kg

The applicant also provided no assessment of the rate of early deaths by allograft characteristics. There were 2691 patients for whom follow-up information and allograft characteristics were available; 155 of the patients received a suitable allograft. Results of the FDA analysis are shown in Table 22.

Table 22: Early Mortality Interactions with Product Characteristics

	All Subjects Transplanted N (%)			Subjects with a Suitable Allograft* N (%)		
Demographic	**Patients**	**Deaths ≤ Day100**	**p**	**Patients**	**Deaths ≤ Day100**	**p**
Number of Units						
Single	2155	792 (37)	<0.0001	84	25 (30)	0.15
Multiple	536	140 (26)		71	14 (20)	
HLA-Match						
2/6	9	4 (44)	<0.0001	0	0 (0)	
3/6	93	49 (53)		0	0 (0)	
4/6	1436	534 (37)		74	18 (24)	0.83
5/6	990	307 (31)		75	20 (27)	
6/6	163	38 (23)		6	1 (17)	
TNC Dose						
$< 2.5 \times 10^7$/kg	575	256 (45)	<0.0001	0	0 (0)	NA
$\geq 2.5 \times 10^7$/kg	2116	676 (32)		155	39 (25)	

* Those who received a unit manufactured with Method #4 and having a TNC dose $\geq 2.5 \times 10^7$/kg

In the univariate analyses of the entire dataset for correlations with early mortality, age group, diagnosis group, number of units transplanted, degree of HLA match and TNC dose group were significant. Dose was also significant when considered as a continuous variable ($p<0.001$). The results are consistent with known factors that are prognostic for mortality for HPC-C transplantation.

In the univariate analyses of the subset of patients with a suitable allograft, none of the demographic or allograft characteristics correlated significantly with early mortality, including when dose was considered as a continuous variable. It should be noted that this subgroup did not include any patients who received allografts having less than a 4/6 HLA match or a TNC dose $< 2.5 \times 10^7$/kg.

Reviewer Comment: For the subgroup of patients who received a suitable allograft, the lack of correlations between early mortality and demographic or allograft characteristics may have resulted from a number of factors. First, the number of patients in this subgroup may have been too small to allow detection of a significant factor. Second, patients with the highest risk of early mortality (i.e., those with a very poorly matched allograft and a very low cell dose)are not included in this subgroup. And, finally, all of these patients were transplanted in the most recent time period, and presumably benefited from advances in supportive care as well as the cumulative experience of the health care providers. Labeling will reflect the limited variability in the subgroup used in the analysis.

7.4.1.4 Transplant-Related Mortality (TRM)

No overall TRM was reported by the applicant. The applicant provided analyses on various subsets of patients in the safety dataset TRM calculated at several years after transplantation. The applicant concluded from this analysis that both TNC dose and HLA mismatch impacted TRM. Additionally, TRM was also altered by the combined effect of TNC and HLA mismatch.

The applicant also assessed whether the direction of the HLA mismatch mattered. They show a numerical increase in TRM for those with bidirectional mismatches or mismatches in the rejection direction only in comparison to those with no mismatches or only mismatches in the GVHD direction, but no statistical inferences were made.

A second analysis evaluated the effect of mismatching for the noninherited maternal allele (NIMA) on TRM in 1121 subjects with various hematological malignancies transplanted 1993-2006 using a myeloablative preparative regimen and a single HPC-C unit. The applicant concluded that subjects who received 1-2 antigen mismatched transplants with at least one NIMA match had lower TRM than those with no NIMA match (RR 0.7, p=0.03).

A third analysis evaluated the effect of duration of cryopreservation (< 2 yrs vs >8 yrs) on TRM in 343 subjects with various diagnoses transplanted 2001-2006. The applicant concluded that there was no difference in TRM between the two groups (35.1% vs 51.7%, p=0.35).

FDA was unable to verify the analyses provided by the applicant, since the subjects for each analysis were not identified in the dataset.

Reviewer Comment: It is acknowledged that numerous complications affect late TRM, and many of these may not be related to the HPC-C unit, limiting any conclusions that can be made about the safety of the product with regard to this outcome. Since assessments of late TRM would not likely provide an accurate appraisal of this applicant's product, no analyses of late TRM were performed.

7.4.2 Serious Adverse Events

Six serious adverse events were reported to the applicant (0.15% of units transplanted). None of these was for a unit manufactured using Method #4. The summaries of these events are presented below verbatim from the applicant:

1. CBU ID: --(b)(6)---; Patient ID: --(b)(6)-- Wrong CBU was shipped and infused. The event resulted from mixing the labels of two CBUs processed on the same day, with very similar HLA-A and -B antigens (confirmatory HLA typing was performed only by serology). The unit mislabeling event took place in 1993, very early after the initiation of the Program. The event was discovered when the post-transplant HLA typing of the patient showed discordant results with donor unit.
Corrective actions included re-enforcement of the "one at a time rule" in handling CB units and samples, as well as confirmatory HLA typing to include high resolution DRB1 typing for all

CBUs prior to release for transplantation. This event was reported to the FDA as soon as it was discovered and was also included in the IND Annual Report.

Reviewer Comment: CMC Review confirms that the corrective actions described have been implemented.

2. CBU ID: *(b)(6)-*; Patient ID: -(b)(6)- Patient was thought to receive a phenotypically "perfectly matched" CBU (0 mismatches at low resolution HLA-A and -B loci and high resolution DRB1); upon further investigation through the collection hospital records, this was his own (autologous) CB unit. The patient died of post-transplant complications; the event was discovered long after the patient's death. Corrective actions included steps to further identify patient and baby donor in cases of 0 HLA mismatches at the HLA-A,-B,-DRB1, as described in SOP CB41.0002.1.

Reviewer Comment: An additional safeguard includes the elicitation and handling of postdonation information as described in SOP CB37.0032.1.

3. CBU ID: (b)(6); Patient ID: -(b)(6)-- Patient died within 48 hours of the CB infusion. Clinical evaluation showed large pericardial effusion and pericardial tamponade and acute decrease in cardiac function by echocardiogram. The cause of death was thought to be cyclophosphamide-induced cardiomyopathy (transplant-related mortality). Post-thaw CBU bacterial cultures were negative. No corrective action was needed for the CB Bank.

4. CBU ID: (b)(6); Patient ID--(b)(6)-- Patient had respiratory decompensation after infusion of a double unit graft: both units were thawed and infused without reconstitution or wash procedures. The first infused CBU (from another CB Bank) was a RBC-replete unit with a total volume 250 ml. The patient developed hypertension and hypoxemia during and after the infusion. The patient's clinical condition worsened after the infusion of the second CBU (NCBP CBU-(b)(6)--) with a total volume of 52 ml, and eventually the patient required intubation. Subsequently the patient improved and was extubated. The event was reported to the NCBP by the NMDP (National Marrow Donor Program). Extensive investigation did not reveal any deviations related to the collection, processing, cryopreservation and shipping of the NCBP CBU. NMDP has issued a summary of events to the transplant centers and suggestions for the infusion and post-infusion management of the patients (see Section 7.3.3.3 below).

5. CBU ID: (b)(6); Patient ID: -(b)(6)-- Patient was scheduled to receive a double unit CB graft with both units from the NCBP. The first NCBP unit was thawed and underwent albumin reconstitution to a total volume of 200 ml. Within a few minutes from the initiation of the infusion, the patient developed severe respiratory distress requiring oxygen and several other medications. Infusion of the CBU was stopped (maximum amount infused: 20 ml including amount left in the IV tubing) and the product was returned to the stem cell laboratory of the transplant center. After the patient was stabilized, the second CBU (CBU --(b)(6)--, AXP-processed CBU) was washed and infused without complications, with a total volume of 223 ml. The following day, the patient received a third CBU ("back-up" CBU --(b)(6)--) after washing, with a total volume of 98 ml, without any complications. Bacterial cultures were negative in

3 CB units. Extensive investigation did not reveal any deviations related to the collection, processing, cryopreservation and shipping of the NCBP CBU --*(b)(6)*. The patient recovered from the acute event, however, he had a similar acute respiratory reaction to a platelet infusion two weeks later. Given the second reaction and the rapidity of the event after initiation of the CBU infusion, the respiratory event was thought to be an anaphylactic reaction. No corrective action was required for the CB Bank.

6. CBU IDs --(b)(6).---(b)(6)----- patient ID: --*(b)(6)*. Patient had renal failure (manifested by elevation of serum creatinine) a few hours after the infusion of a double unit CB graft. Both units were from the NCBP, they were thawed and underwent albumin reconstitution to a total volume of 100 ml each. Patient was hypertensive during the infusion and had elevation of serum creatinine the day after. Event was thought to be related to the infusion. Extensive investigation did not reveal any deviations related to the collection, processing, cryopreservation and shipping of both NCBP CBUs. The event was reported to the NCBP by the NMDP. The patient recovered and engrafted after the double unit CB transplant.

NMDP Summary was received on 1/5/2011. NMDP Assessment: The recipient experienced acute renal failure within 24 hours of double cord transplant. We agree that the transient high cyclosporine level was likely spurious. The lack of schistocytes on the peripheral smear and uneventful recovery exclude TMA as a cause of renal failure. A normal CK value excludes rhabdomyolysis. Non-oliguric renal failure makes volume depletion unlikely. Imaging studies ruled out post-renal causes. The elevation of LD and absent haptoglobin suggest that intravascular hemolysis occurred, and this may have been a factor in the acute renal failure episode. Because the renal failure and hemolysis were temporally associated with the cord product infusions, the red cell-reduced HPC-C units cannot be excluded as at least partially causative of the adverse event of acute renal failure. No product deviations with the HPC-C units themselves were identified. The recipient required only supportive care during the episode of renal failure and did go on to engraft and recover.

Reviewer Comment: Additional warnings and precautions should be added to the Administration section of the Prescribing Information to address this type of event. Additional measures may be required to ensure that the users understand the risks regarding failure to follow the manufacturer's instructions regarding thaw and infusion.

7.4.3 Infusion Reactions

7.4.3.1 Docket Review (Appendix 9.6)

The COBLT dataset was used for the assessment of infusion reactions. This included 523 infusions of HPC-C in 511 patients. The population included 310 males and 201 females of median age 6 years (range 0.1-67 years). Preparative regimens and graft-vs-host disease prophylaxis were not standardized amongst the patients. Infusion reactions were defined as events usually associated with HPC infusions and occurring within 24 hours of transplantation. These were graded by NCI CTC. The most common infusion reactions were hypertension,

vomiting, nausea and bradycardia (Table 23). The rate of serious adverse cardiopulmonary events was 0.8%.

Table 23: Incidence of Infusion-Related Adverse Events Occurring in ≥1% of Subjects in The COBLT Study

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

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

7.4.3.2 Infusions Reactions Reported

Infusion reactions for units manufactured by Method # 4 are listed in Table 24 as summarized by the applicant.

Table 24: Infusion Reactions Reported by Applicant

Description of Adverse Infusion Reactions	N	% (of CBU transplanted)	% (of CBU with report)
No report, no data	200	45%	
No adverse reactions encountered	203	46%	85%
Hypertension, nausea, vomiting	28	6%	10%
Hypoxia, chest pain, shortness of breath, hemoglobinuria, hypotension	14	3%	6%
Severe (hematuria, seizure, acute renal/pulmonary/cardiac failure, death within 48 h)	0	0%	0%
Total AXP-processed CB units transplanted	445		
Total CB units with infusion reports	245		

On review of the application, the infusion reaction dataset was found to have 244 unique units. Both demographic and product data were available for 243 units. The FDA analysis of the infusion reactions is shown in Table 25.

Table 25: Infusion Reactions for Unit Manufactured Using Method #4 – FDA Analysis

	All Units Transplanted N (%)	**Units with a TNC dose ≥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)

There were 153 patients who received a TNC dose ≥2.5 x 10^7/kg. An adverse reaction was reported in association with the infusion for approximately 18% of the units infused; 9% 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 (Table 25). None of the patients were reported to have fever, headache, hives, hematuria, hypotension or rigors.

7.4.3.3 Infusion Reaction Interactions with Demographic and Product Characteristics

The applicant provided no assessment of the rate of infusion reactions by demographic characteristics. There were 243 infusions for which any demographic information was available; 153 of the units infused had a TNC dose $\geq$ 2.5 x 10^7/kg. Results of the FDA analysis are shown in Table 26.

Table 26: Infusion Reaction Interactions with Demographic Characteristics

	All Units Transplanted N (%)			**Units with a TNC dose $\geq$2.5 x 10^7/kg N (%)**		
Demographic	**Infusions**	**Reactions**	**p**	**Infusions**	**Reactions**	**p**
Age Group						
$\leq$ 2 yrs	28	6 (21)	0.24	28	6 (21)	0.14
2 yrs – 12 yrs	54	11 (20)		53	11 (21)	
13 yrs – 16 yrs	23	7 (30)		13	5 (38)	
17 yrs – 64 yrs	123	15 (12)		54	6 (11)	
> 65 yr	14	2 (14)		4	0 (0)	
Gender						
Male	135	25 (19)	0.44	85	17 (20)	0.54
Female	108	16 (15)		68	11 (16)	
Race/Ethnicity						
African American	26	6 (23)	0.92	17	5 (29)	0.73
Asian	13	3 (23)		10	2 (20)	
Caucasian	51	8 (16)		25	6 (24)	
Hispanic	22	4 (18)		16	3 (19)	
Other	9	1 (11)		7	1 (14)	
Unknown	123	19 (15)		78	11 (14)	
Diagnosis Group						
Marrow Failure	14	4 (29)	0.32	12	3 (25)	0.64
Hemoglobinopathy	4	2 (50)		4	2 (50)	
Heme Malignancy	199	32 (16)		114	20 (18)	
Immunodeficiency	12	2 (17)		12	2 (17)	
Metabolic Disorder	10	1 (10)		10	1 (10)	
Unknown	5	0 (0)		1	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 (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=NS). There were no correlations between having a reaction and any of the demographic characteristics tested. It should be noted that 2 of the patients with hemoglobinopathy had beta thalassemia, and 5 of the patients with metabolic disorders had adrenoleukodystrophy (n=2) and Hurlers syndrome (n=3). The other patients in each of these categories had other hemoglobinopathies or metabolic disorders, and were categorized as shown to facilitate analysis.

The applicant provided no assessment of the rate of infusion reactions by product characteristics. There were 243 infusions for which any product information was available; 153 of the units infused had a TNC dose $\geq 2.5 \times 10^7$/kg. Results of the FDA analysis are shown in Table 27.

Table 27: Infusion Reaction Interactions with Product Characteristics

	All Units Transplanted N (%)			Units with a TNC dose $\geq 2.5 \times 10^7$/kg N (%)		
Demographic	**Infusions**	**Reactions**	**p**	**Infusions**	**Reactions**	**p**
Number of Units						
Single	102	17 (17)	0.94	93	17 (18)	0.99
Multiple	141	24 (17)		60	11 (18)	
HLA-Match						
4/6	108	16 (15)	0.70	69	9 (13)	0.28
5/6	116	22 (19)		77	17 (22)	
6/6	19	3 (16)		7	2 (29)	
TNC Dose						
$\leq 2.5 \times 10^7$/kg	90	13 (14)	0.43	0	0 (0)	NA
$\geq 2.5 \times 10^7$/kg	153	28 (18)		153	28 (18)	

The median TNC dose was 3.3 (1.5-57.6) 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 (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 $\geq 2.5 \times 10^7$/kg) (p=NS). There were no correlations between having a reaction and any of the product characteristics tested. Information regarding the volume of the products infused and the method used for preparation of the product is not available, so whether total volume or volume of DMSO infused was a factor in the development of infusion reactions could not be tested.

7.4.3.4 NMDP Safety Report

The applicant submited a safety report from the NMDP dated 8/31/2009. This report describes four cases of double cord transplant infusions 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 total number of infusions evaluated was not provided, so an incidence could not be calculated. NMDP concluded that the events resulted from improper preparation of the units for infusion.

Ma et al[27] have published a complete summary of these four cases of acute cardiopulmonary toxicity from the NMDP and two additional cases (Table 28). They conclude that the events represent hypersensitivity reactions to dextran in the infusions.

Table 28: Summary of Serious Cardiopulmonary Infusion Reactions
From Reference 27.

Case	1	2	3	4	5	6
Authors	This report	NMDP case 1	NMDP case 2	NMDP case 3	NMDP case 4	Petropolou et al.
Age	50	44	65	34	20	60
Gender	Male	Female	Male	Female	Female	Not specified
Diagnosis	Transformed mycosis fungoides	Burkitt lymphoma	Acute myeloid leukemia, myocardial infarct	Acute myeloid leukemia	Hodgkin's lymphoma	Atypical chronic myeloid leukemia
Transplant conditioning	Flu/cyclo/TBI	Flu/cyclo/TBI	Flu/cyclo/TBI	Flu/cyclo/TBI	Not reported	Flu/cyclo/TBI
Washed or unwashed	Unwashed	Unwashed	Unwashed	Reconstituted with dextran/albumin 1:4	First bag: unmanipulated; Second and third bag: resuspended in albumin/dextran	Centrifuged and resuspended
Volume	262 mL	First: 251 mL Second: 52 mL	First: 200 mL Second: 50 mL	500 mL	First: 50 mL Second: not reported Third: 114 mL	175 mL
Onset	During first and second infusions	During first and second infusions	During first infusion	During first and second infusions	During first, second and third infusions	15 min
Clinical findings	Chest pain, nausea, hypertension, hypoxia, pul edema, raised troponin, and acute renal failure	Chest pain, hypoxia, pul edema, raised troponin, and acute renal failure	Chest pain, hypoxia, pul edema, raised troponin, and acute renal injury	Chest pain, nausea, hypoxia, pul edema, and raised troponin	Chest pain, nausea, hypertension, hypoxia, pul edema, raised troponin, and acute renal injury	Abdominal pain, nausea, hypertension, raised troponin, and normal coronary angiogram
Organ involvement	Heart Lungs Kidneys	Heart Lungs Kidneys	Heart Lungs Kidneys	Heart Lungs	Heart Lungs Kidneys	Heart
Contains dextran	Yes	Yes	Yes	Yes	Yes	Probably
Outcome	Engraftment day 37. Patient died with sepsis, gastrointestinal GVHD, and hepatic failure at day 57*	Recovery, with slightly elevated creatinine status	Complete recovery, 23 days later, patient died from cardiac failure, complicated by sepsis and renal failure*	Complete recovery. Engraftment with no further cardiac events	As of 8/12/09 patient doing well. No further complaints	Complete recovery. Patient died several weeks after the transplantation from multiorgan failure*

Flu, fludarabine; cyclo, cyclophosphamide; TBI, total body irradiation.
*No autopsy data is available for these patients.

7.4.3.5 Summary – Infusion Reactions

Using a TNC dose $\geq$ 2.5 x 107/kg, 18.3% of the infusions were associated with an adverse reaction. The most common ($\geq$2%) infusion reactions reported by the applicant are hypertension, nausea, vomiting, hypoxemia. The rate of serious adverse cardiopulmonary events was 0.1%. The rate of infusion reactions reported in the COBLT Study was higher, 65.4% for any infusion-related adverse event, and 27.6% for grades 3-4 events. The most common infusion-related events in the COBLT Study were hypertension, vomiting, nausea, sinus bradycardia, fever, sinus tachycardia, allergy, hypoxia, hypotension, and hemogloburia. The rate of serious adverse cardiopulmonary events was 0.8% in the COBLT Study. Younger age and higher volumes of infusate correlated with development of grades 3-4 adverse reactions or any grade of hypertension.

Known side effects of Dextran 40 include acute renal failure, pulmonary edema, congestive heart failure, bleeding disorders and anaphylactoid reactions, so the reactions reported with HPC-C infusions may be related to the Dextran 40. The recommended infusion rates[1] are 100 - 200 mL/hr in otherwise healthy adults (ASA I classification) of normal weight; rates in ASA II-IV should be adjusted as clinically indicated. For children, infusions should begin at 0.5 mL/kg/hr and be increased as tolerated to a maximum of 4 mL/kg/hr.

Reviewer Comment: The spectrum of adverse events reported by the applicant appear to be similar to those reported for the COBLT Study. The rates of adverse events in the prospective trial are higher than those for voluntary reporting to the applicant. Both sets of data should be included in the labeling.

For the COBLT Study, the volume of infusate correlated with development of grades 3-4 adverse reactions and development of hypertension. In addition, the spectrum of adverse events is similar to that reported for Dextran 40. One HPC-C unit diluted according to instructions would provide 170 mL of 4.4% Dextran 40 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. Labeling should include instructions for safe use that include limits on volume and/or the infusion rate, especially for children. In addition, the applicant should determine the lowest volume and concentration of Dextran 40 that can be used to prepare the unit for administration without negatively impacting the function of the product.

7.5 Other Events of Interest

7.5.1 Graft Failure

7.5.1.1 Docket Review – Graft Failure (Appendix 9.6)

The primary graft failure rate was 16.4% (14.4-18.6%) for subjects receiving a TNC dose $\geq$2.5 x 10^7/kg. The graft failure rates fell below 20% only for incremental TNC doses $\geq$4 x 10^7/kg and remained at approximately 5-20% until falling further at TNC doses $\geq$17 x 10^7/kg. On multivariate analysis, there was a significant association between graft failure and diagnosis ($p=0.006$), degree of HLA mismatch ($p<0.001$), and TNC dose group ($P<0.001$). The literature review also suggests that alloimmunization may increase the risk of graft failure.

The graft failure rate varied with diagnosis and ranged from 9.5% to 31.1%. When assessed by individual diagnosis, there was a significant inverse correlation between TNC dose group and graft failure for the subjects transplanted with hematological malignancies, bone marrow failure and immunodeficiency disorders. For Hurler syndrome and bone marrow failure, a substantial decrease in graft failure especially occurs with a TNC dose $\geq$5 x 10^7/kg. The literature review

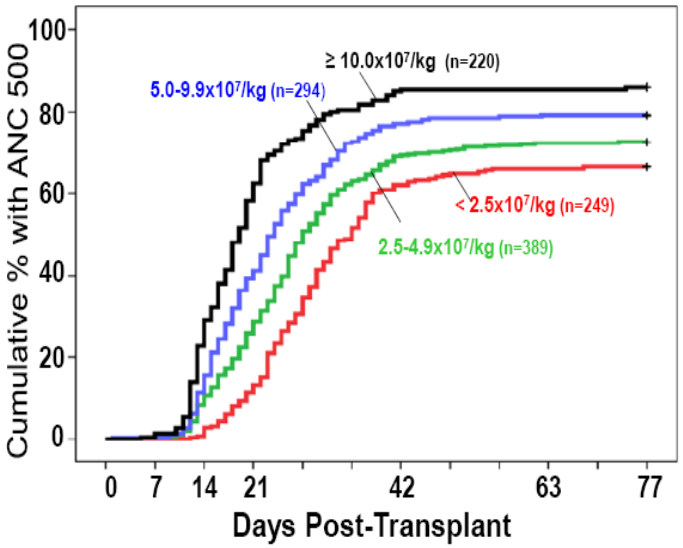
[1] Source: BLA 125397 Consultation Report by Lawrence Landow, MD (CBER/OBRR) dated 10/7/2011.

suggests that a higher TNC dose may also be associated with improved engraftment in patients transplanted for thalassemia.

7.5.1.2 Applicant's Analyses of Hematopoietic Recovery

No overall time to neutrophil recovery was reported by the applicant. The applicant provided analyses on various subsets of patients in the safety dataset. Figure 4 shows the cumulative incidence of neutrophil recovery for 1202 subjects 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 4: Time to Neutrophil Recovery by TNC Dose
From Applicant's submission



A second analysis evaluated the combined effects of TNC dose and HLA mismatch on neutrophil recovery in 1061 subjects with various hematological malignancies transplanted 1993-2006 using a myeloablative preparative regimen and a single HPC-C unit. The applicant concluded that both TNC dose and the degree of HLA mismatch affect the time to neutrophil recovery.

A third analysis evaluated the effect of mismatching for the noninherited maternal allele (NIMA) on neutrophil recovery in 1121 subjects with various hematological malignancies transplanted 1993-2006 using a myeloablative preparative regimen and a single HPC-C unit. The applicant concluded that subjects who received 1-2 antigen mismatched transplants that were NIMA matched had faster engraftment than those with no NIMA match (RR 1.3, p=0.04).

A fourth analysis evaluated the effect of duration of cryopreservation (< 2 yrs vs >8 yrs) on neutrophil recovery in 343 subjects with various diagnoses transplanted 2001-2006. The applicant concluded that there was no difference in time to neutrophil recovery between the two

groups (RR 0.8, p=0.31), and no difference in the rates of neutrophil recovery (80.5% vs 73.3%, p=0.35).

7.5.1.3 FDA Analyses of Graft Failure

FDA was unable to verify the analyses provided by the applicant, since the subjects for each analysis were not identified in the dataset. FDA performed an analysis of hematopoietic recovery on the entire safety population and on the subset of subjects who received a unit manufactured with Method #4 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 29. The primary graft failure rate was 15% for the subset of patients who received a suitable allograft.

Table 29: FDA Analysis of Graft Failure – Applicant's Dataset

	All Subjects Transplanted		**Subjects with a Suitable Allograft***	
	N		N	
Primary graft failure (%, 95% CI)+	2363	19% (17-21%)	150	15% (9-21%)

* Those who received a unit manufactured with Method #4 and having a TNC dose >2.5 x 10^7/kg
+ Including death, 2nd transplantation or autologous recovery for patients surviving at least 14 days without neutrophil recovery

7.5.1.4 Hematopoietic Recovery – Additional Analyses

Graft failure in the applicant's dataset was also assessed by TNC dose and degree of HLA mismatch. Table 30 shows the incidence of primary graft failure for 125 subjects with hematologic malignancy who received a suitable allograft. Graft failure rates for the same population in the docket dataset are provided for comparison. The only cell where the graft failure rate exceeded that in the docket dataset is for patients with a 5/6 match receiving ≥10 x 10^7 TNC/kg (40% vs 9.0%). However, the numbers of subjects is small, and the difference is not significant by Fisher's exact test (p=0.09).

Table 30: Incidence of Graft Failure by HLA Mismatch for Hematologic Malignancies

	TNC Dose (x 10^7/kg)		
HLA Match	**2.5 - <5**	**5 - <10**	**≥10**
4	7/45 (15.6%) (Docket - 21.4%)	2/19 (10.5%) (Docket - 15.2%)	0/4 (0.0%) (Docket - 9.0%)
5	5/31 (16.1%) (Docket - 16.1%)	3/16 (18.8%) (Docket - 18.7%)	***2/5 (40.0%)*** ***(Docket – 9.0%)***
6	0/4 (0.0%) (Docket - 18.4%)	0/1 (0.0%) (Docket - 2.9%)	-

Delayed Neutrophil Recovery: There were 106 subjects with hematological malignancies who received a suitable allograft and achieved neutrophil recovery. The expected upper 95% confidence intervals were calculated for each subject in the applicant's dataset using the model

built on the pooled docket dataset. Two (1.9%) of the 106 subjects had an actual time to neutrophil recovery that exceeded the upper 95% limit.

Reviewer Comment: The primary graft failure rate (15%) for the applicant's product falls within the 95% confidence interval for the docket data, and the graft failure rates broken out by TNC dose and HLA match have no apparent differences from those calculated for the docket data. The median time to neutrophil recovery and the cumulative incidence of neutrophil recovery by day 42 are also not worse than those reported for the pooled dataset from the docket. Further, application of the model for the upper limit of the expected time to neutrophil recovery shows only <2% of the subjects with longer times than expected within the 95% confidence interval. These results raise no additional safety concerns for Hemacord regarding graft failure.

7.5.2 Acute Graft-vs-Host Disease

7.5.2.1 Docket Review – Acute GVHD (Appendix 9.6)

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

7.5.2.2 Analysis of Acute GVHD

The applicant provided no analysis of acute GVHD for their product. Available data included only the maximum grade of acute GVHD that occurred and the date of onset of any grade of acute GVHD. The dataset listed 2326 patients with GVHD outcomes, 1286 (55%) of whom developed acute GVHD (grades are available for 1911 patients and 364 are not evaluable due to early death). The dataset included 141 patients with GVHD outcomes who had received a suitable graft, 89 (63%) of whom developed acute GVHD (grades are available for 116 patients and 20 were not evaluable). The results are shown in Table 31.

Table 31: FDA Analysis of GVHD – Applicant's Dataset

	All Subjects N (%)	**Subjects with a Suitable Allograft* N (%)**
Maximum grade 0	676 (30%)	32 (24%)
1	378 (17%)	26 (19%)
2	423 (19%)	31 (23%)
3	259 (11%)	19 (14%)
4	175 (8%)	8 (6%)
Not evaluable	364 (16%)	20 (15%)

* Those who received a unit manufactured with Method #4 and having a TNC dose $\geq 2.5 \times 10^7$/kg

For the subset of patients who received a suitable allograft, 43% developed grades 2-4 GVHD, and 20% developed grades 3-4 GVHD. The proportions of patients by grade within this subset did not differ substantially from the whole group of patients for whom information is available.

Reviewer Comment: The interpretation of the data on GVHD is limited by the fact that only the proportion of patients with GVHD rather than the cumulative incidence could be calculated. How competing risks would alter the estimates in unknown. Moreover, there is a substantial amount of missing data, further raising a question about the accuracy of the information. However, the risk of GVHD itself is clear, and with these caveats described, the potential for GVHD to occur should be included in the labeling.

It is noteworthy that the proportion of patients with moderate-to-severe GVHD does not increase at the higher TNC doses in the docket dataset analysis, as this will preserve the benefit of use of those higher doses without the added risk of GVHD. This conclusion, however, is applicable only to the dose range reported in the dataset.

7.5.3 Engraftment Syndrome (ES)

From the Docket Review (Appendix 9.6), ES was reported in 14.7% (11.7-18.0%) of the patients in the COBLT study. Median time to onset of the event was 10 days after transplantation (range, 5-35 days). In literature reports, the incidence of ES varies from 30% to 78%. The applicant provided no information on the occurrence of engraftment syndrome. There are no instances of engraftment syndrome listed as cause of death.

Reviewer Comment: Labeling should include the risk of engraftment syndrome.

7.5.4 Malignancies of Donor Origin

From the Docket Review (Appendix 9.6), the risk of donor cell leukemia, myelodysplastic syndrome and myeloproliferative disorders after HPC-C transplantation was estimated as 9/10,000. The applicant reported that no leukemia of donor origin was reported to the bank. EBV-related lymphoproliferative disorder (PTLD), presumed to be of donor origin, was reported as the cause of death for 17 patients (0.6% of patients with follow-up information).

Reviewer Comment: The risk of donor-derived EBV-PTLD appears to be largely related to treatment factors rather than being an inherent risk of the product. Donor cell leukemia, however, has no apparent relation to other factors. The risk of donor cell leukemia should be included in the labeling.

7.5.5 Transmission of Serious Infection

From the Docket Review (Appendix 9.6), the risk of transmission of serious infection is 1/10,000 based on a single case report. However, in vitro testing suggested that 0.6% of units may be positive for HHV-6, and 0.15% of units from CMV-seronegative donors may be positive for CMV. The applicant reported that no cases of transmission of infection were reported to the bank.

Reviewer Comment: Labeling should include the risk of transmission of serious infection.

7.5.6 Transmission of Rare Genetic Disorders

There are no reported cases of transmission of a rare genetic disorder by HPC-C transplantation in the docket or in the literature (Appendix 9.6). The applicant reported that no cases of transmission of a genetic disease were reported to the bank. FDA review of the serious adverse event reports revealed one case of an HPC-C unit from a donor with an inherited immunodeficiency disease being transplanted (see Section 7.4.2 Case 2 above).

Reviewer Comment: Although the system for collection of post-donation information that the applicant has put into place limits the risk of transmission of genetic disorders, the possibility that this may occur should be included in the labeling.

7.6 Additional Safety Evaluations

7.6.1 Overdosage

7.6.1.1 Docket Review- Overdosage (Appendix 9.6)

The three major components of HPC-C that may contribute to clinical overdosage include the cell content, Dextran 40 and DMSO. The literature provides no reports on overdosage due to an excessive number of nucleated cells infused for either HPC-C or other HPC types; the upper limit of the tolerable cell dose range has not been established. Additionally, there are no reports of overdosage from Dextran 40. There are two reports of overdosage with DMSO, one with direct infusion of DMSO (approximately 1.5 gm/kg/day intravenously for 2 days)[28] and one with DMSO in an autologous blood HPC-A infusion (approximately 3.2 gm/kg over 10 hours).[29] There were no reports in the literature of a DMSO overdose related to HPC-C transplantation. The published experience suggests that doses of DMSO up to 1 gm/kg/day are safe.

7.6.1.2 Applicant's Data - Overdose

The applicant did not address overdosage. The maximum TNC dose administered was 71.1 x 10^6/kg for all patients and 57.6 x 10^6/kg for the subset of subjects who received a unit manufactured with Method #4 and having a TNC dose $\geq$2.5 x 10^7/kg. In the exploratory analyses described in Section 7.4.1.3, there were no correlations between TNC dose and early deaths or infusion reactions. Of the SAEs reported in Section 7.4.2, none had a TNC dose >9 x 10^7/kg, but 20% of the patients had received a TNC dose >9 x 10^7/kg. There is no evidence that a serious toxicity would be predicted for any of the TNC doses within the range reported by the applicant. Post-thaw information is not provided, so the maximum amount of DMSO infused could not be calculated.

Reviewer Comment: Labeling should reflect the upper limit of DMSO for safe use.

8 Postmarket Experience

The applicant provided information on 3946 units released for transplantation 8/1993 – 1/2011. These included 2621 (66%) units used in the US and 1325 (34%) units used for transplantation in 38 foreign countries. The safety information available for these units is provided in Section 7.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

The major recommendations for labeling resulting from this review are:

- Include a black box warning for fatal infusion reactions.
- Include in the instructions for dosage a minimum TNC dose of 2.5 x 10^7 /kg at cryopreservation for units with at least 4 of 6 antigens matching for HLA-A,-B and –DRB1.
- Include in the instructions for administration the recommendations for prehydration, premedication, peri-infusion monitoring, and discontinuation of the infusion if an allergic reaction occurs or if the volume load is not tolerated.
- Specify infusion rates for adults and children separately.
- Include a contraindication for those who are allergic to DMSO, Dextran 40 or other components in the preparation for infusion.
- Include warning and precautions that address allergic reactions and anaphylaxis, infusion reactions, graft versus host disease, engraftment syndrome, graft failure, malignancies of donor origin, transmission of serious infection, and transmission of rare genetic disease.
- Identify the most common infusion reactions (>5%) and the rates of serious cardiopulmonary reactions for both The COBLT Study and Hemacord. Highlight the increased risk of grades 3-4 infusion reactions and hypertension in pediatric patients and with large volumes of infusate.
- Include data on hematopoietic recovery for both The COBLT Study and Hemacord.
- Include a precaution regarding the maximum dose of DMSO, a description of the clinical manifestations of DMSO overdosage, and management of DMSO overdosage.
- Include instructions for patient counseling regarding infusion reactions and GVHD.

9.3 Advisory Committee Meeting

BLA 125397 was discussed at the Cellular, Tissue and Gene Therapies Advisory Committee Meeting held September 22, 2011. The committee was asked to provide advice on the safety and efficacy of Hemacord. The following observations and recommendations were made by the committee:

The literature review provided supports the efficacy of unrelated donor HPC-C transplantation for the treatment of acute leukemias, and the indication should be expanded to all hematological malignancies for which unrelated donor HPC transplantation is already established as effective.

HPC transplantation is an established treatment option for patients with Hurler Syndrome, Krabbe Disease and X-Linked Adrenoleukodystrophy, and use of unrelated donor HPC-C has an acceptable risk benefit when better donors are not available within the needed timeframe for treatment.

HPC transplantation is an established treatment for severe combined immunodeficiency disorders (SCID), and transplantation using unrelated donor HPC-C is an acceptable alternative. Extrapolating from SCID to other immunodeficiencies requires caution, but unrelated donor HPC-C transplantation should be an option in the other immunodeficiencies where HPC transplantation is otherwise established as effective.

Unrelated donor HPC-C transplantation should be available for treatment of patients with beta thalassemia major when conventional treatment, such as transfusion therapy and chelation, are ineffective, unavailable or resulting in a poor quality of life. The total nucleated cell dose available should be taken into consideration as well.

For Fanconi Anemia, transplantation of HPC-M would be the preferred choice, but unrelated donor HPC-C transplantation should be considered for disease states where there is no other donor available and the benefit outweighs the risk of graft failure. Similarly, for aplastic anemia, therapy with HPC transplantation should be considered for those who fail immunosuppression, and HPC-M from a related donor is the HPC of choice, but HPC-C should be considered when no such donor is available. There is insufficient information about the other marrow failure disorders individually, but the efficacy in hematopoietic reconstitution could be extrapolated from that for aplastic anemia, so unrelated donor HPC-C should be an option when a matched related donor is not available and the disease status warrants HPC transplantation.

The minimum cell dose of (2.5×10^7/kg) and minimum degree of HLA matching (at least a 4 of 6 match) should be including in the labeling. It is likely that a higher minimum dose is needed for some of the diseases, but that is an evolving area, so specific recommendations could not be made.

The safety concerns that should be addressed in labeling include early mortality, graft failure, delayed neutrophil recovery and GVHD. Warning should be issued about the risk of infection and transmissible diseases, and specifying the infusion rate and volume of DMSO. There should

be guidance for thawing and washing, expected viability of the cells, assessment of enzyme activity when treating a patient with an inherited metabolic disorder, assessment of container integrity, and assuring unit identification. HPC-C should be used only by physicians who do transplantations regularly and are familiar with the procedure.

Mathematical models for graft failure and early mortality based on the docket data could be used to assess the safety of Hemacord. The limitations of such models include the heterogeneity of the population, the relatively small number of patients with diseases other than hematological malignancies, and the lack of other relevant baseline information, such as the comorbidity index, in the dataset.

9.4 Efficacy Review (Oncology) – Dockets and Public Information

9.5 Efficacy Review (Non-Oncology) – Dockets and Public Information

9.6 Safety Review – Dockets and Public Information