CLINICAL AND STATISTICAL JOINT REVIEW

Application Type	Original
Application Number	BLA 125391
Priority or Standard	Standard
Submit Date	April 29, 2011
Received Date	May 2, 2011
PDUFA Goal Date	June 2, 2012
Review Completion Date	May 23, 2012
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Established Name	Hematopoietic Progenitor Cells – Cord Blood (HPC-C)
Proposed Trade Name	Not provided
Therapeutic Class	Allogeneic cord blood hematopoietic progenitor cell therapy
Applicant	ClinImmune Labs, University of Colorado Cord Blood Bank (UCCBB)
Formulation(s)	Intravenous
Dosing Regimen	Recommended minimum dose is 2.5×10^7 nucleated cells/kg cryopreserved given by intravenous infusion
Indication(s)	For use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

TABLE OF CONTENTS

Table of Tables

Table of Figures

1 Recommendations/Risk-Benefit Assessment

1.1 Recommendation on Regulatory Action

The reviewers recommend approval of Hematopoietic Progenitor Cells-Cord (HPC-C) manufactured by ClinImmune Labs as a source of hematopoietic progenitor cells for hematopoietic and immunologic reconstitution. HPC-C can be used in unrelated donor transplantation procedures in conjunction with an appropriate preparative regimen in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

The risk-benefit assessment for an individual patient depends on the patient characteristics, including the disease, specific stage and manifestations of the disease, risk factors, characteristics of the graft, and on the availability of other types of hematopoietic progenitor cells.

1.2 Risk-Benefit Assessment

The applicant submitted its own clinical data and referenced data in the dockets FDA-1997-N-0010 and FDA-2006-D-0157 to support its BLA application. The risk-benefit analysis to support the indications listed in Section 1.1 is mainly based on the data submitted by the applicant in the BLA, the docket data, and other information in the public domain, including the COBLT study dataset. The clinical review of the data in the BLA is compared to the docket data in evaluating the relative safety and efficacy of ClinImmune product.

The clinical data demonstrated that transplantation of HPC-C manufactured by ClinImmune Labs, resulted in hematopoietic reconstitution. In 293 patients transplanted for various disorders affecting the hematopoietic system, the cumulative incidence of neutrophil recovery defined as absolute neutrophil count > 500 / mm^3 by Day 42 was 78%, similar to that demonstrated in the pooled docket dataset (77%) and in the Cord Blood Transplantation (COBLT) study (76%). In 54 patients with available data on platelet engraftment, 61% (33/54) patients have reached the platelet count > 20,000 / mm^3 by Day 100.

The data submitted by the applicant did not include information for evaluation of immune reconstitution. Reviews of data in the dockets and of published data demonstrated that immune reconstitution occurs after HPC-C transplantation (see Appendices 9.2 and 9.3) for patients with primary immunodeficiencies as well as for other malignant diseases. For example, HPC-C transplantation improved survival in severe combine immunodeficiency disorders (SCID), which otherwise carry extremely high mortality[1]. Survival of 47 patient with SCID for whom data were available in the docket datasets is about 65% by the end of the first year after HPC-C

[1] Hitzig WH and AB Kenny 1978. Inheritance, incidence and epidemiology of severe combined immunodeficiency syndromes. In: International Symposium on Immunodeficiency (1976), pp. 257-270, University Park Press: Baltimore.

transplantation; mortality is low thereafter (See Appendices 9.4). We rely on these data to support the claim that HPC-C transplantation can lead to immunologic reconstitution when treating primary immunodeficiencies.

The submitted data include only disease diagnosis, but do not include clinical outcomes for each disease or condition for which cord blood transplantations were performed. Therefore disease-specific risk and benefit analysis cannot be performed based on data in this BLA application. Reviews of docket data and published information indicate that successful hematopoietic reconstitution after transplantation with hematopoietic progenitor cells has been demonstrated to be a potential curative treatment for hematological malignant diseases and for primary immunodeficiencies. However, the clinical outcomes and risk-benefit assessment of HPC-C transplantation in inborn errors of metabolism or other genetic disease such as hemoglobin disorders remain uncertain. Engrafted hematopoietic cells may function as "normal cells" to replace those in patients with conditions where hemoglobin or enzymes are either structurally abnormal or missing due to genetic mutations. Currently marketed enzyme replacement therapies through intravenous infusion of these enzymes cannot reach the central nervous system, an important limitation in the treatment of Hurler Syndrome or other enzyme deficiencies. A potential benefit of HPC-C is that the engrafted cells of hematopoietic origin "home" to a few tissues and organs, including the central nervous system. However the clinical benefits resulting from partial correction or replacement of enzyme activity need further investigation for determination of the magnitude of clinical benefits. Furthermore, the timing of transplantation may also play a key role at different stages of certain progressive conditions.

While transplantation for hematopoietic and immunological reconstitution presents as a potential life-saving treatment for certain diseases, the risks are substantial. The risks associated with HPC-C include death, infusion reaction, graft versus host disease (GVHD), engraftment syndrome, infusion reactions and potential transmission of malignancy, infection or a genetic disorder from the donor to the recipient. The risk-benefit assessment for an individual patient depends on the disease characteristics and its specific manifestations, including disease stage, risk factors of the disease versus risks from those of the transplantation procedures, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

We do not recommend any Risk Evaluation and Mitigation Strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

We do not recommend any Postmarket Requirements or Commitments.

2 Introduction and Regulatory Background

Identification of hematopoietic stems cell in human umbilical cord blood (HPC-C) was first reported by Knudtzon in 1974[2]. Further *in vitro* studies[3],[4] established the transplant potential of cord blood. Comparative work *in vitro* concerning the reconstituting cellular contents of cord blood and bone marrow showed that the number of hematopoietic progenitors present in umbilical cord blood is within the range of bone marrow[5]. The use of HPC-C as a source of hematopoietic stem cells transplantation was tested in an animal model in 1984 by Dr. Boyse's laboratory. In 1989, Gluckman et al. reported the first successful hematopoietic reconstitution after HPC-C transplantation from an HLA-matched sibling donor in a child with Fanconi anemia[6]. In 1996, Kurtzburg at al[7] and Wagner et al[8] published data from the first transplants using HPC-C from unrelated donors. Since then, the number of HPC-C transplants for patients with malignant and non-malignant disorders has grown. More than 10,000 unrelated-donor cord blood stem cell transplants for a variety of hematological malignancies, immunologic disorders, and inborn errors of metabolism have been performed to date[9,10]. HPC-C has several potential advantages over bone marrow. These include the ready availability of cord blood units and increased tolerance of HLA disparity in terms of successful engraftment and risk of graft versus host disease (as compared to adult donor bone marrow or apheresis). The major limitation of HPC-C is the limited number of hematopoietic progenitor cells in each unit and the resultant delays in time to engraftment.

On November 10, 2011, FDA approved HPC-C manufactured by New York Blood Center for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

The purpose of this review is to provide an assessment of the safety and efficacy of minimally manipulated, unrelated donor, cord blood hematopoietic progenitor cells manufactured by ClinImmune Labs, and to evaluate whether or not HPC-C manufactured by ClinImmune Labs, can be used as an alternative source of hematopoietic progenitor cells for transplantation. The

[2] Knudtzon S et al. In vitro growth of granulocytic colonies from circulating cells in unman cord blood. Blood 1974;43(3):357-361
[3] Nakahata T et al. Hemopoietic colony-forming cells in umbilical cord blood with extensive capability to generate mono-and multi-potential hemopoietic progenitors. J Clin Invest. 1982 Dec;70(6):1324-8
[4] Leary AG et al. Single cell origin of multilineage colonies in culture. Evidence that differentiation of multipotent progenitors and restriction of proliferative potential of monopotent progenitors are stochastic processes. J Clin Invest. 1984 Dec;74(6):2193-7.
[5] Boyse EA et al. Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells. Proc Natl Acad Sci U S A. 1989 May;86(10):3828-32.
[6] Gluckman E et al. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. N Engl J Med 1989; 321:1174-1178
[7] Kurtzberg J et al. Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. N Engl J Med 1996; 335:157-166
[8] Wagner JE et al. Successful transplantation of HLA-matched and HLA-mismatched umbilical cord blood from unrelated donors: analysis of engraftment and acute graft-versus-host disease. Blood 1996;88:795-802
[9] American Academy of pediatrics: Cord Blood Banking for potential future transplantation. Pediatrics 2007: 119, 1: 165-170
[10] Gracia J Trahsfu Apher Sci 2010;42:275-263

efficacy review focused solely on hematopoietic reconstitution. The safety review focused primarily on transplantation-related adverse events, including allergic reactions, anaphylaxis and other infusion reactions, death within 100 days after HPC-C transplantation, graft versus host disease and engraftment syndrome.

2.1 Product Information

Established Name: Hematopoietic Progenitor Cells-Cord

Proposed Trade Name: None

Therapeutic Class: Somatic Cell

Applicant: ClinImmune Labs

Applicant's Proposed Indication and Intended Use: For use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

Dose and Regimen: not provided.

Product Description: Hematopoietic Progenitor Cells, Cord Blood Units (HPC-C) manufactured and issued by the ClinImmune Labs, University of Colorado Cord Blood Bank are minimally manipulated human cord blood cells that contain live human cord blood cells after volume reduction and partial red cell and plasma depletion using the ----------(b)(4)---------- methods. Cord blood collection is performed in-utero, before the placenta delivery in the hospital's labor and delivery area. After collection, the bag is transported at controlled ----------(b)(4)---------- to the bank for processing and cryopreservation, the final cell suspension ((b)(4)) is cryopreserved by addition of ---(b)(4)--- DSMO in (b)(4) Dextran 40, so that the final concentration of DMSO is 10% and that of Dextran 40 is 1%. The final product is taken to the permanent storage facility and stored at $\leq$ -150^{0}C after all release criteria are met.

The label of each individual HPC-C unit manufactured by ClinImmune Labs, provides information about the total nucleated cells, post-processing viability, and number of viable CD34+ cells contained in the unit. The minimum nucleated cell content is $5x10^8$ cells per unit.

2.2 Currently Available Treatments for Proposed Indications

There are several stem cell sources for allogeneic hematopoietic stem cell transplantation, including hematopoietic progenitor cells from bone marrow (HPC-M) or peripheral blood apheresis (HPC-A) from related or unrelated donors. The choice of HPC source for allogeneic

transplantation is individualized for each recipient as it will depend on donor availability, HLA-matching, and risk-benefit assessment.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient in the HPC-C manufactured by ClinImmune labs is the cells derived from umbilical cord blood from allogeneic sources. HemaCord is an HPC-C manufactured by the National Cord Blood Program (NCBP) of the New York Blood Center (NYBC), and has been licensed in the US for use for the same indication proposed in the current application.

2.4 Summary of Pre-submission Regulatory Activity Related to Submission

A Pre-BLA meeting was held on June 14, 2010 between the FDA and the representatives from ClinImmune Labs.

2.5 Other Relevant Background Information

On January 20, 1998, FDA issued a notice in the Federal Register (63 FR 2985) 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) was convened on February 27, 2003, to discuss issues related to the use of unrelated allogeneic hematopoietic stem/progenitor cells derived from placental/umbilical cord blood for hematopoietic reconstitution, including the analysis of clinical outcome data submitted to the public docket. On the basis of the assessment of submitted information, discussion of the BRMAC, and review of published literature on this subject, the FDA determined that the data were sufficient to provide recommendations for establishment and processing controls and product characteristics for these products and to establish the safety and effectiveness of HPC-Cs for allogeneic transplantation in the treatment of hematologic malignancies.

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

In a Federal Register notice of October 20, 2009 (74 FR 53753), FDA announced the availability of the "Guidance for Industry - Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications". In this notice of availability, the FDA also announced that it would end the period of phased-in implementation of IND and BLA requirements for HPC-C. This announcement established a two-year implementation period, which ended October 20, 2011, by which all distribution of HPC-C for clinical use in the United States would need to be done under an approved BLA or active IND.

The applicant's original BLA submission proposed an indication statement consistent with the "Guidance for Industry - Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications" However, after consideration of the proceedings of the meeting of the Cellular, Tissue, and Gene Therapy Advisory Committee, the applicant revised the proposed indication statement with the following: For use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

2.6 Pediatric Issues

HemaCord, HPC-C manufactured and issued by the National Cord Blood Program (NCBP) of the New Your Blood Center (NYBC), received approval from the Pediatric Regulatory Committee (PeRC). The current BLA has the same formulation, active ingredient, dosing regimen, dosage and router of administration and the same clinical indications as the ones for HemaCord and therefore does not trigger PREA.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

BLA B125391 was an electronic submission received on 05/02/2011. With the submission of amendment 1, the application was complete and filed on 07/01/2011.

The datasets were submitted in an Excel format, which include outcome information submitted to the Stem Cell Therapeutic Outcomes Database (SCTOD) by individual transplantation centers. Overall, the applicant's data quality and the data tracking and recording system are of concern. The reviewers have had multiple communications with the applicant in order to obtain the missing data and clarify data inconsistencies. The major issues related to the datasets include the following (also see the data analysis in Sections 6 and 7 for details):

Incompleteness

The datasets include outcome information consisting of neutrophil and platelet engraftment information, transplantation-related complications, and mortality. However, the datasets lack information on diagnostic criteria for each different condition being treated with cord blood transplantation and patient status at the time of transplantation and disease-specific outcomes. The datasets are not accompanied by case report forms for deaths or for follow-up information on the survivors.

Data discrepancies

The reviewers found many examples of data discrepancies. For example, some recipients were shown as alive at a certain date in one dataset while they were recorded as dead a few months/years earlier in another dataset. The review team discussed these cases with the applicant, and the applicant corrected most of these discrepancies. The few remaining unclear cases were excluded from data analysis in this review.

Considering the voluntary nature of the data collection, the review team considers the data collected and reported as being sufficient for review.

Missing data

As summarized in Table 1, in each outcome category, there is a significant percentage of patients with missing or unknown information, i.e., nearly 40% of hematopoietic recovery information was not reported and only a small proportion (<20%) of infusions containing infusion reaction information were reported. Missing data are big issues for some of the key analyses.

The applicant submitted safety data on 457 /499 (90 %) (Table 1) of patients with information on cord blood characteristics: HLA matching and the number of units received by each patient: 431 patients received one unit of the product (94.3%) and 26 patients (5.7%) received multiple units of the HPC-C manufacturing by ClinImmune labs. If a patient received multiple units on the same date that counted as one infusion unit but the dose received by the patient reflected the combined actual number of total nucleated cell (TNC).

Table 1: Safety and Efficacy Outcomes Dataset – Cord Blood Unit Characteristics

Data file subset	**Number of Patients**
Submitted data file	499 Patients with 542 units
Restricted to records with transplantation date	462 Patients with 499 units
Limited to units manufactured using processing methods #1-(b)(4)- or #3 -(b)(4)-	462 Patients with 498 units
Limited to records with TNC dose reported	460 Patients with 496 units
Limited to records with HLA matching information	459 Patients with 495 units
Limited to records with either age or gender information	457 Patients with 493 units
If a patient had multiple units on the same day, the multiple units were combined to one infusion with the TNC doses summed up.	457 Patients with 465 infusions
All the records for units were used for hematopoietic reconstitution (TNC count) and include allograft information (HLA matching).	
Subsets in this step are used for analysis of infusion reactions	
Limited to units with infusion reaction data	71 Patients with 71 infusions
Limited to TNC dose $\geq 2.5x10^7$/kg	47 Patients with 47 infusions
Subsets in this step are used for analysis of death	
If a patient had multiple infusions on different days, only one of it was counted	457 Patients with infusions
Limited to patients with survival information reported	313 patients
Limited to TNC dose $\geq 2.5x10^7$/kg	241 patients
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	293 patients
Limited to TNC dose $\geq 2.5x10^7$/kg	226 patients

3.2 Compliance with Good Clinical Practices

Compliance with GCP cannot be evaluated from the datasets provided by the ClinImmune Labs. No clinical trials were conducted or submitted by the applicant.
The applicant submitted informed consent forms for the following five centers were collection was performed: Exempla St. Joseph's Hospital, Denver Health Medical Center Hospital, Maricopa Medical Center, St. Joseph's Hospital and Medical Center, Phoenix Baptist Hospital. Every consent form was approved by IRB but no clinical protocols were submitted.

3.3 Financial Disclosures

No financial disclosures were submitted by the applicant. The applicant cited the data in the docket to support this application, so the application does not rely on clinical trial data. Consequently, there are no financial disclosures submitted with the application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

4.1.1 Collection Procedures

The collection of HPC-C was performed at five sites: Exempla St. Joseph's Hospital, Denver Health Medical Center Hospital, Maricopa Medical Center, St. Joseph's Hospital and Medical Center, Phoenix Baptist Hospital. The collection was also performed from non-fixed (remote) sites statewide.

The applicant prepares the collection kits and sends them to the collection sites. The applicant trains and qualifies staff to perform aseptic in-situ (in utero) gravity collection, to consent and obtain donor medical history screening documentation.

All collections are performed prior to the delivery of the placenta (in-utero) regardless of vaginal delivery or cesarean section. The collection staff checks the donor ID, disinfects the umbilical cord, inserts the needle and drains the cord blood to the collection bag.

.The collected Cord Blood Units (CBUs) are shipped to ClinImmune for processing.

All the collection SOPs submitted by the applicant were reviewed and found to be acceptable.

4.1.2. Product information

4.1.2.1 Manufacturing procedures

The applicant has used two manufacturing methods ----------(b)(4)---------- for manufacturing HPC-C units. The applicant has requested licensure for all the units obtained using both manufacturing processes.

4.1.2.2. Preparation for infusion

The HPC-C units manufactured by ClinImmune Labs, are cryopreserved in 10% DMSO with 1% Dextran 40. The applicant provides thawing and washing instructions with the HPC-C unit that is shipped to a transplant center. The thawed Cord Blood Unit (CBU) is washed using 2X of the CBU volume of the washing solution consisting of 50% (vol/vol) of 5% human serum albumin and 50% of 10% Dextran 40. The washed CBU is re-suspended in the mixture of 5% human serum albumin and 10% Dextran for infusion.

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 were required. No preclinical pharmacology/toxicology studies were conducted with HPC-C manufactured by ClinImmune Labs, due to the minimal manipulation of the HPC-Cs and the previous human experience with HPC-Cs. Please see preclinical review memo.

DMSO represents a potentially toxic component of HPC-C. Published studies report teratogenic responses were caused by intraperitoneal administration of DMSO to rodents, and intravenous administration of DMSO to rodents caused hemolysis.

4.3 Pharmacovigilance

4.3.1 Outcomes Analysis

The applicant collects clinical outcome data and routinely reviews the safety data

Operational procedures to relational databases Cord Blood Bank Manager (CBBM) and Cord Blood Outcomes Manager (CBOM) are detailed in SOP E8.110.5. The CBBM database provides cord blood unit information to CBOM. Data from both databases are integrated and accessed simultaneously in CBBM queries for outcome analyses.

SOP#E8.100 adequately describes the procedures in place for periodic analysis of safety outcomes: product expiration dating, outcome documentation analysis, reporting of released CB unit thaw yield, infusion dose, engraftment, adverse events, survival rate, and GVHD follow-up.

4.3.2 Adverse Event Reporting

SOP B5.400.5 "Quality process improvement" 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.

5 Sources of Clinical Data

5.1 Tables of Studies / Clinical Trials

No clinical trials were conducted by the applicant. The outcome data were reported to the Stem Cell Therapeutic Outcomes Database (SCTOD) by the individual transplantation center. There were no SAE reports to the applicant. There was no case report form for each individual patient, so that the information submitted by the applicant cannot be further validated. There were no protocols describing patient selection or the analysis plan for clinical outcomes. The applicant referred to the docket data for support of its product's evidence of efficacy and safety. The key materials used in this review are the data provided by the applicant including:

- BLA 125391/0 submission
- Amendments to the original submission:
    - 125391/1 received June 28, 2011
    - 125391/2 received September 17, 2011
    - 125391/3 received December 14, 2011
    - 125391/4 received January 31, 2012
    - 125391/5 received March 9, 2012

In addition, the applicant has cited Docket 1997N-0497 for the efficacy information to support this application. To augment this review, the FDA reviews of the docket information and public information are referenced, which include the following Appendices:

- Safety Review of Dockets and Public Information (Appendix 9.2), including the following data:
    - Dataset for The COBLT Study (Available from the National Heart, Lung, and Blood Institute (NHLBI) via its data-sharing portal at https:/biolincc.nhlbi.nih.gov/home/)
    - Docket FDA- 1997- N- 0010 (Legacy Docket number 97N- 0497)
    - Docket FDA- 2006- D- 0157 (Legacy Docket number 06D- 0514)
    - Relevant literature and datasets available in the public domain
- Efficacy Review (Oncology) – Docket and Public Information (Appendix 9.3)
- Efficacy Review (Non-Oncology) – Docket and Public Information (Appendix 9.4).

5.2 Review Strategy

5.2.1. Scope of Efficacy Review

Due to the limitation of available data, demonstration of efficacy relies on the product's ability to reconstitute the hematopoietic system, as demonstrated by neutrophil and platelet engraftments. Immunologic reconstitution and reconstitution of erythrocytes rely on the reviews of the docket information and publications (Appendices 9.2, 9.3 and 9.4). This review is not intended to assess clinical benefits for any specific disease or condition; disease-specific risk-benefit analyses are addressed in the docket review and review of publications (Appendices 9.2, 9.3, and 9.4).

5.2.2 Scope of Safety Review

The safety review was based primarily on the outcome dataset submitted by the applicant. The safety review was focused on the adverse events that are primarily transplantation-related, including allergic reactions and anaphylaxis, infusion reactions, death within the first 100 days after transplantation (100-day death), Graft Versus Host Disease (GVHD), engraftment syndrome, malignancies of donor origin, and transmission of serious infections and genetic diseases.

5.2.3 Controls

The data provided by the applicant reflect essentially only uncontrolled experience with HPC-C transplantation. The reviews of outcome analysis of the docket and publications (Appendices 9.2, 9.3 and 9.4) serve as references in evaluating the incidences of hematopoietic reconstitution for the efficacy review (see Section 6) and transplantation-related adverse events for the safety review (see Section 7).

5.2.4 Statistical Considerations

Methodologies used in this review are primarily descriptive. This review does not intend to replicate the applicant's statistical analyses because slightly different datasets were used to report results in this review memo (see Table 1). In addition, for the analysis of hematopoietic recovery, the competing risk model treating death as a competing risk was used in this review, while the applicant excluded from the analysis those patients who died

6 Review of Efficacy

6.1 Efficacy Summary

The efficacy analyses assessed the ability of HPC-C manufactured by ClinImmune Labs, to reconstitute the hematopoietic system. In 293 patients transplanted with HPC-C manufactured by ClinImmune Labs, for various disorders, the cumulative incidence of neutrophil recovery by Day 42 was 78%, similar to that seen in the pooled docket dataset (77%) and in the COBLT

study (76%). The proportion of neutrophil recovery varies with HLA match status, TNC dose, and underlying conditions. In addition, 61% of 54 patients reached the clinically meaningful platelet count > 20,000 / mm^3 by Day 100.

The data submitted by the applicant included only diagnosis of the disease, but did not include disease status: stage, refractoriness to prior treatment, prognostic markers, and clinical outcomes for each disease or condition following transplantation, so that no disease-specific risk and benefit analysis was performed.

6.2 Hematopoietic Reconstitution

Of 457 transplanted patients whose clinical data were submitted in this BLA, 293 patients have available data for neutrophil engraftment analysis (see Table 4).

The data analyses were performed for all 293 patients as a group, with separate analyses in patients with vs. without a suitable allograft. A suitable allograft is defined as HPC-C with a total nucleated cells (TNC) dose ≥2.5 x 10^7/kg and HLA match 4/6 or more. Patients who have received HPC-C transplantation either at a TNC dose < 2.5 x 10^7/kg or HLA match 3/6 or less were considered not to have a suitable allograft.

Demographics and Diagnoses

As demonstrated in Table 2, a majority (220/293) of patients received transplantation with a suitable allograft. At the time of transplantation for these 220 patients, the median age was 6.9 years with 52/220 being younger than 2 years. One potential advantage in the use of cord blood is the ready availability of compatible units, which is especially important for treating diseases with a rapidly progressive clinical course. Of 293 patients, 169 were male and 122 were female (2 had missing gender information). The information on ethnic background is largely missing (248/293, 85%). Among the remaining 45 patients (45/293, 15%), the majority (33/45 or 73%) were Caucasian.

Seventy three (73) patients received transplantation with a non-suitable allograft. These patients were older, with a median age of 36.4 years. For the majority of these patients (67/73), the allograft was non-suitable because of a lower dose of TNC (<2.5 x 10^7/kg), because of a limited volume of cord blood. Thus, the majority of patients with a suitable allograft were in the pediatric population.

HPC-C manufactured by ClinImmune Labs,, transplantation was performed for various clinical indications, as presented in Table 2. The majority of patients were transplanted for treatment of a variety of hematological malignant diseases (214/293), followed by bone marrow failure (42/293); primary immunodeficiency (14/293) due to genetic defect or deficiency in immune system; inborn errors of metabolism, mainly including Hurler syndrome, Krabbe disease, and X-linked adrenoleukodystrophy; and hemoglobinopathies, including sickle cell disease and beta-thalassemia.

Table 2: Hematopoietic Recovery Dataset – Demographics and Diagnoses

Patient Characteristics	All Patients Transplanted (N=293)	Patients with a Suitable Allograft* (N=220)	Patients without a Suitable Allograft** (N=73)
Median Age (Range)	9.7 (<1-77)yrs	6.9 (<1-73)yrs	36.4 (<1-77)yrs
Age Category			
<2 yrs	53 (18.1%)	52 (23.6%)	1 (1.4%)
2 – <17 yrs	133 (45.4%)	116 (52.7%)	17 (23.3%)
≥17 yrs	102 (34.8%)	50 (22.7%)	52 (71.2%)
Unknown	5 (1.7%)	2 (0.9%)	3 (4.1%)
Gender			
Female	122 (41.6%)	94 (42.7%)	28 (38.4%)
Male	169 (57.7%)	125 (56.8%)	44 (60.3%)
Unknown	2 (0.7%)	1 (0.5%)	1 (1.4%)
Ethnicity			
White	33 (11.3%)	24 (10.9%)	9 (12.3%)
African-American	4 (1.4%)	2 (0.9%)	2 (2.7%)
Hispanic	6 (2.1%)	5 (2.3%)	1 (1.4%)
Asian	1 (0.3%)	0	1 (1.4%)
Other	1 (0.3%)	1 (0.5%)	0
Unknown	248 (84.6%)	188 (85.5%)	60 (82.2%)
Diagnosis			
Hematologic malignancies	214 (73.0%)	154 (70.0%)	60 (82.2%)
Inborn Errors of Metabolism	8 (2.7%)	8 (3.6%)	0 (0%)
Primary immunodeficiency	14 (4.8%)	13 (5.9%)	1 (1.4%)
Bone marrow failure	42 (14.3%)	33 (15.0%)	19 (12.3%)
Hemoglobinopathy	2 (0.7%)	2 (0.9%)	0 (0%)
Others	13 (4.4%)	10 (4.6%)	3 (4.1%)

*: Those who received a unit having a TNC dose ≥2.5 x 10^7/kg and HLA match 4/6 or more
**: Those who received a unit having a TNC dose <2.5 x 10^7/kg or HLA match 3/6 or less

HLA Matching

Table 3 provides information on the degree of HLA match between the donor and recipient. The majority of patients were mismatched at 1-2 alleles.

Table 3: HLA Matching

HLA Match	Number of Patients N = 293
6/6	46 (15.7%)
5/6	121 (41.3%)
4/6	120 (41.0%)
3/6	6 (2.0%)

Neutrophil and Platelet Engraftment

Engraftment is measured as time to myeloid engraftment, which was defined as the first of three consecutive days of absolute neutrophil cell count (ANC) ≥ 500/µl and platelets > 20,000/µl. Primary graft failure is defined for patients surviving at least 14 days as either:
a) Never achieved ANC > 500/µl by Day 42, or
b) Death after 14 days without ANC engraftment.

Engraftment was assessed for the 293 patients as a whole and also based on whether they received a suitable or non-suitable allograft (Table 4).

Two hundred twenty-two of 293 (222/293, 75.8%) patients achieved an ANC > 500/µl by Day 42. The engraftment rate is slightly higher in patients who received a suitable allograft (169/220, 76.8%) than in patients who received a non-suitable allograft (53/73, 72.6%).

The primary graft failure rate for patients receiving a TNC dose ≥ 2.5 x 10^7/ kg was 19.5%, which is similar to the failure rate 16.4% (14.4- 18.6%) in the pooled docket dataset (Appendix 9.2) for patients receiving a TNC dose ≥ 2.5 x 10^7/ kg.

Table 4: Neutrophil Engraftment

	All patients with Hematopoietic Recovery data	Patients with a Suitable Allograft*	Patients without a Suitable Allograft**
N (total)	293	220	73
ANC>500/µl by Day 42 (percentage)	222 (75.8%)	169 (76.8%)	53(72.6%)
Cumulative incidence of ANC>500 by Day 42*** (95% CI)	77.6% (72.8%, 82.4%)	78.9% (73.5%, 84.4%)	73.6% (63.3%, 84.0%)
Median time to ANC>500/µl by Day 42 (range)	24.5 days (5-42)	24 days (5-42)	26 days (6-40)
ANC >500/µl without time limit (percentage)	240 (81.9%)	183 (83.2%)	57 (78.1%)
Median time to ANC >500/µl without time limit (range)	26 days (5-387)	25 days (5-387)	26 days (6-59)
Subtotal for evaluation of graft failure	279	210	69
Graft failure (percentage)	57 (20.4%)	41 (19.5%)	17 (23.2%)

* Patients who received a unit having a TNC dose ≥2.5 x 10^7/kg and HLA match 4/6 or more

** Patients who received a unit having a TNC dose <2.5 x 10^7/kg or HLA match 3/6 or less
*** Death as a competing risk

Platelet engraftment data were collected from two data sources: 1) the larger dataset which only reported the days to platelets >20,000/µl for those patients who reached platelets > 20,000/µl; 2) the smaller dataset which reported whether patients had reached platelets either > 20,000/µl or > 50,000/µl and by what day. Therefore, as for the proportion of patients with platelets >20,000/ µl or > 50,000/µl by Day 100, the analyses were only based on the smaller dataset of 54 patients. 33/54 (61%) achieved a platelet count > 20,000/µl by Day 100 (see Table 5). As for the analyses of the median time to platelet engraftment, data from both datasets were pooled (see Table 5).

Table 5: Platelet Engraftment

	All Patients With Hematopoietic Recovery data		**Patients with a Suitable Allograft**		**Patients without a Suitable Allograft**	
	N		N		N	
Platelets >20,000/µl by Day 100	54	33 (61.1%)	37	23 (62.2%)	17	10 (58.8%)
Median time to PLT >20,000/µl by Day 100 (range)	118	46 days (2-98)	97	47 days (2-98)	21	43 days (13-92)
Median time to PLT >20,000/µl (range)	151	55 days (2-831)	122	55 days (2-427)	29	48 days (13-831)
Platelets >50,000/µl by Day 100	47	25 (53.2%)	31	17 (54.8%)	16	8 (50.0 %)
Median time to PLT >50,000/µl by Day 100 (range)	25	46 days (23-98)	17	44 days (23-98)	8	47 days (28-93)
Median time to PLT >50,000/µl (range)	28	48.5 days (23-190)	19	49 days (23-190)	9	48 days (28-101)

The graft failure was further examined by HLA matching status and the TNC doses as demonstrated in Table 6. As we can see from the Table 6, the patients with the higher TNC dose and the higher degree of HLA match had fewer graft failure rates.

Table 6: Incidence of Graft Failure by HLA Match and TNC dose

HLA Match	**TNC Dose (x 10^7/kg)**		
	2.5 - <5	**5 - <10**	**≥10**
4/6	12/44 (27.3%)	13/60 (21.7%)	4/14 (28.6%)
5/6	9/36 (25.0%)	9/46 (19.6%)	3/29 (10.3%)
6/6	2/9 (22.2%)	3/25 (12.0%)	1/9 (11.1%)

Figures 1 and 2 further demonstrated the cumulative incidence function for absolute neutrophil cell engraftment (ANC > 500/µl), using death as a competing factor.

Figure 1: Time from transplantation to ANC engraftment

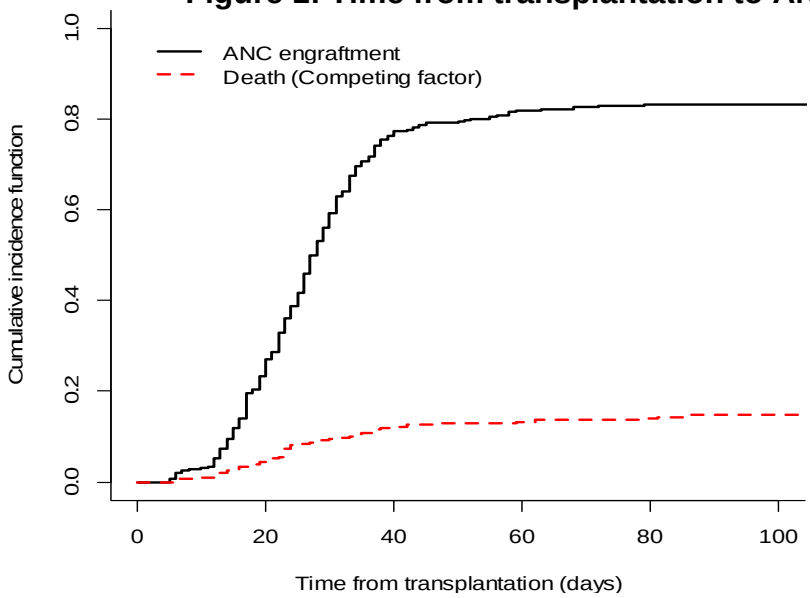
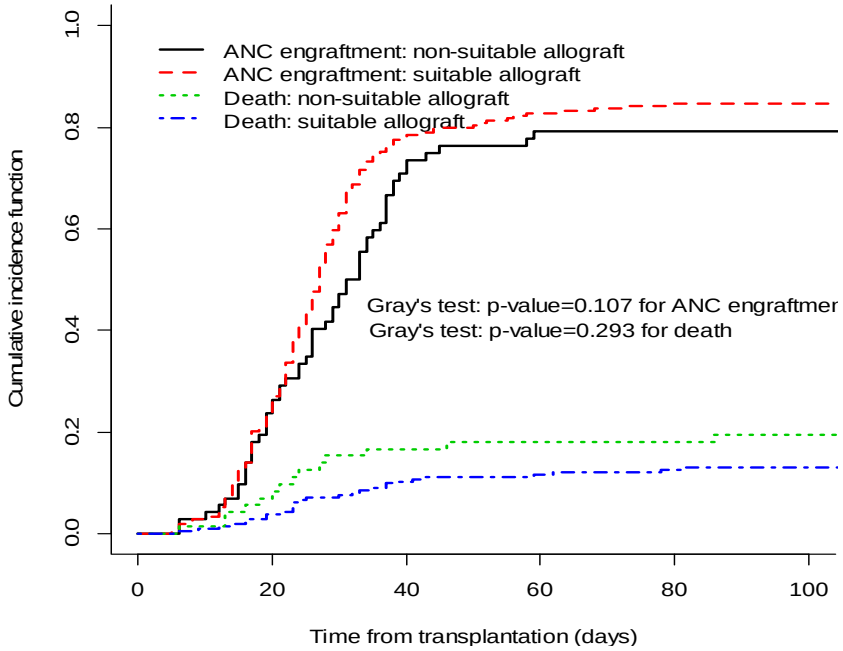


Figure 2: Time from transplantation to ANC engraftment by suitable allograft



Neutrophil Engraftment and TNC Dose

The number of patients receiving a TNC dose ≥2.5 x 10^7/kg by age category is shown in Table 8. The majority of patients (226/293) received a TNC dose ≥2.5 x 10^7/kg. A total of 173/186 (93%) patients younger than 17 years of age received TNC dose ≥2.5 x 10^7/kg.

Table 7: TNC Dose by Age Categories

	Recipient Age				
	Missing N=5	**<2 yrs N=53**	**2-17 yrs N=133**	**≥ 17 yrs N=102**	**Total**
TNC dose ≥2.5 x 10^7/kg	2	53	120	51	226
TNC dose <2.5 x 10^7/kg	3	0	13	51	67

Neutrophil engraftment is further analyzed in the patients who received TNC dose more or less than 2.5 x 10^7/kg and the results are shown in Table 9. There was an increase in the proportion of engraftment in patients receiving TNC dose ≥ 2.5 x 10^7/kg (77.4% versus 70.1%)

Table 8: Engraftment vs. Cell Dose

	TNC Dose ≥ 2.5 x 10^7/kg N=226	**TNC Dose <2.5 x 10^7/kg N=67**
ANC>500/µl by Day 42	175/226 (77.4%)	47/226 (70.1%)

In the analyses of causes for engraftment failure in the docket data, the review team developed a multivariate logistic regression model starting with the factors significant on a preliminary univariate analysis. The final model identified diagnosis, degree of HLA mismatch and TNC dose group as significantly associated with primary graft failure (Appendix 9.3). The docket data reviewers considered the model to be most appropriately applicable to hematologic malignancies, as this was the largest subgroup with sufficient homogeneity to examine how these factors (degree of HLA mismatch and TNC dose group) affected engraftment or failure to engraft.

By applying this model to the 128 patients with hematologic malignancy with engraftment data available in the application, eight patients (6%) exceeded the expected upper 95% confidence limit for the time to engraftment, based on the factors accounted for in the model. This percentage of patients who had excessive days to ANC engraftment is similar to the percentage in the docket data (4.6%). Of these eight patients, seven had only a slight prolongation to ANC engraftment beyond the 95% CI, with the excess ranging from 1 day to 32 days. One patient had an extended time to engraftment of 340 days; it was not reported whether this patient had received a second transplantation at a later time. Five of these eight patients died from non-transplant-related causes, including cardiac failure, pulmonary toxicity, relapse of a persistent disease, and infection.

Based on application of this model to the applicant's dataset, the safety of the ClinImmune product appears comparable to the safety of the HPC-C products that contributed to the docket.

HLA Matching and Engraftment

Table 9 provides information on the degree of HLA mismatch between the donor and recipient. The majority of patients were mismatched at one (121/293 or 41.3%) or two alleles (120/293 or 41%). The percentage of patients who engrafted shown in Table 8 is derived from the number of patients who achieved an ANC >500/µl by Day 42. Due to the small number of patients in the group with more than two alleles mismatched, the association between the degree of HLA mismatch and the engraftment rate is not clearly demonstrated.

Table 9: HLA Matching and Neutrophil Engraftment

HLA Match	Number of Patients N = 293	Patients Engrafted N =222	Patients not Engrafted N =71
6/6	46 (15.7%)	37 (80 %)	9 (20%)
5/6	121 (41.3%)	90 (74%)	31 (26%)
4/6	120 (41.0%)	89 (74%)	31 (26%)
3/6	6 (2.0%)	6 (100%)	0

While primary engraftment failure varies greatly with the underlying disease, it was further examined by a degree of HLA mismatch for hematological malignancies (Table 11) and non-malignant indications (Table 12). However, due to the small number of patients, these analyses are only exploratory.

6.3 Immune Reconstitution

The data submitted by the sponsor did not include information for evaluation of immune reconstitution. Reviews of docket information and published data provide evidence that immune reconstitution occurs after HPC-C transplantation (see Appendices 9.2 and 9.3) for patients with primary immunodeficiencies as well as for other malignant and nonmalignant diseases. Based on docket information and published data, HPC-C transplantation improves survival in SCID, which otherwise carries extremely high mortality. 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. We rely on these data, external to the application, to infer that the same effect applies to ClinImmune product.

6.4 Disease–specific Clinical Outcomes

The applicant did not submit data on disease-specific clinical outcomes following transplantation of HPC-C manufactured by ClinImmune Labs. Early death, defined as death occurring within 100 days after HPC-C manufactured by ClinImmune Labs, transplantation, is reviewed in Section 7 Safety Review, since early death is most likely related to transplantation. Disease-specific outcomes and disease-specific risk and benefit analysis based on data from the docket and literature were previously reviewed (see Appendices 9.2, 9.3, and 9.4)

While transplantation for hematopoietic and immunological reconstitution is a potentially life-saving treatment for certain diseases, the risks are substantial. The risks associated with HPC-C

include death, infusion reaction, GVHD, and engraftment syndrome. The risk-benefit assessment for an individual disease depends on the disease characteristics, including disease stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

7. Review of Safety

7.1 Safety summary

The safety of HPC-C manufactured by ClinImmune Labs, was based on a review of the outcome dataset of 499 patients (Table 1) transplanted with 542 HPC-C units manufactured by ClinImmune Labs for treatment of a variety of clinical indications. The safety review was focused on early death within the 100 days after transplantation, infusion reaction, acute and chronic graft versus host disease (GVHD), and transmission of malignancy, infection, or a genetic disorder from the donor to the recipient. The incidences of these adverse events are compared with the incidences documented in the safety review of the docket information (see Appendix 9.2).

Deaths

Follow-up information is available for 313 of the 499 patients who received HPC-C manufactured by ClinImmune Labs transplantation; 162 (51.8%) of these 313 patients died. The proportions of patients who died by Day 100 varied significantly by indication and ranging from 3% to 36.4% for those who received a TNC dose $\geq 2.5 \times 10^7$/kg. The most common causes of death from the data submitted by the applicant were infection (26.5%), organ failure (16.1%) and graft failure (11.5 %).

Graft versus Host Disease (GVHD)

Information about presence or absence of GVHD was reported in 63/499 (13%) patients; GVHD was reported among 38 out of those 63 (60%) patients. Of those 38 patients with GVHD, 76.3% (29/38) had acute GVHD and 23.7% (9/38) had chronic GVHD. The numbers of cases of acute or chronic GVHD were higher in patients without suitable allograft.

Infusion Reactions

The applicant defined infusion reactions as events usually associated with HPC infusions and occurring within 24 hours of transplantation. The applicant reported very limited infusion reaction information on 71 patients out of 499 (14%). Twenty two (31%) of the 71 reported patients had adverse infusion reactions. The most common adverse reaction was hypertension: 13 (18%) of 71 patients. The applicant did not grade the severity of infusion reactions.

Engraftment Syndrome, **Transmission of malignancy, Infection or a genetic disorder from the donor to the recipient**

No information on adverse events of engraftment syndrome, or transmission of malignancy, infection, or genetic disorders were included in the application.

7.2 Methods

7.2.1 Clinical Studies Used To Evaluate Safety

No clinical trials or studies were conducted to assess the safety or efficacy of the applicant's product. This safety review was based primarily on the outcomes dataset and voluntary adverse event reports submitted by the applicant. The safety datasets include 499 patients transplanted with 542 units.

The University of Colorado Cord Blood Bank (UCCBB) is a public cord blood bank and a major component of ClinImmune Labs, and has a fourteen year history of collecting, processing, banking and distributing cord blood for human transplantation. To date, (b)(4) HPC-C batches have been collected, of which (b)(4) units were banked and 536 units have been transplanted at 138 different hospitals.

ClinImmune Labs, University of Colorado Cord Blood bank (UCCBB) is the manufacturer of the minimally manipulated, unrelated placental/umbilical hematopoietic progenitor cells, HPC-C, under this license application.
The applicant has 14 years history of cord blood banking prior to the submission of this BLA. Prior to the use of the ------(b)(4)------ processing method on January 30, 2007, there were (b)(4) CBUs ---(b)(4)--- processed and banked. The applicant is seeking licensure of the CBUs that are manufactured using both --------(b)(4)-------- methods if meet the licensure requirements.

ClinImmune is currently actively collecting CBUs at five (5) fixed sites: Exempla St. Joseph's Hospital (Denver and Phoenix), Denver Health Medical Center Hospital, Maricopa Medical Center (Phoenix) and Phoenix Baptist Hospital. CBUs are also collected at non-fixed (remote) sites statewide.

7.2.2 Adequacy of Data

The data quality and integrity are discussed in Section 3.1. During the review process, the reviewers requested and obtained relevant safety data from the applicant,

Considering the voluntary nature of the outcome data collection, these data provided by the applicant are adequate for the assessment of safety of the product.

7.3 Adequacy of Safety Assessments

The applicant submitted a very limited safety outcome dataset that includes lists of patients transplanted from 1998 through 2010. Patients' information, including demographics,

hematopoietic recovery, allograft characteristic and outcomes data were not complete for all patients. (See Table 1)

7.3.1 Overall exposure for the dataset

Of 499 patients in this safety dataset, demographic information was available for 457 patients (92%). Table 10 includes a comparison of the demographic parameters for patients with and without a suitable allograft.

Table 10: Safety Outcomes Dataset-Patient Demographics

Patient Characteristics	All Patients Transplanted (N=457)	Patients with a Suitable Allograft (N=332)	Patients without a Suitable Allograft (N=125)
Median Age (Range)	11 (<1-78)yrs	7 (<1-73)yrs	36 (<1-78)yrs
<2 yrs	76 (16.6%)	74 (22.3%)	2 (1.6%)
2 – <17 yrs	197 (43.1%)	171 (51.5%)	26 (20.8%)
≥17 yrs	171 (37.4%)	78 (23.5%)	93 (74.4%)
Unknown	13 (2.8%)	9 (2.7%)	4 (3.2%)
Gender			
Female	189 (41.4%)	141 (42.5%)	48 (38.4%)
Male	266 (58.2%)	190 (57.2%)	76 (60.8%)
Unknown	2 (0.4%)	1 (0.3%)	1 (0.8%)
Ethnicity			
White	39 (8.5%)	27 (8.1%)	12 (9.6%)
African-American	4 (0.9%)	2 (0.6%)	2 (1.6%)
Hispanic	11 (2.4%)	8 (2.4%)	3 (2.4%)
Asian	2 (0.4%)	1 (0.3%)	1 (0.8%)
Other	2 (0.4%)	1 (0.3%)	1 (0.8%)
Unknown	399 (87.3%)	293 (88.3%)	106 (84.8%)
Diagnosis			
Hematologic malignancies	332 (72.7%)	229 (69.0%)	103 (82.4%)
Inborn Errors of Metabolism	16 (3.5%)	16 (4.8%)	0 (0%)
Primary immunodeficiency	24 (5.3%)	22 (6.6%)	2 (1.6%)
Bone marrow failure	64 (14.0%)	48 (14.5%)	16 (12.8%)
Hemoglobinopathy	3 (0.7%)	3 (0.9%)	0 (0%)
Others	18 (3.9%)	14 (4.2%)	4 (3.2%)

At the time of transplantation, the median age of the patients was 11 years. The largest age group of patients who received transplantation was in 2 - <17 years (197/457 or 43.1%). However, the age distribution was different between the groups with and without a suitable allograft. The median age of the patients in the group without a suitable allograft was 36 yrs as opposed to 7 yrs in the group which received a suitable allograft. More males were

transplanted compared to females (58% vs. 41%). The majority (72.7%) of the patients were transplanted for treatment of hematological malignancies.

7.3.2 Explorations of safety for Dose Response

Characteristics of the allografts transplanted are summarized in Table 11. The dose of cells to be administered was chosen by the treating physician and not stipulated by the manufacturer. The dose range listed in Table 11 refers to the total cell dose cryopreserved for all units administered. The dataset did not provide the volume of administration.

Table 11: Safety outcomes Dataset-Cord Blood Unit Characteristics

Patient Characteristics	All Patients Transplanted (N=457)	Patients with a Suitable Allograft (N=332)	Patients without a Suitable Allograft (N=125)
Number of units transplanted			
1	431 (94.3%)	311 (93.7%)	120 (96.0%)
>1	26 (5.7%)	21 (6.3%)	5 (4.0%)
HLA Match Level			
3	13 (2.8%)		13 (10.4%)
4	191 (41.8%)	137 (41.3%)	54 (43.2%)
5	187 (40.9%)	147 (44.3%)	40 (32.0%)
6	66 (14.4%)	48 (14.5%)	18 (14.4%)
Median Dose (TNC x 10^7/kg) (Range)	4.2 (0.5, 65)	5.4 (2.5, 65)	2.0 (0.5, 38.6)
Manufacturing Method			
(b)(4)	28 (6.1%)	18 (5.4%)	10 (8.0%)
(b)(4)	429 (93.9%)	314 (94.6 %)	115 (92.0%)

The applicant submitted safety data outcome on 457/499 (90 %) (Table 1) patients with information on cord blood characteristics: HLA matching and the number of units received by patients. In regard to the latter, 431 patients received one unit of the product (94.3%) and 26 patients (5.7%) received multiple units of the HPC-C manufactured by ClinImmune Labs. If a patient received multiple units on the same date, the multiple units were combined to one infusion, and the TNC dose computed was the sum of the TNCs in each unit. Most of the patients who had a suitable allograft had a 4/6 (41.3 %) or 5/6 (44.3%) HLA match level. The assessment of safety for HPC-C units from other manufacturers is provided in the dockets Safety Review (appendix 9.2).

7.4. Major Safety Results

7.4.1 Deaths

There were 162 deaths among 313 patients with available follow-up information (i.e., survival or not), out of a total number of 499 patients who received transplantation. The proportion of patients who died by Day 100 (104/313 or 33%) varied significantly according to the underlying disease, ranging from 3% to 36.4% for those who received a TNC dose ≥2.5 x 10^7/kg. The most common causes of death from the data submitted by the applicant were infection (26.5%), organ failure (16.1%) and graft failure (11.5%).

The evaluation of early mortality (i.e. <100 days after transplantation) showed that younger patients, males, with HLA match >4/6 had better survival rates. The highest mortality was noted in the age group ≥17 years (48 out of 103 or 46.6%). The proportion of deaths by Day 100 from all causes among those who received a suitable allograft (71/202 or 35 %)
From the data provided by the applicant, the incidence of early death and the causes of death were similar to the docket data set. From the applicant data provided, the most common cause of death >5% were infection (10%), and organ failure (6%) and it is similar to the docket dataset.

Available data from the docket dataset showed that the most common (>5%) causes of death by Day 100 after transplantation for those who received a TNC ≥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 74% of the deaths due to graft failure occurred by Day 100 (See Table 12). When comparing patients who received a TNC ≥2.5 x 10^7/kg vs <2.5 x 10^7/kg, patients with the higher TNC dose had a lower death rate by Day 100 (25% vs 52%). (Appendix 9.2)

The death rate through Day 100 from all causes among patients with suitable allograft was 71/202 (35%) in the applicant dataset; this death rate was higher than the 25.3% rate in the pooled data from the docket (see Table 12). Since the applicant provided very limited data, it is difficult to explain the clinical significance of this difference in early mortality.

Table 12: Causes of Death after Transplantation

	Applicant's dataset				Docket dataset	
	All Patients N=313		Patients with a Suitable Allograft N=202		Patients with a Suitable Allograft (N=1289)	
Causes of Death N	**Total Reported** 162 (52%)	**Deaths≤ Day100** 104(33%)	**Total Reported** 110(54%)	**Deaths ≤ Day 100** 71(35%)	**Total Reported** 35(49%)	**Deaths ≤ Day 100** 328(25.3%)
Graft Failure (n %)	11 (3.5%)	7 (2%)	5 (2.5%)	2 (1%)	48 (3.7%)	33 (2.5%)
Organ failure (n %)	26 (8%)	21 (7%)	16 (8%)	13 (6%)	115 (8.9%)	84 (6.5%)
Infection (n %)	43 (14%)	32 (10%)	26 (13%)	20 (10%)	170 (13.2%)	101 (7.8%)
GVHD (n %)	13 (4%)	6 (2%)	11 (5.0%)	6 (3%)	72 (5.6%)	39 (3.0%)
Primary disease (n%)	7 (2%)	3 (1%)	5 (2.5%)	2 (1%)	168 (13.0%)	42 (3.2%)
2nd Malignancy (n%)	1 (0.3%)	0	0	0	4 (0.3%)	0
Prior malignancy (n%)	24 (8%)	11 (3.5%)	15 (7%)	8 (4%)	-	-
Hemorrhage (n%)	10 (3%)	10 (3%)	8 (4%)	8 (4%)	-	-
Pulmonary toxicity (n%)	7 (2%)	4 (1.3%)	6 (3%)	4 (2%)	-	-
Unknown (n%)	9 (3%)	1 (0.3%)	9 (4.5%)	1 (0.5%)	-	-
Other (n%)	11 (3.5%)	9 (8.7%)	9 (4.0 %)	7 (3.5%)	-	-

7.4.2 Early mortality analyzed against demographic characteristics

Since most of the deaths possibly related to the cord blood unit occurred within the first 100 days after transplantation, additional exploratory analyses were conducted to assess the patients' demographics and treatment parameters that may have been associated with such early deaths. The data presented in Table 13 are based on analyses of the 273 patients for whom early mortality information was available.

This submission has limited data regarding the race and ethnicity of the patients. For comparison the table also includes information from the review of the docket datasets (Appendix 9.2).

Table 13: Early Mortality Interactions with Demographic Characteristics

	All patients N (%)		Patients with a Suitable Allograft N (%)		Dockets Dataset Patients with TNC ≥ 2.5 x 10^7/kg
Demographic	**Patients N=273**	**Deaths ≤ Day100 N=104**	**Patients N=202**	**Deaths ≤ Day100 N=71**	**Deaths ≤ Day100**
<2 yrs	41	12 (29.3%)	40	11 (27.5%)	22.3%
2 – <17 yrs	125	42 (33.9%)	108	36 (33.3%)	27.4%
≥17 yrs	103	48 (46.6%)	52	23 (44.2%)	48.6%
Unknown	5	2 (40.0%)	2	1 (50.0%)	-----
Gender					
Male	154	48 (31.2%)	113	33 (29.2%)	18.1%
Female	117	56 (47.9%)	88	38 (43.2%)	27.0%
Unknown	2	0	1	0	---------
Ethnicity					
African American	4	1 (25.0%)	2	0	28.9%
Asian	0	0	0	0	19.4%
Caucasian	35	12 (34.3%)	26	10 (38.5%)	22.3%
Hispanic	6	0	6	0 (0)	18.9%
Other	1	1 (100%)	1	1 (100%)	31.3%
Unknown	227	90 (39.7%)	167	60 (35.9%)	
Diagnosis					
Marrow Failure	41	23 (56.1%)	30	16 (53%)	46.5%
Heme Malignancy	181	66 (36.5%)	140	49 (35.0%)	32.0%
Immunodeficiency	11	1 (9.1%)	10	1 (10.0%)	17.7%
Other	32	12 (37.5%)	15	4 (26.7%)	23.4%
Unknown	8	2 (25.0%)	7	1 (14.3%)	--------

From the data submitted by the applicant, 104/273 (38%) patients died before Day 100. Two hundred and two patients were transplanted with suitable allograft and from this group 71 (71/202) or 35% of patients died before Day 100. The data show better survival in the youngest patients: best survival in younger than 2 yrs of age followed by patients in the age group of 2 - <17. The highest mortality (48 /103 or 46.6%) occurred in the age group ≥17 years. In general, males had better survival rates than females. Patients with bone marrow failure had the highest mortality before Day 100 (56%). Overall, the early mortality data reported by the applicant appears to be similar to the data available in the docket.

7.4.3 Early Mortality Analyzed Against Product Characteristics

Table 14 provides information on correlations between product characteristics and early mortality.

Table 14: Early Mortality Interactions with Product Characteristics

	All patients N (%)		Patients with a Suitable Allograft N (%)	
Product characteristic	**Patients N=273**	**Deaths ≤ Day 100 N=104**	**Patients N=202**	**Deaths ≤ Day 100 N=71**
Single unit	257	93 (36.3%)	188	63 (33.5%)
Multiple units	17	11 (64.7%)	14	8 (57.1%)
HLA-Match				
3/6	6	4 (66.7%)	0	0
4/6	114	43 (37.7%)	82	31 (37.8%)
5/6	108	40 (37.0%)	89	29 (32.6%)
6/6	45	17 (37.8%)	31	11 (35.5%)
TNC dose				
$< 2.5 \times 10^7$/kg	65	29 (44.6%)		
$\geq 2.5 \times 10^7$/kg	208	75 (36.1%)	202	71 (35.1%)

These data come from the 273 patients for whom information on death ≤ Day 100 was available.

The early mortality rate analyzed according to HLA match level revealed the worst survival in the 3/6 match group (4/6 or 66.7 %). Mortality from all causes at 100 days post-transplant in patients who received TNC $\geq 2.5 \times 10^7$/kg was 36.1% (75/208). The early mortality was higher in patients who received TNC dose $< 2.5 \times 10^7$/kg (29/65 or 44.6%) compared to patients who received TNC $\geq 2.5 \times 10^7$/kg (75/208 or 36%).

7.4.4 Infusion Reactions

Infusion reactions were defined as events usually associated with HPC-C infusions and occurring within 24 hours of transplantation.

The applicant's data collection questionnaire only captured whether a "serious adverse reaction" occurred, and whether specific reactions (bradycardia, hypertension, hypotension, hemolytic reactions, anaphylaxis or dyspnea) required intervention (specified as oxygen administration, blood pressure support).

The applicant reported very limited infusion reaction information on 71 patients (14% of the 499 patients who received the HPC-C product manufactured by ClinImmune Labs,). Forty seven of these received TNC dose $\geq 2.5 \times 10^7$/kg.

Twenty two of 71 (31%) patients reported adverse infusion reactions and some of them had more then one adverse event (AE). The most frequent adverse reactions in patients were hypertension (13/71; 18 %) and nausea (4/71; 6 %). The applicant did not grade the severity of infusion reactions. None of the adverse events were life-threatening or resulted in death.

The safety data provided by the applicant were compared to the COBLT dataset. An infusion reaction was reported for 65% of the COBLT patients. The most common infusion reactions noted were hypertension (48%), nausea (12.7 %) and hypoxia (2%).

Table 15: Incidence of Infusion Reactions in applicant data and the COBLT Study

	All Units Transplanted N (%)	**Units with a TNC dose ≥2.5 x 10^7/kg N (%)**	**Infusions with a TNC Dose >2.5 x 10_7/kg**
Number of infusions assessed	71	47 (66%)	442
Number with any reaction	22 (31%)	17 (36%)	65.4%
Hypertension	13 (18 %)	5 (11 %)	48.0%
Hypoxia	1 (1 %)	1 (2%)	2%
Nausea	4 (6 %)	4 (8 %)	12.7%
Headache, other unexplained	1 (1 %)	1 (2%)	------
Vomiting	2 (3 %)	2 (4 %)	14.5%
Facial Flushing	2 (3 %)	2 (4%)	---
Fever Rigor,, Chills	1 (1 %)	1 (2 %)	0.9%
Hematuria	2 (3 %)	1 (2 %)	
Bradycardia	2 (3 %)	1 (2 %)	10.4%

The applicant investigated three of the 22 reports:

One case of mild rigors and chills was reported. The HPC-C manufactured by ClinImmune Labs, was not washed but was diluted to 255 mL and infused. There were no reported post-thaw infusion sterility cultures on the HPC-C or recipient. Two cases of transient bradycardia were reported but were considered isolated symptoms. Despite the absence of detailed information, the overall rates of infusion reactions in the subset of patients in whom the data were collected are similar to the rates in the COBLT Study.

7.4.5 Infusion Reaction Interactions with Demographic Characteristics

Information on infusion reactions was available from voluntary reports for 47 patients who received HPC, Cord Blood manufactured by ClinImmune Labs at a total nucleated cell dose ≥2.5 x 10^7/kg. The population included 72% males and 28% females, with median age 12 years (range 0.4 - 67.5 years). Preparative regimens and graft-vs-host disease prophylaxis were not standardized. Seventeen patients (36%) had an infusion reaction. Infusion reactions

included hypertension (11%), nausea (8%), vomiting (4%), facial flushing (4%), hypoxia (2%), headache (2%), fever and chills (2%), hematuria (2%), and bradycardia (2%).

Table 16: Infusion Reaction Interactions with Demographic Characteristics

	All Units Transplanted N (%)		Units with a TNC dose ≥2.5 x 10^7/kg N (%)	
Demographic	**Infusions (71)**	**Reactions (22)**	**Infusions (47)**	**Reactions (17)**
≤ 2 yrs	3	2 (66.7%)	3	2 (66.7%)
2 – <17 yrs	24	11 (45.8%)	23	11 (47.8%)
≥17 yrs	42	8 (19.1%)	20	3 (15.0%)
Unknown	2	1 (50%)	1	1 (100%)
Gender				
Male	51	16 (31.4%)	32	11 (34.4%)
Female	20	6 (30.0%)	15	6 (40.0%)
Ethnicity				
African American	4	1 (25.0%)	2	1 (50.0%)
Asian	2	1 (50.0%)	1	1 (100%)
Caucasian	39	12 (30.8%)	27	8 (29.6%)
Hispanic	11	6 (54.6%)	8	5 (62.5%)
Others+unknown	15	2 (13.3%)	9	2 (22.2%)
Diagnosis				
Marrow Failure	8	3 (37.5%)	5	3 (60.0%)
Heme Malignancy	54	16 (29.6%)	35	12 (34.3%)
Immunodeficiency	1	0	1	0
Others+unknown	8	3 (37.5%)	6	2 (33.3%)

Of the 499 patients transplanted with HPC-C manufactured by ClinImmune Labs, only 71 (14.2%) patients had information on demographic characteristics and assessment of the infusion during the transplantation. Preparative regimens and GVHD prophylaxis were not standardized. The population included 72% males and 28 % females of median age 32 years (range 0.4-70 years). Adverse reactions in association with the infusion were reported in 22/71 (31%). The patients were categorized in different demographic groups to facilitate the analysis. There was no correlation between having a reaction and demographic group.

The number of patients within particular diagnostic groups was small. The largest subgroup consisted of patients with hematologic malignancy. From this group 16/54 patients (30%) developed infusion reactions.

7.4.6 Infusion Reaction Interactions with Product Characteristics

There was no correlation between infusion reaction and product characteristics. The rates of any infusion reactions were similar in the groups of patients with and without a suitable allograft (see Table 17).

Table 17: Infusion Reaction Interactions with Product Characteristics

	All Units Transplanted N (%)		Units with a TNC dose $\geq 2.5 \times 10^7$/kg N (%)	
Product Characteristics	**Infusions (71)**	**Reactions (22)**	**Infusions (47)**	**Reactions (17)**
Number of Units				
Single	66	22 (33.3%)	42	17 (40.5%)
Multiple	5	0	5	0
HLA-Match				
4/6	29	8 (28%)	17	5 (29%)
5/6	35	10 (29%)	23	9 (39%)
6/6	13	4 (31%)	7	3 (43%)
TNC Dose				
$\leq 2.5 \times 10^7$/kg	30	5 (17%)		
$\geq 2.5 \times 10^7$/kg	47	17 (36%)	47	17 (36%)

7.4.7 Acute and Chronic Graft versus Host Disease

GVHD is a frequent complication after stem cell transplantation. Patients may develop acute GVHD, chronic GVHD, or both. Acute GVHD is defined as occurring before 100 days post-transplant. Chronic GVHD occurs after Day 100 after transplantation and can last a lifetime.

Acute GVHD and chronic GVHD were reported by the transplant centers; grades of acute GVHD (I- IV) and chronic (limited or extensive) were assigned by the transplant centers. The presence or absence of GVHD was documented in 63/499 (13%) patients. The results of analyses of the applicant data are shown in Tables 18, and 19.

Table 18: Analysis of GVHD

	Acute GVHD Applicant's data		Docket data	
	Total reported N = 63	**Patients with a Suitable Allograft N = 43**	**Patients reported (N=1381)**	**Patients with a TNC Dose $\geq 2.5 \times 10^7$/kg (N=1182)**
None	34	24 (55.8%)		
Yes	29	19 (44.2%)	451 (32.7%)	369 (31.2%)
Grade 1	8	4 (21.1%)	347 (25.1%)	315 (26.7%)
2	10	7 (36.8%)	314 (22.7%)	276 (23.4%)
3	9	6 (31.6%)	176 (12.7%)	149 (12.6%)
4	1	1 (5.3%)	93 (6.7%)	73 (6.2%)
Unknown	1	1 (5.3%)	347 (25.1%)	369 (31.2%)

Table 19: Analysis of Chronic GVHD

		All patients	Patients with a Suitable Allograft	Patients without a Suitable Allograft
Total reported (yes or no)		63	43	20
Reported	Yes	9 (14.3%)	5 (11.6%)	4 (20.0%)
	Limited	5	3	2
	Extensive	4	2	2

The applicant provided data on 63 patients; 29/63 (46%) had acute GVHD and 9/63 (14.3 %) had chronic GVHD.
Of the 43 patients who received suitable allograft, 19/43 (44%) developed acute GVHD, and 5/43 (12%) developed chronic GVHD.

Of the 19 patients who received a suitable allograft and developed acute GVHD, 74% developed acute grades 2-4 GVHD, and 37% developed acute grades 3-4 GVHD. The number of cases too small for are meaningful analysis of the relative rates of chronic GVHD.

For comparison, the summary GVHD data from the docket showed a prevalence of 42.5% for acute GVHD grades 2-4, and 21% for grades 3-4.

Several risk factors for acute GVHD have been reported in the medical literature, including CMV serostatus, pretransplant infection, age, CD34 cell dose and HLA mismatch. Without this information in the ClinImmune and docket datasets, it is difficult to adequately compare these datasets.

7.4.8 Engraftment Syndrome

Engraftment syndrome (ES) is an inflammatory condition during neutrophil recovery after hematopoietic stem cell transplantation (HSCT). Symptoms and signs include fever, erythrodermatous skin rash, and noncardiogenic pulmonary edema. The applicant did not include any reports of ES associated with HPC, Cord Blood manufactured by ClinImmune Labs.

7.4.9. Malignancies of Donor Origin, Transmission of Serious Infection, Rare Genetic Disease

The applicant did not report any cases of possible transmission of malignancy, serious infection, or genetic disease from the donor material.

7.5 Overdose

Three major components of HPC-C that may contribute to clinical overdosage include the cell content, Dextran 40 and DMSO. Toxic overdose of DMSO has been reported in a patient

undergoing autologous transplantation; there were no reports in the literature of a DMSO overdose related to HPC-C transplantation.

The applicant did not address issues associated with overdose. The maximum TNC dose administered was 6.5 x 10^8/kg for all patients. In the exploratory analyses described in Sections 7.3.1.2 and 7.3.2.2, there were no correlations between TNC doses and early deaths or infusion reactions.

8 Post-marketing Experience

There is no post-marketing experience with this product.

The applicant will continue to collect clinical outcome data including any adverse experiences and report these in annual summary reports.

The applicant will analyze information that they receive from the transplant centers and evaluate the data to determine whether any adverse experiences or other unexpected outcomes identified may be due to problems with their product manufacture and whether corrective actions are needed. Serious unexpected adverse experiences will be reported to FDA as required by 21 CFR Part 600.80 within the required timeframe of 15 days using Form 3500A. The sponsor will also maintain for a period of 10 years at a minimum all adverse experiences as required by 21 CFR 600.80 (i), including toxicity associated with infusion of the HPC-C, and delayed or failed engraftment that may relate to the HPC-C manufacture.

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

9 Appendices

9.1 Literature Review/References

1.Variation in dimethyl sulfoxide use in stem cell transplantation: a survey of EBMT centers. Windrum P. et al, Bone Marrow Transplantation 2005

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9.2 Clinical Safety and Statistical Joint Review – Dockets and Public Information

9.3 Clinical Efficacy Review – Malignant Indications – Docket and Public Information

9.4 Clinical Efficacy Review - Nonmalignant Indications – Docket and Public Information