Mid-Cycle Clinical and Statistical Summary - ALLOCORD

BLA 125413

Applicant: SSM Cardinal Glennon Children's Medical Center and the St. Louis University School of Medicine, St. Louis Cord Blood Bank (SLCBB)

Received Date: 10/21/2011; PDUFA Goal Date: 8/20/2012

Clinical Reviewer: Lei Xu, Team leader: Changting Haudenschild; Branch Chief: Ilan Irony (OCTGT)

Statistical Reviewer: Renee Rees (OBE); Team leader (acting): Shiowjen Lee; Branch chief: Boguang Zhen **Chemical Name:** Hematopoietic progenitor cells, cord (HPC-C)

Trade Name: AlloCORD

Proposed Indications: For use inunrelated 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.

Final formulation: Each unit of AlloCORD contains a minimum of 5 x 108 total nucleated cells (TNC) with a minimum of 1.25 x 106 viable CD34+ cells, suspended in 10% dimethyl sulfoxide (DMSO), and 1% dextran 40, at the time of cryopreservation

Dosing: The recommended minimum dose is2.5 x 107 TNC/kg at cryopreservation, matching for at least 4 of 6 HLA-A antigens, HLA-B antigens, and HLA-DRB1 alleles is recommended.

Route of Administration: IV infusion

- Adult: begin infusion at 100ml /hour and increase the rate as tolerated
- Children: begin infusion at 1ml/kg/hour and increase as tolerated

Cord Blood Collection Sites: 33 sites:

- 29 in metropolitan St. Louis region (eastern Missouri and southern Illinois)
- 4 in Kansas City region

Collection time range (submitted dataset): 1996-2011

Registered patients in dataset: 1055 single-unit recipients; 75 multi-unit recipients (mostly 2 units)

Mid-Cycle Summary
The applicant applied for licensure of its cord blood product indicated for use inunrelated 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 applicant referred to the COBLT data and the docket data to support the efficacy of its product.The applicant submitted a dataset of 1130 cord blood recipients (1055 subjects with single unit infusions and 75 subjects with more than one unit infusions) to support the safety of its product.These units of the cord blood were collected from 33 collection sites in the States of Missouri, Illinois and Kansas from 1996 to 2011.The following summarizes our joint preliminary data analyses from the raw dataset provided by the applicant.

1. The FDA data analyses are based on an incomplete dataset of patients who received a single unit of the product.Missing data occur in various degrees for the different variables; this is largely due to the retrospective and passive nature of data collection.In addition, multiple miscodings and inconsistencies within the dataset have been identified.

2. The main age category consists of pediatric patients (1 month to < 18 years) - 52% and young adults (18 to <65) - 44%.Neonates (1 month or younger) and geriatric patients (≥ 65) are represented in a small proportion (3.5%)(Table 1).

3. 82.9% of cord blood units are given to patients with hematological malignancies, and 7.1% of cord blood units are given to patients with immunodeficiency. Other categories include metabolic disorders, bone marrow failure, hemoglobinopathy and autoimmune diseases (Table 1).

4. Among the 644 recipients with information on the number of total nuclear cells infused, the median dose is 4.4 x 107 /kg (Table 1).

5. The data regarding HLA match are missing in the raw data sheet (Table 2).

6. Hematopoietic recovery of neutrophil and platelet are calculated from this retrospective dataset. They are consistent with those from the COBLT study and the Docket (Table 3).

7. Overall reported death rate is 51% (392/764). The rate is compatible with docket data, as is the rate of death < 100 days post-transplant. The main causes of death include primary diseases, infection, pulmonary etiologies, GVHD, graft failure, and organ failure.Death due to graft failure or GVHD accounts for 5.1% and 4.6% of deaths, respectively (Table 4).

8. About 54% of 742 patients with reported information developed acute GVHD, and 71% with mild grade (≤ grade 2) (Table 5).

9. Infusion reactions occurred in 18% of 453 patients. The most common reaction is hypertension, followed by other relatively common ones, including nausea, vomiting, bradycardia, headache, and chest pain (Table 6). 10.The preliminary analyses of the safety outcomes areroughly compatible with Docket/public data. Therefore, the current assessment is

that a post-market study (REMS or PMR) may not be necessary.However, the final review may suggest otherwise.

Table 1. Demographic Characteristics

Category		St. Louis	Docket
Number of patients		N=1055 (%)	N=1572 (%)
Age	Median (range)	16 yrs (25 d-73 yrs)	6 yrs (<1-66 yrs)
	< 1 month	2 (0.19)	
	1 month – < 18 years	549 (52)	1296 (82)
	18 - < 65 years	469 (44)	276 (17.7)
	≥ 65 years	35 (3.3)	
Gender	Male	601 (57)	
	Female	454 (43)	
Race/Ethnicity	Caucasian African American Hispanic Asian American Indian Other / Unknown	669 (63.4) 88 (8.3) 9 (0.9) 27 (2.6) 4 (0.3) 258 (24.4)	
Diagnosis	Malignancy Metabolic disorder Immunodeficiency Marrow failure Hemoglobinopathy Autoimmune disorder Other	755 (71.5) 48 (4.6) 73 (7.1) 36 (3.4) 22 (2.0) 1 (1.0) 120 (11.4)	1103 (70.2) 140 (8.9) 96 (6.1) 114 (7.3) 8 (0.5) 111 (7.0%)
Median dose/kg (TNC x 107)		4.4 (0.03-553.9) (N = 644)	5.3 (0.7-74)

Table 2. HLA Match

Category	St. Louis	Docket
HLA Match	3/6	Data Missing (N=?)	55 (3.5)
	4/6		723 (46)
	5/6		
	6/6		170 (10.8)
	Unknown		11 (0.7%)

Table 3.Hematopoietic recovery in patients transplanted with TNC Dose ≥2.5x107/kg (ANC: neutrophil, PLT: Platelet)

Data Source	St. Louis	COBLT	Docket
Study Design	Retrospective	Prospective	Retrospective
Number of Patients	N=282-516	N=324	N=1299
ANC recovery at Day 42 (%)	77	76	77
PLT recovery at Day 100 (20k) (%)	76	57	
Platelet recovery at Day 100 (50k) (%)	70	46	45
Median time in days to ANC recovery (>500)	20 (0- 1122) (N = 516)	27	25
Median time in days to PLT recovery (20k)	46 (0-271)	90	

Data Source	St. Louis	COBLT	Docket
	(N = 359)		
Median time in days to PLT recovery (50k)	51 (0-302) (N = 337)	113	122

Table 4. Safety Outcome: Death (Primary Cause)

Death Rate and Cause of Death	St. Louis	Docket
Total Number of patients	N=764 (%)	N=1572 (%)
Total Number of Deaths	392 (51)	838 (53.3)
Death $\leq$ 100 days post-transplant	180 (23.6%)	469 (29.8)
Cause of Death	(N=391)	
Primary disease	138 (35.2)	
Infection	79 (20.2)	(7.8)
Pulmonary	36 (9.2)	
Organ failure	16 (4.1)	(6.5)
Graft Failure	18 (4.6)	(3.7)
GVHD	24 (5.1)	
Secondary malignancy	4 (1.0)	
Other	77 (19.6)	

Table 5. Safety Outcomes: GVHD

GVHD	St. Louis	Docket
Number of Patients	N=742 (%)	1381
Acute GVHD	403 (54)	1569 (88)
Grade 0 1 2 3 4	120 (30) 164 (41) 74 (18) 39 (9.8)	451 (33) 347 (25) 314 (23) 176 (13)
Unknown	3 (0.8)	93 (6)

Table 6. Safety Outcome: Infusion Reactions

Infusion Reactions	St. Louis	COBLT
Number of Patients or Units of Infusion	Patient N=453 (%)	Infusion N=523 (%)
Any Infusion Reaction	82 (18)	65.4
Hypertension	59 (72)	46.5
Nausea	16 (19.5)	14.8
Vomiting	13 (15.9)	15.7
Brachycardia	12 (14.6)	10.3
Headache	7 (8.5)	
Chest pain	6 (7.3)	
Hypoxia	2 (2.4)	2.9
Shortness of breath	3 (3.7)	1.7
Chills	2 (2.4)	1.3
Hemoglobinuria	2 (2.4)	1.9

Infusion Reactions	St. Louis	COBLT
Tachycardia	3 (3.7)	5.2
Hypotension	2 (2.4)	2.9
Hives		
Rigor	3 (3.7)	
Fever	6 (7.3)	5.5
Other	9 (11)	