HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use REGENECYTE safely and effectively. See full prescribing information for REGENECYTE.

REGENECYTE (HPC, Cord Blood)
Injectable Suspension for Intravenous Use
Initial U.S. Approval: XXXX

WARNING: FATAL INFUSION REACTIONS, GRAFT VERSUS HOST DISEASE, ENGRAFTMENT SYNDROME,AND GRAFT FAILURE

See full prescribing information for complete boxed warning.

- **Fatal infusion reactions: Monitor patients during infusion and discontinue for severe reactions. (5.1, 5.2)**
- **Graft-versus-host disease (GVHD): GVHD may be fatal. Administration of immunosuppressive therapy may decrease therisk of GVHD. (5.3)**
- **Engraftment syndrome: Engraftment syndrome may be fatal. Treat engraftment syndrome promptly with corticosteroids. (5.4)**
- **Graft failure: Graft failure may be fatal. Monitor patients forlaboratory evidence of hematopoietic recovery. (5.5)**

----------INDICATIONS AND USAGE----------

REGENECYTE, HPC (Hematopoietic Progenitor Cell), Cord Blood, is an allogeneic cord blood hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. (1)

----------DOSAGE AND ADMINISTRATION----------

- **For intravenous use only.**
- **Do not irradiate**.
- Physicians experienced in hematopoietic progenitor cell transplantation should direct the unit selection and administration of REGENECYTE. (2)
- The recommended minimum dose is 2.5×10^7 nucleated cells/kg at cryopreservation. (2.1)
- Do not administer REGENECYTE through the same tubing with other products except for normal saline. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Each unit contains a minimum of 9.0×10^8 total nucleated cells with at least 1.25×10^6 viable CD34+ cells at the time of cryopreservation. The exact pre-cryopreservation nucleated cell content of each unit is provided in the accompanying records. (3)

----------CONTRAINDICATIONS----------

Do not administer to patients with known sensitivity to dimethyl sulfoxide (DMSO), Dextran 40 or plasma proteins. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Reactions: Reactions include bronchospasm, wheezing, angioedema, pruritus, and hives. Monitor patients with a history of allergic reactions to antibiotics (5.1)
- Infusion Reactions: Infusion reactions can be severe and may begin within minutes of the start of infusion of REGENECYTE. Many of these reactions are related to the amount of DMSO administered. Monitor patients closely several hours after completion of the infusion. (5.2)
- Graft-versus-Host Disease (GVHD): Immunosuppressive drugs should be administered to decrease the risk of GVHD (5.3)
- Engraftment Syndrome: It is manifested as unexplained fever and rash in the peri-engraftment period. Treatment with corticosteroids should be initiated to ameliorate the symptoms. (5.4)
- Graft Failure: Monitor patients for laboratory evidence of hematopoietic recovery. (5.5)
- Malignancies of Donor Origin: Cord Blood transplantation may cause post-transplant lymphoproliferative disorder (PTLD). High-risk patients should be monitored for EBV (Epstein-Barr virus) DNA. (5.6)
- Transmission of Serious Infections: REGENECYTE is derived from human blood therefore it may transmit infectious diseases. (5.7)
- Transmission of Rare Genetic Diseases: REGENECYTE may transmit rare genetic diseases involving the hematopoietic system (5.8)

---------- ADVERSE REACTIONS ----------

The most common infusion-related adverse reactions (≥5%), from pooled safety population are hypertension, vomiting, nausea, bradycardia, and fever. (6.1)

Mortality, from all causes, at 100 days post-transplant was 25%. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact StemCyte at 1-626-646-2485 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: XX/XXXX

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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FULL PRESCRIBING INFORMATION

WARNING: FATAL INFUSION REACTIONS, GRAFT VERSUS HOST DISEASE, ENGRAFTMENT SYNDROME, AND GRAFT FAILURE

Fatal infusion reactions: HPC, Cord Blood administration can result in serious, including fatal, infusion reactions. Monitor patients and discontinue HPC, Cord Blood infusion for severe reactions. ***[See Warnings and Precautions (5.1, 5.2)]***

Graft-versus-Host disease (GVHD): GVHD is expected after administration of HPC, Cord Blood, and may be fatal. Administration of immunosuppressive therapy may decrease the risk of GVHD. ***[See Warnings and Precautions (5.3)]***

Engraftment syndrome: Engraftment syndrome may progress to multi-organ failure and death. Treat engraftment syndrome promptly with corticosteroids. ***[See Warnings and Precautions (5.4)]***

Graft failure: Graft failure may be fatal. Monitor patients for laboratory evidence of hematopoietic recovery. Prior to choosing a specific unit of HPC, Cord Blood, consider testing for HLA antibodies to identify patients who are alloimmunized. ***[See Warnings and Precautions (5.5)]***

1 INDICATIONS AND USAGE

REGENECYTE, HPC (Hematopoietic Progenitor Cell), Cord Blood, is an allogeneic cord blood hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. The risk benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

2 DOSAGE AND ADMINISTRATION

For intravenous use only.

Do not irradiate.

Complete unit selection and administration of REGENECYTE under the direction of a physician experienced in hematopoietic progenitor cell transplantation.

2.1 Dosing

The recommended minimum dose is 2.5×10^7 nucleated cells/kg at cryopreservation. You may require multiple units in order to achieve the appropriate dose.

Matching for at least four of six HLA-A antigens, HLA-B antigens, and HLA-DRB1 alleles is recommended. See the container label and/or accompanying records for documentation of the HLA typing and nucleated cell content for each individual unit of REGENECYTE.

2.2 Preparation for Infusion

A trained healthcare professional should prepare REGENECYTE.

- Do not irradiate REGENECYTE.
- See the appended detailed instructions for preparation of REGENECYTE for infusion.
- Store REGENECYTE after thaw, wash and final formulation at 2-8°C for up to 2 hours from time of thaw [See Instructions for Preparation for Infusion].
- The recommended limit on DMSO administration is 1 gram per kg body weight per day. *[See Warnings and Precautions (5.2) and Overdosage (10)]*

2.3 Administration

A qualified healthcare professional experienced in hematopoietic progenitor cell transplantation should supervise the administration of REGENECYTE.

1. Confirm the identity of the patient for the specified unit of REGENECYTE prior to administration.
2. Confirm that emergency medications are available for use in the immediate area.
3. Ensure the patient is adequately hydrated.
4. Premedicate the patient 30 to 60 minutes before administering REGENECYTE. Premedication should include any or all the following: antipyretic, histamine antagonists, and corticosteroids.
5. Inspect the product for any abnormalities, such as unusual particulates, and for breaches of container integrity prior to administration. Prior to infusion, discuss all such product irregularities with the laboratory issuing the product for infusion.
6. Administer REGENECYTE by intravenous infusion. Do not administer in the same tubing concurrently with products other than 0.9% Sodium Chloride, Injection (USP). You may filter REGENECYTE through a 170-to-260-micron filter designed to remove clots. Do NOT use a filter designed to remove leukocytes.
7. Infuse over 15 to 60 minutes depending on the volume of the product and the weight of the patient. For adults, begin infusion rate at 100 milliliters per kilogram per hour and increase the rate as tolerated. For children, begin infusion rate at 1 milliliters per kilogram per hour and increase as tolerated. Reduce the infusion rate if the fluid load is not tolerated. Discontinue the infusion in the event of an allergic reaction or if the patient develops a moderate to severe infusion reaction. *[See Warnings and Precautions (5.2) and Adverse Reactions (6)]*
8. Monitor the patient for adverse reactions during, and for at least six hours after, administration. Because REGENECYTE contains lysed red cells that may cause renal failure, careful monitoring of urine output is recommended.

NOTE: If product is being prepared for a multi-unit infusion, infuse units independently and repeat steps 1 through 8 for each infused unit.

9. Should a reaction occur, appropriately manage the reaction before you thaw the second unit for infusion.

3 DOSAGE FORMS AND STRENGTHS

Each unit of REGENECYTE contains a minimum of 9.0×10^8 total nucleated cells with a minimum of 1.25×10^6 viable CD34+ cells, suspended in 10% dimethyl sulfoxide (DMSO) and 1% Dextran 40, at the time of cryopreservation.

The pre-cryopreservation nucleated cell content is provided in accompanying records.

4 CONTRAINDICATIONS

Do not administer REGENECYTE to patients with known sensitivity to dimethyl sulfoxide (DMSO), Dextran 40 or plasma proteins.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Patients may experience allergic reactions with infusion of HPC, Cord Blood, including REGENECYTE. Reactions include bronchospasm, wheezing, angioedema, pruritus, and hives *[see Adverse Reactions (6)]*. Serious hypersensitivity reactions, including anaphylaxis, also have been reported. These reactions may be due to dimethyl sulfoxide (DMSO), Dextran 40, hydroxyethylstarch, or a plasma component of REGENECYTE.

REGENECYTE may contain residual antibiotics if the cord blood donor was exposed to antibiotics in utero. Monitor patients with a history of allergic reactions to antibiotics for allergic reactions following REGENECYTE administration.

5.2 Infusion Reactions

Infusion reactions are expected to occur and include nausea, vomiting, fever, rigors, or chills; flushing, dyspnea, hypoxemia, chest tightness, hypertension, tachycardia, bradycardia, dysgeusia, hematuria, and mild headache. Premedication with antipyretic, histamine antagonists, and corticosteroids may reduce the incidence and intensity of infusion reactions.

Patients may also experience severe reactions, including respiratory distress, severe bronchospasm, severe bradycardia with heart block or other arrhythmias, cardiac arrest, hypotension, hemolysis, elevated liver enzymes, renal compromise, encephalopathy, loss of consciousness, and seizures. Many of these reactions are related to the amount of DMSO administered. Minimizing the amount of DMSO administered may reduce the risk of such reactions, although idiosyncratic responses may occur even at DMSO doses thought to be

tolerated. The actual amount of DMSO depends on the method of preparation of the product for infusion. Limiting the amount of DMSO infused to no more than 1 gram per kilogram per day is recommended. *[See Overdosage (10)]*

Infusion reactions may begin within minutes of the start of infusion of REGENECYTE, although symptoms may continue to intensify and not peak for several hours after completion of the infusion. Monitor the patient closely during this period. If a reaction occurs, discontinue the infusion and institute supportive care as needed. If infusing more than one unit of REGENECYTE on the same day, do not administer subsequent units until all signs and symptoms of infusion reactions from the prior unit have resolved. Consult the transplant physician before continuing to infuse subsequent units.

5.3 Graft-versus-Host Disease

Acute and chronic graft-versus-host disease (GVHD) may occur in patients who have received REGENECYTE. Classic acute GVHD is manifested as fever, rash, elevated bilirubin, and liver enzymes, and diarrhea. Patients transplanted with REGENECYTE also should receive immunosuppressive drugs to decrease the risk of GVHD. *[See Adverse Reactions (6.1)]*

5.4 Engraftment Syndrome

Engraftment syndrome is manifested as unexplained fever and rash in the peri-engraftment period. Patients with engraftment syndrome also may have unexplained weight gain, hypoxemia, and pulmonary infiltrates in the absence of fluid overload or cardiac disease. If untreated, engraftment syndrome may progress to multiorgan failure and death. Once engraftment syndrome is recognized, begin treatment with corticosteroids to ameliorate the symptoms. *[See Adverse Reactions (6.1)*]

5.5 Graft Failure

Primary graft failure, which may be fatal, is defined as failure to achieve an absolute neutrophil count greater than 500 per microliter blood by Day 42 after transplantation. Immunologic rejection is the primary cause of graft failure. Patients should be monitored for laboratory evidence of hematopoietic recovery. Consider testing for HLA antibodies to identify patients who are alloimmunized prior to transplantation and to assist with choosing a unit with a suitable HLA type for the individual patient. *[See Adverse Reactions (6.1)]*

5.6 Malignancies of Donor Origin

Post-transplant lymphoproliferative disorder (PTLD) may develop in patients who have undergone HPC, Cord Blood transplantation. PTLD can manifest as a lymphoma-like disease in non-nodal sites.

PTLD can be fatal if not treated.

The incidence of PTLD appears to be higher in patients who have received antithymocyte globulin. The etiology is thought to be donor lymphoid cells transformed by Epstein-Barr virus (EBV). Consider serial monitoring for EBV DNA in blood of patients under high-risk groups.

Leukemia of donor origin also has been reported in HPC, Cord Blood recipients. The natural history is presumed to be the same as that for *de novo* leukemia.

5.7 Transmission of Serious Infections

Transmission of infectious disease may occur because REGENECYTE is derived from human blood.

Known or unknown infectious agents may cause disease. Donors undergo screening for increased risk of infection with human immunodeficiency virus (HIV), human T-cell lymphotropic virus (HTLV), hepatitis B virus (HBV), hepatitis C virus (HCV), *T. pallidum*, *T. cruzi*, West Nile Virus (WNV), transmissible spongiform encephalopathy (TSE) agents, and vaccinia. Donors complete screening for clinical evidence of sepsis, and communicable disease risks associated with xenotransplantation.

Maternal blood samples are tested for HIV types 1 and 2, HTLV types I and II, HBV, HCV, *T. pallidum*, WNV, and *T. cruzi*. REGENECYTE is tested for sterility. There may be an effect on the reliability of the sterility test results if the cord blood donor was treated with antibiotics. These measures do not completely eliminate the risk of transmitting these or other transmissible infectious diseases and disease agents. Call 626-646-2485 to report the occurrence of a transmitted infection to StemCyte.

Testing is also performed for evidence of donor infection due to cytomegalovirus (CMV).

Accompanying records may contain test results.

5.8 Transmission of Rare Genetic Diseases

REGENECYTE may transmit rare genetic diseases involving the hematopoietic system for which donor screening and/or testing has not been performed *[see Adverse Reactions (6.1)]*. Cord blood donors have been screened by family history to exclude inherited disorders of the blood and marrow. REGENECYTE has been tested to exclude donors with sickle cell anemia, and anemia due to abnormalities in hemoglobins C, D, and E. Because of the age of the donor at the time REGENECYTE collection takes place, the ability to exclude rare genetic diseases is severely limited.

6 ADVERSE REACTIONS

6.1 Clinical Study Experience

Because clinical trials occur under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety assessment of REGENECYTE is based primarily on the dataset for the COBLT Study (Study 1; n= 324), review of the data submitted to the FDA dockets from various sources (Study 2; n=1,299), and published reports of patients who received REGENECYTE (Study 3; n=54).

The most common infusion-related adverse reactions (≥5%), from pooled safety population (Study 1, Study 2 and Study 3) are hypertension, vomiting, nausea, bradycardia, and fever.

Study 1 (COBLT Study)

In Study 1, 324 patients received 442 infusions of HPC, Cord Blood (from multiple cord blood banks) using a total nucleated cell dose ≥ 2.5×10^7 /kg *[see Clinical Studies (14)]*. The most common infusion reactions are shown in Table 1. Day 100 mortality from all causes was 25% for patients transplanted with HPC, Cord Blood (from multiple cord blood banks) with total nucleated cell dose ≥ 2.5×10^7 /kg. Hypertension and any grades 3-4 infusion-related reactions occurred more frequently in patients receiving HPC, Cord Blood in volumes greater than 150 milliliters and in pediatric patients. The rate of serious adverse cardiopulmonary reactions was 0.8%. Engraftment syndrome developed in 15% of patients.

Table 1. Incidence of Infusion-Related Adverse Reactions Occurring in ≥ 1% of Infusions (COBLT Study; n=442 infusions)

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

Study 2 (Docket and Public Data)

Clinical data from the docket were pooled for 1,299 patients (120 adult and 1,179 pediatric) in Study 2. These were transplanted with HPC, Cord Blood (from multiple cord blood banks) with total nucleated cell dose ≥ 2.5×10^7 /kg *[see Clinical Studies (14)]*.

Day 100 mortality from all causes in Study 2 was 25%. Primary graft failure occurred in 16%; 42% developed grades 2-4 acute graft-vs-host disease; and 19% developed grades 3-4 acute graft-vs-host disease.

Data from Study 2 revealed nine cases of donor cell leukemia, one case of transmission of infection, and one report of transplantation from a donor with an inheritable genetic disorder. The data are not sufficient to support reliable estimates of the incidences of these events.

Study 3 (REGENECYTE)

Among the 54 patients who received REGENECYTE at a total nucleated cell dose of ≥2.5×10^7 /kg, there were voluntary reports for 388 infusions yielded information on infusion reactions *[see Clinical Studies (14)]*. Seven percent of patients (n=4) had an infusion reaction. The most common infusion reactions, occurring in > 1% of patients were hypertension (3.7%), nausea (3.7%) or vomiting (1.9%), hypotension (1%), and chest pain (1%).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

HPC, Cord Blood has been used in pediatric patients with disorders affecting the hematopoietic system that are inherited, acquired, or resulted from myeloablative treatment. *[See Dosage and Administration (2), Adverse Reactions (6), and Clinical Studies (14)]*

8.5 Geriatric Use

Clinical studies of HPC, Cord Blood (from multiple cord blood banks) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. In general, use caution when administering REGENECYTE to patients over age 65 considering their greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Disease

REGENECYTE contains Dextran 40 which is eliminated by the kidneys. The safety of REGENECYTE has not been established in patients with renal insufficiency or renal failure.

10 OVERDOSAGE

10.1 Human Overdosage Experience

There has been no experience with overdosage of HPC, Cord Blood in human clinical trials. Single doses of REGENECYTE up to 9.1×10^8 TNC/kg have been administered. HPC, Cord Blood prepared for infusion may contain dimethyl sulfoxide (DMSO). The maximum tolerated dose of DMSO has not been established, but it is customary not to exceed a DMSO dose of 1 gm/kg/day when given intravenously. Several cases of altered mental status and coma have been reported with higher doses of DMSO.

10.2 Management of Overdose

For DMSO overdosage, general supportive care is indicated. The role of other interventions to treat DMSO overdosage has not been established.

11 DESCRIPTIONS

REGENECYTE consists of hematopoietic progenitor cells, monocytes, lymphocytes, and granulocytes from human cord blood for intravenous infusion. Blood recovered from umbilical cord and placenta is volume reduced and partially depleted of red blood cells and plasma. The active ingredient is hematopoietic progenitor cells which express the cell surface marker CD34. The potency of cord blood is determined by measuring the numbers of total nucleated cells (TNC) and CD34+ cells, and cell viability. Each unit of REGENECYTE contains a minimum of 9×10^8 total nucleated cells with at least 1.25×10^6 viable CD34+ cells at the time of cryopreservation. The cellular composition of REGENECYTE depends on the composition of cells in the blood recovered from the umbilical cord and placenta of the donor. The actual nucleated cell count, the

CD34 cell count, the ABO group, and the HLA typing are listed in the accompanying records sent with each individual unit.

REGENECYTE has the following inactive ingredients: dimethyl sulfoxide (DMSO), citrate phosphate dextrose (CPD), hydroxyethylstarch, and Dextran 40. When prepared for infusion according to instructions, the infusate contains the following inactive ingredients: Dextran 40, human serum albumin, residual DMSO, and CPD.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hematopoietic stem/progenitor cells from HPC, Cord Blood migrate to the bone marrow where they divide and mature. The mature cells are released into the bloodstream, where some circulate and others migrate to tissue sites, partially or fully restoring blood counts and function, including immune function, of blood-borne cells of marrow origin. *[See Clinical Studies (14)]*

In patients with enzymatic abnormalities due to certain severe types of storage disorders, mature leukocytes resulting from HPC, Cord Blood transplantation may synthesize enzymes that may be able to circulate and improve cellular functions of some native tissues. However, the precise mechanism of action is unknown.

14 CLINICAL STUDIES

The effectiveness of REGENECYTE as defined by hematopoietic reconstitution, was demonstrated in the single-arm prospective COBLT study (Study 1), data in the FDA dockets and public information (Study 2), and in retrospective reviews of data from an observational database for REGENECYTE, using data from the Center for International Blood and Marrow Transplant Research (Study 3).

Study 1

A prospective, single-arm study conducted by the Cord Blood Transplantation study group (COBLT) of unrelated cord blood transplantation (CBT) to better define the role of this stem cell source for patients requiring unrelated allogeneic transplantation. The primary end point of the study was survival at 180 days. Secondary end points included engraftment, graft-versus-host disease, relapse, and long-term survival. Of the 324 patients enrolled in the study, 79% (n=257) were treated for hematologic malignancies. Preparative regimens and graft-vs-host disease prophylaxis were not standardized.

Study 2

A retrospective review of data from published literature and from observational registries, institutional databases, and cord blood bank reported to the docket for HPC, Cord Blood (from multiple cord blood banks. Of the 1,299 patients in the dockets and public data, 66% (n=862)

underwent transplantation as treatment for hematologic malignancy. The preparative regimens and graft-vs-host disease prophylaxis varied.

Study 3

In the REGENECYTE database, 81.5% of patients (44 of 54) underwent transplantation for a hematologic malignancy. The study group did not standardize preparative regimens and graft-vs-host disease prophylaxis or grade the reactions.

Table 2 shows results for patients who received a total nucleated cell dose ≥ 2.5×10^7/kg from at least a single cord blood unit manufactured at StemCyte Cord Blood Bank, alone or in combination with another unit of HPC, Cord Blood and who had an HLA match ≥ 4/6, as well as the outcomes from the COBLT study and the docket data. Neutrophil recovery is defined as the time from transplantation to the first of 3 successive days with an absolute neutrophil count ≥ 500 per microliter after post-transplantation nadir. Platelet count recovery is the time to the first of 3 consecutive days with an absolute platelet count of 20,000 cells per microliter or higher in the absence of platelet transfusion for 7 consecutive days. Erythrocyte recovery is the time to a reticulocyte count greater than 30,000 cells per microliter. The total nucleated cell dose and degree of HLA match were inversely associated with the time to neutrophil recovery in the docket data.

Table 2. Hematopoietic Recovery in Patients Transplanted with HPC in Study 1, 2, and 3

Data Source	**Study 1 (The COBLT Study) ***	**Study 2 (Docket and Public Data) ****	**Study 3 (REGENECYTE)**
Design	Single-arm prospective	Retrospective	Retrospective
Number of patients	324	1299	54***
Median age (range) years	4.6 (0.07- 52.5)	7.0 (<1- 65.7)	37.5 (<1- 70.3)
Sex	59% male 41% female	57% male 43% female	48% male 52% female
Median TNC Dose (range) (x 10^7/kg)	6.7 (2.6-38.8)	6.4 (2.5-73.8)	5.8 (2.2-34.4)
Neutrophil Recovery at Day 42 (ANC >500/μL) (95% CI)	76% (71%, 81%)	77% (75%, 79%)	91% (81%, 97%)
Platelet Recovery at Day 100 (20,000/uL) (95% CI)	57% (51%, 63%)	-	72% (58%, 83%)
Platelet Recovery at Day 100 (50,000/uL) (95% CI)	46% (39%, 51%)	45% (42%, 48%)	73% (54%, 88%)
Erythrocyte Recovery at Day 100 (95% CI)	65% (58%, 71%)	-	-
Median time to Neutrophil Recovery	27 days	25 days	22 days
Median time to Platelet Recovery (20,000/uL) ##	90 days	-	50 days

Data Source	Study 1 (The COBLT Study) *	Study 2 (Docket and Public Data) **	Study 3 (REGENECYTE)
Median time to Platelet Recovery (50,000/uL) ##	113 days	122 days	64 days
Median time to Erythrocyte Recovery	64 days	-	-

* Data available from the National Heart, Lung, and Blood Institute

** FDA-1997-N-0010

*** Not all 54 patients had evaluable data for the listed outcome parameters. Forty-four (44) patients had evaluable data for median TNC dose (from units $\geq 2.0 \times 10^7$) and 34 patients had evaluable data for platelet recovery $\geq 50{,}000/\mu L$ (excludes 20 patients with missing data).

Eleven (11) subjects (20%) died before platelet recovery. They were imputed with the longest recovery time in the analysis.

16 HOW SUPPLIED/STORAGE AND HANDLING

REGENECYTE is supplied as a cryopreserved cell suspension in a sealed bag containing a minimum of 9×10^8 total nucleated cells with a minimum of 1.25×10^6 viable CD34+ cells in a volume of 25 milliliters (ISBT 128, Product Code S1393000, ISBT 128 Facility Identifier Number W2199). The pre- cryopreservation nucleated cell content is provided in the accompanying records.

Store REGENECYTE at or below -150° C until ready for thawing and preparation.

17 PATIENT COUNSELING INFORMATION

Discuss the following with patients receiving REGENECYTE:

- Hypersensitivity and Infusion Reactions: Inform patient that hypersensitivity and infusion reactions may occur after REGENECYTE administration. Advise patient to seek immediate medical evaluation if any signs and symptoms of hypersensitivity or acute infusion reactions occur, such as fever, chills, itching, rash or hives, swollen tongue, lips and face, fatigue, breathing problems, dizziness, nausea, vomiting, headache, or muscle aches. *[see Warnings and Precautions (5.1, 5.2)]*

- Graft-versus-Host Disease: Inform patient that graft-versus-host disease may occur after REGENECYTE administration. Advise patient to seek immediate medical evaluation if any signs or symptoms suggestive of graft-vs-host disease occur, including fever, rash, diarrhea, or yellowing of the eyes. *[see Warnings and Precautions (5.3)]*

- Engraftment Syndrome: Inform patient that engraftment syndrome may occur after REGENECYTE administration. Advise patient to seek immediate medical evaluation if any signs or symptoms suggestive of engraftment syndrome occur including fever, rash, difficulty breathing, and weight gain. *[see* Warnings and Precautions (5.4)*]*

- Graft Failure: Inform patient about the possible risk of graft failure with REGENECYTE administration. *[see* Warnings and Precautions (5.5)*]*

- Malignancies of Donor Origin: Inform patient about the possible risk of cancer of blood cells with REGENECYTE administration. *[see* Warnings and Precautions (5.6)*]*

- Transmission of Serious Infections and Rare Genetic Diseases: Inform patient about the possible risk of transmission of serious infections and genetic diseases with REGENECYTE administration. *[see Warnings and Precautions (*5.7, 5.8*)]*

INSTRUCTIONS FOR PREPARATION FOR INFUSION

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INSTRUCTIONS FOR PREPARATION FOR INFUSION

StemCyte recommends washing of REGENECYTE prior to infusion. Once the wash procedure is complete, the product must be infused within two hours. Included below are instructions for washing REGENECYTE. Prior to thawing of the unit, read the thaw and wash instructions below. Prepare all required reagents, supplies, equipment, and forms listed, and ensure they are readily available.

1. Materials and Equipment

1.1 Materials:

- Human Albumin 25% USP (OctaPharma, Ref. NDC 68982-643-02)
- 10 % LMD Dextran 40 in 0.9 % Sodium Chloride Injection USP (Hospira, Ref. NDC 0409-7419-14)
- Fenwal Transfer Pack container with 8 Couplers — 600 mL (required number: 1) (Fenwal, Ref. 4R2027)
- Fenwal Transfer Pack container with Coupler — 300 mL (required number: 2) (Fenwal, Ref. 4R2014)
- Sampling Site Coupler (Fenwal, Ref. 4C2405)
- 50-mL Sterile Disposable Syringe (Becton Dickinson, Ref. 309653) or equivalent (required number: 4)
- 18G x 1" Injection Needle (McKesson, Ref. 102-N18153) or equivalent
- Isopropyl Alcohol Spec-Wipes (VWR, Ref. 115-0034) or equivalent
- Isopropyl Alcohol Swab-Sticks (McKesson, Ref. NDC 68599-8635-1) or equivalent
- Sterile zip-lock 20 cm × 25 cm (LK, Ref. LAB20810) or equivalent
- Sterile gauze pads 4 × 4 (McKesson, Ref. 44082000) or equivalent
- Centrifuge Bag 18 cm × 25 cm (Fenwal, Ref. 4R4424)
- Sterile scissors
- Sterile hemostats (optional)
- Reusable Cold Packs (Ice-Brix) or equivalent
- PPE (gloves, sleeves, lab coat, face shield)
- Product labels
- 1.5 mL sampling tubes
- 2 mL cryovials (Corning, Ref. 430659)

1.2 Equipment:

- Biological Safety Cabinet (Class II Type A/B)
- Refrigerated Blood Bank Centrifuge (Sorvall, Model BP16, Max. speed 5000 rpm)
- Centrifuge Buckets (Haemaflex, Catalog Number: 75003846)
- Sterile Tubing Welder (Terumo, Model ME-SC203A)
- Plasma Extractor (Fenwal, Model Number: 4R4414)

- Digital Scale (1- 2000 grams)
- Heat Sealer (Fresenius Kabi, Hand-Held 902403 F3003, Main Unit 902566b Universal)
- 37 °C Water Bath (Thermo Scientific, Model TSGP02)
- Refrigerator (LabRepCo, Model LABHP-10-HG)
- Cryoshipper (MVE, Manufacturer's Part Number: 14146924)
- Vapor-phase Liquid Nitrogen Freezer (MVE, Ref. 21093075)
- Automated cell counter

2. Product Receipt

2.1 REGENECYTE is shipped frozen in a dry-shipper that maintains the temperature at ≤ -150°C.

2.2 The dry shipper can maintain the temperature of ≤ -150°C for 5 days from the shipping date. If the unit will not be used within that timeframe, transfer the unit into a storage device capable of maintaining the unit at ≤ -150°C.

NOTE: *Handle the cryobag with extreme caution when removing it from the liquid nitrogen, metal cassette, and protective overwrap, and during the thaw procedure. Cryobags can be very fragile.*

2.3 Inspect the shipper for tampering or damage prior to opening.

2.4 Inspect the temperature datalogger on the shipper.

NOTE: *If the Alarm indicator shows up, immediately contact StemCyte.*

2.5 Open the shipper and remove the metal cassette that contains REGENECYTE.

2.6 Carefully open the cassette. The cassette will contain REGENECYTE in a cryobag sealed in an overwrap and padded in an absorbent sheet. Cracks or breakages in the overwrap do not indicate damage to the unit.

2.7 Inspect the integrity of the cryobag.

NOTE: *If there is damage to cryobag, place the cryobag back into storage at ≤ -150°C (place the cryobag in additional overwrap if necessary). Consult with the transplant physician and contact StemCyte.*

2.8 Verify that the unit ID number on the cryobag matches the unit ID number on all applicable paperwork, and the unit ID number matches the expected unit for the intended recipient.

NOTE: *If there are any discrepancies in unit ID, consult with the transplant physician and contact StemCyte.*

3. Preparation

3.1 General

3.1.1 Verify equipment are within calibration range and available for use.

3.1.2 Verify processing area is clean and sterilized accordingly.

3.1.3 Verify the water bath is set at 37 °C and ready for use.

3.1.4 Verify the BSC is functional, and the cabinet has been sterilized prior to use.

NOTE: *Allow cabinet blowers to operate for at least 3 to 5 minutes before beginning work to allow the BSC to "purge" particulates.*

3.1.5 Verify the centrifuge is set at 2-8 °C and programmed at 880 × g for 20 minutes with brakes off.

3.1.6 Verify the cryoshipper is charged with liquid nitrogen and the temperature is ≤ -150 °C prior to use.

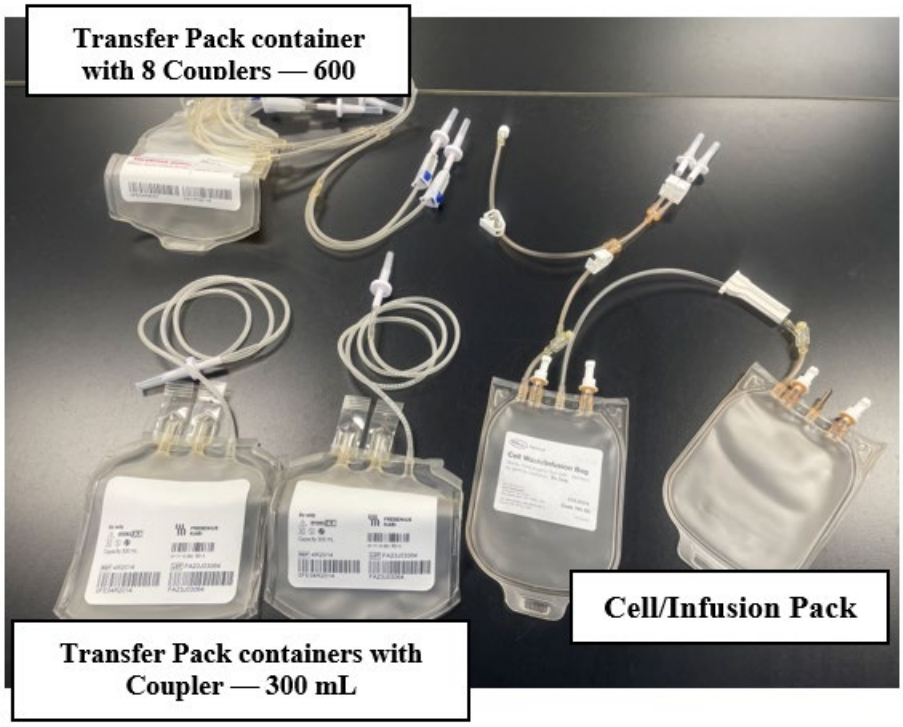
3.1.7 Verify materials are sterile and within expiration date.

3.1.8 Record manufacturer information, lot number, expiration date and calibration date (if available).

3.2 Preparation of Cell Wash Kit

3.2.1 Acquire 1x Transfer Pack container with 8 Couplers — 600 mL, and 2x Transfer Pack container with Coupler — 300 mL and a Cell Wash/Infusion Pack shown in **Figure 1**.

Figure 1

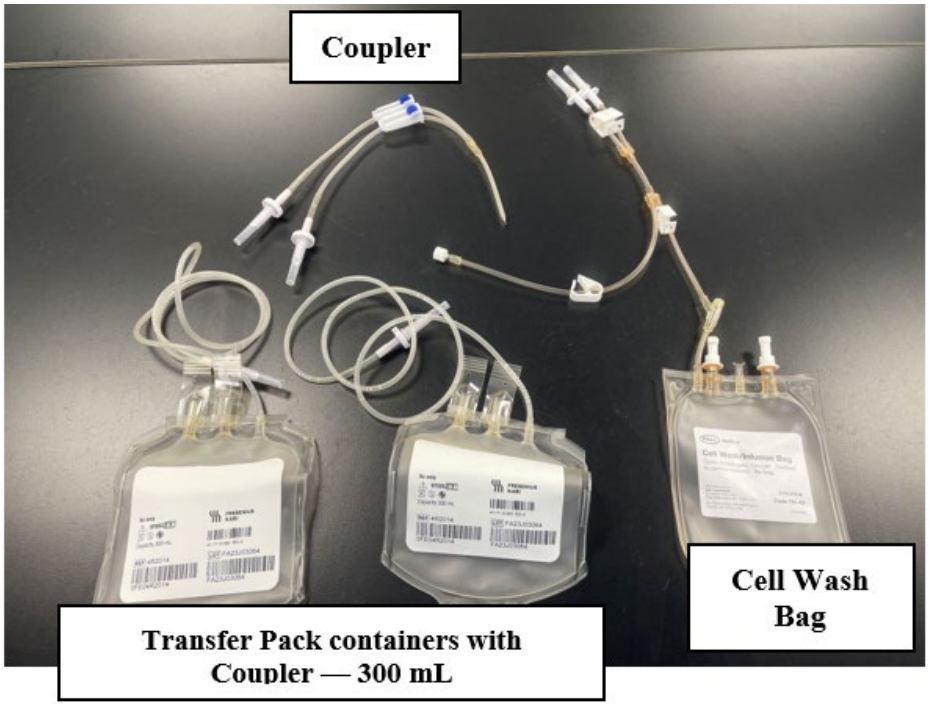


3.2.2 From the Transfer Pack container with 8 Couplers — 600 mL, heat seal off 1 set of couplers using the heat sealer and discard the rest of the transfer pack and 7 couplers.

3.2.3 From the Cell Wash/Infusion Pack, heat seal off the Infusion Bag and discard.

3.2.4 **Figure 2** shows the necessary components to generate the cell wash kit. Ensure that the roller clamps and pinch clamps are retained on each tube.

Figure 2



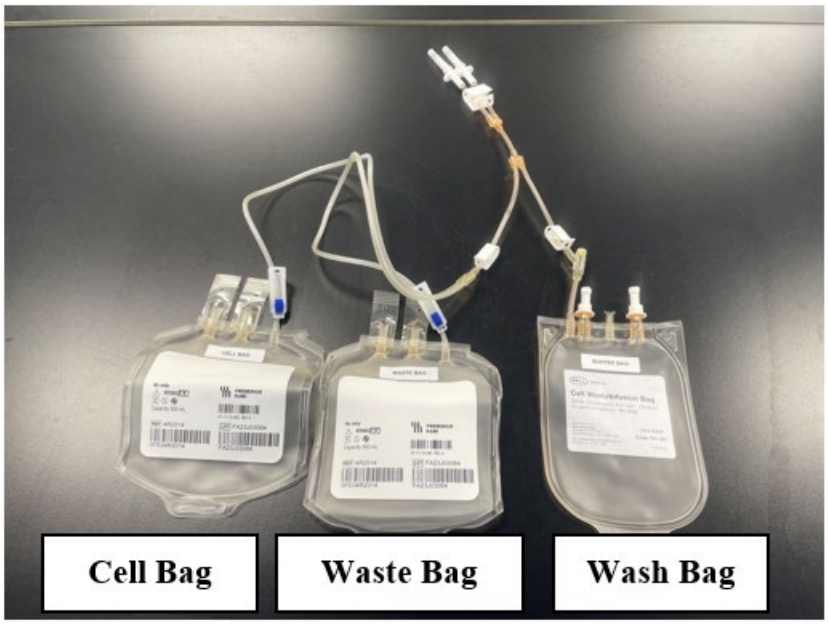
3.2.5 Sterile connect the end of the coupler to each 300 mL Transfer Pack so that each 300 mL Transfer Pack is connected and ending in a singular tubing.

3.2.6 With the free end of the coupler, sterile connect to the free end of the remaining Cell Wash kit. Do not use the dual spike end of the Cell Wash kit.

3.2.7 **Figure 3** shows the final Cell Wash kit with the 300 mL Transfer Pack labelled as "Cell Bag" and "Waste Bag." The remaining Cell Wash bag is labelled as "Wash Bag."

3.2.8 Transfer the Cell Wash kit to the Biological Safety Cabinet (BSC).

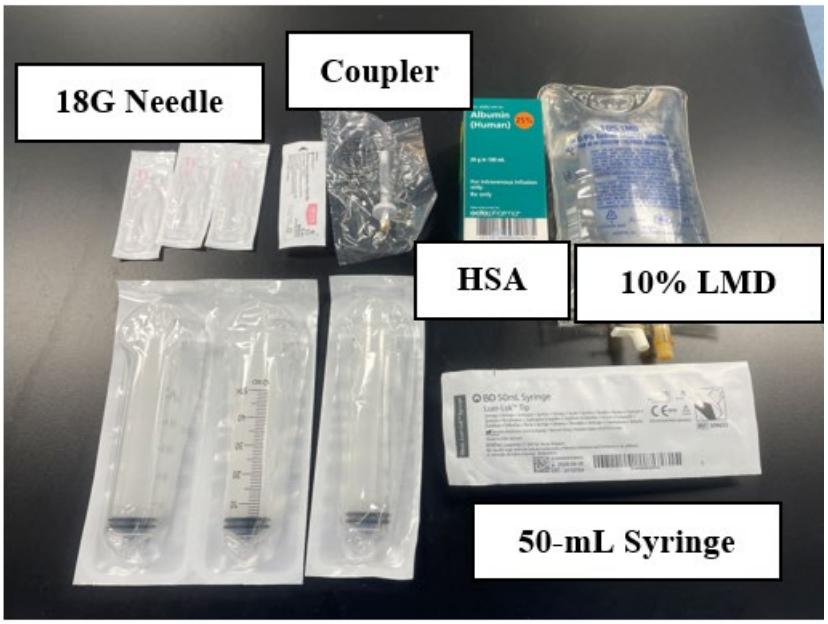
Figure 3



3.3 Preparation of Wash Buffer

3.3.1 Acquire a sample coupler, 4 × 18G × 1" injection needles, 4 × 50 mL syringes, 1 bottle of 25% Human Serum Albumin (HSA) and 1 bag of 10% LMD (shown in **Figure 4**) and transfer to the BSC.

Figure 4



3.3.2 Connect each 18G × 1" needle to each 50 mL syringe.

3.3.3 Open the HSA bottle and expose the puncture top. Swipe the top with an isopropyl alcohol (IPA) swab stick to sterilize.

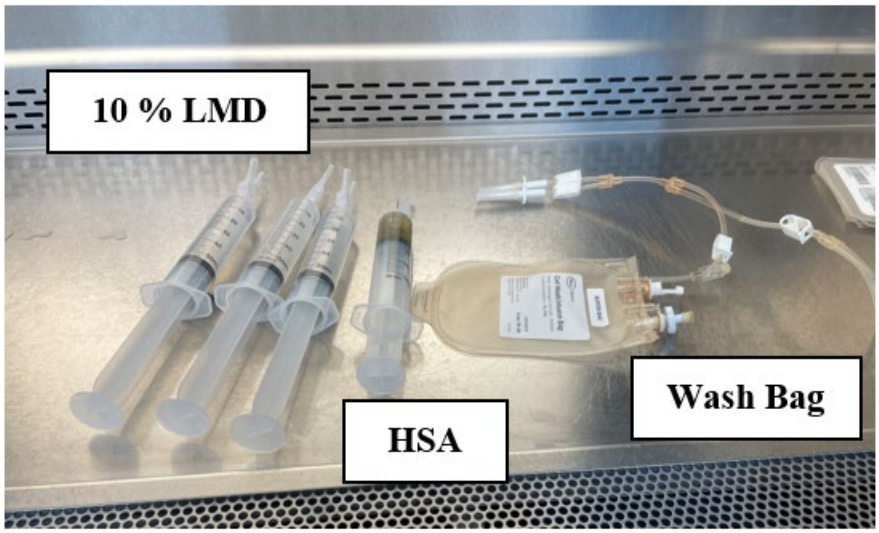
3.3.4 Remove the 10% LMD solution bag from the outer bag and swipe the puncture port to sterilize.

3.3.5 Using one 50 mL syringe with needle, puncture the top of the Human Serum Albumin (HSA) bottle and draw out 20 mL of the 25% HSA solution.

3.3.6 Using the 50 mL syringe with needle attached, draw out 50 mL of 10% LMD solution through the injection port. Continue with the other two 50 mL syringes with needles to end with 3 syringes filled with 50 mL of 10% LMD solution.

3.3.7 Connect the sample site coupler to an open port on the "Wash Bag" as shown in **Figure 5**.

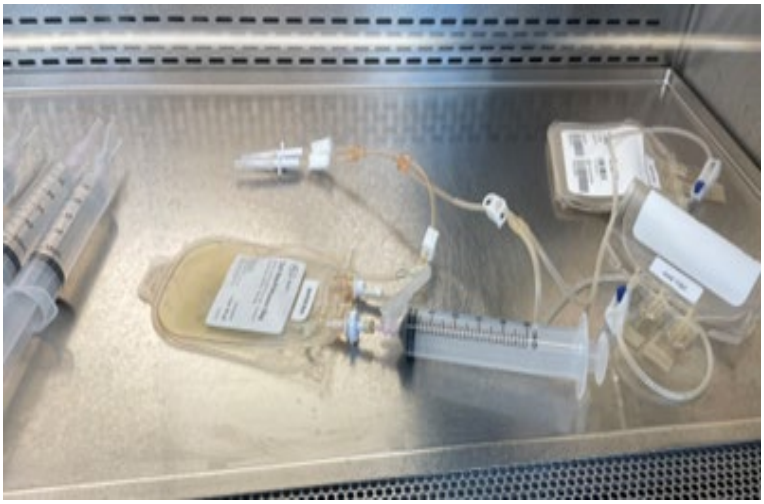
Figure 5



3.3.8 Ensure the roller clamps and pinch clamps are all closed on the Cell Wash kit.

3.3.9 Inject the contents of the syringes to the "Wash Bag" through the sample site coupler shown in **Figure 6.**

Figure 6



3.3.10 The "Wash Bag" should now contain 20 mL of 25 % HSA and 150 mL of 10% LMD (approximately 3% human albumin in Dextran 40 and 0.9 % Sodium Chloride) and designated as Wash Buffer.

3.3.11 Refrigerate the Cell Wash kit containing the Wash Buffer at 2-8 °C for at least 30 minutes prior to use.

4. Procedure

4.1 Thawing

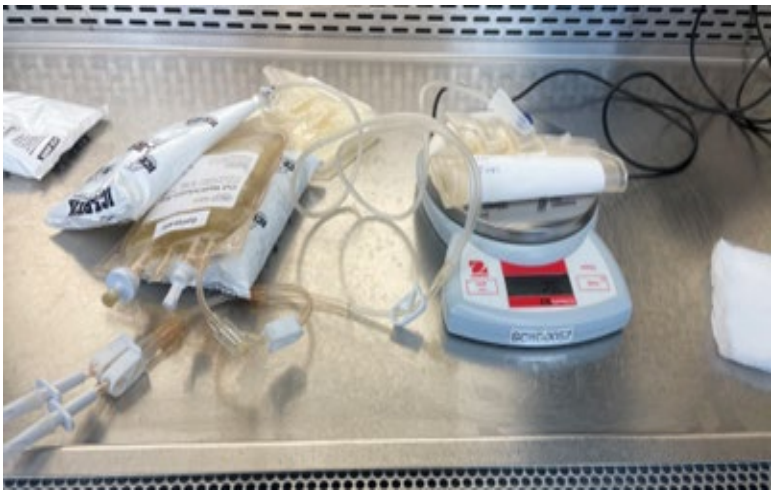
4.1.1 Acquire sterile zip-lock bag.

4.1.2 Ensure the water bath is ready at 37 °C.

4.1.3 Ensure the cryoshipper temperature is ≤ -150 °C.

4.1.4 Place the “Wash Bag” between ice packs and the “Cell Bag” on the scale as shown in **Figure 7**.

Figure 7



4.1.5 Retrieve the frozen REGENECYTE from the Liquid Nitrogen Freezer and transfer quickly to the cryoshipper. Use the cryoshipper to temporarily store and transport the frozen REGENECYTE until ready to thaw.

4.1.6 Inside the laboratory, remove the frozen REGENECYTE from the cryoshipper.

4.1.7 Remove the frozen REGENECYTE from the cassette as shown in **Figure 8**.

Figure 8

4.1.8 Remove the overwrap to expose the frozen cryobag (REGENECYTE). Check the integrity of the cryobag for cracks. If the cryobag is compromised, do not continue

with the thaw procedure, and quickly return the frozen cryobag to the cassette and back into the cryoshipper.

4.1.9 Using sterile scissors, separate the frozen segments from the frozen cryobag as shown in **Figure 9**.

Figure 9

4.1.10 Place frozen segments into labelled 2-ml cryovials and store segments in liquid or vapor phase of liquid nitrogen at or below -150^0 C until they are thawed for testing.

4.1.11 Place the frozen cryobag inside the ziplock bag and place into the water bath as shown in **Figure 10** and **Figure 11**.

4.1.12 Thaw the frozen cryobag until the product reaches a slushy/liquid consistency (approximately 4 – 6 minutes).

4.1.13 Remove the thawed cryobag from the ziplock bag and gently wipe the cryobag with IPA wipes before placing inside the BSC.

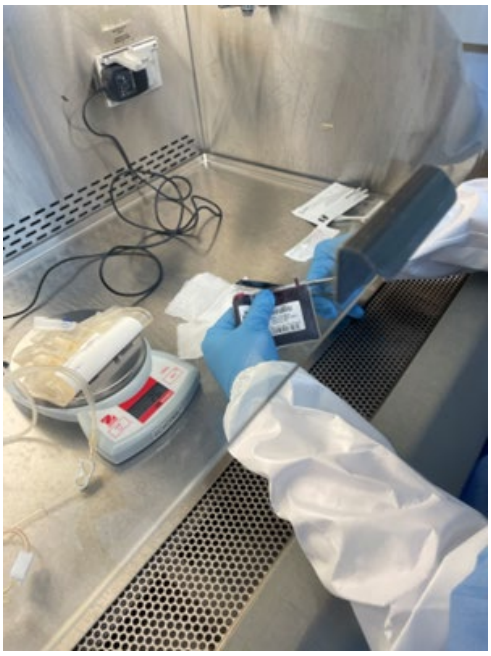
Figure 10

Figure 11

4.2 Diluting

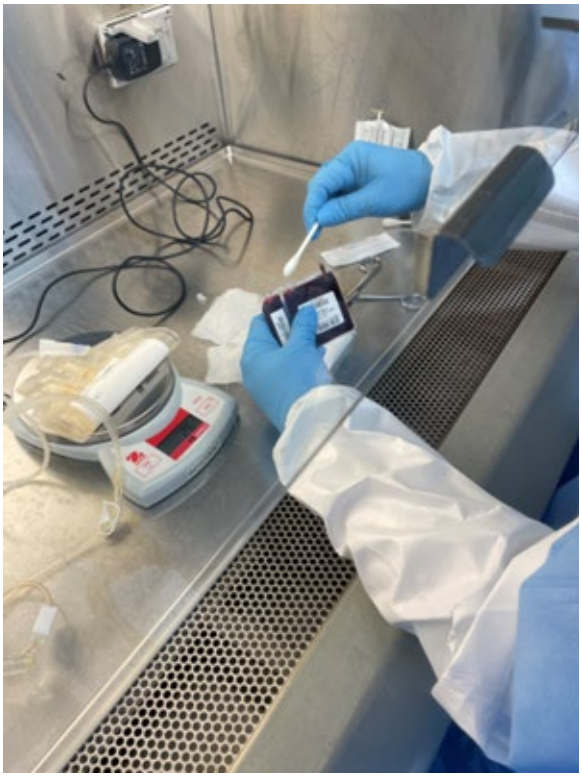
4.2.1 Inside the BSC, cut the port of the cryobag with sterile scissors (**Figure 12**).

Figure 12



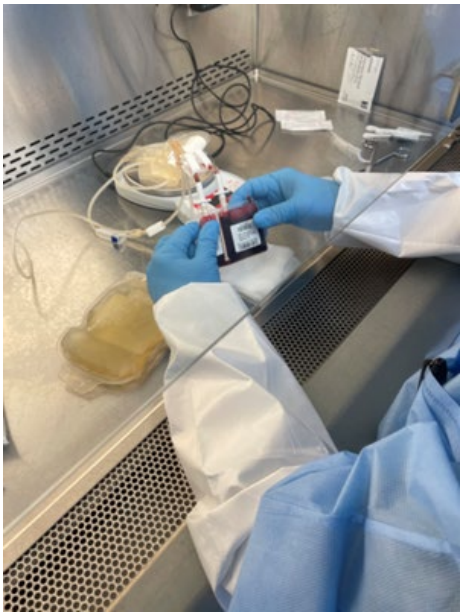
4.2.2 Wipe down the open ports with IPA swab sticks (**Figure 13**).

Figure 13



4.2.3 Open the roller clamps on pinch clamps to the “Cell Bag” and connect the Cell Wash kit to the thawed cryobag using the two spike ends to the open ports (**Figure 14**).

Figure 14

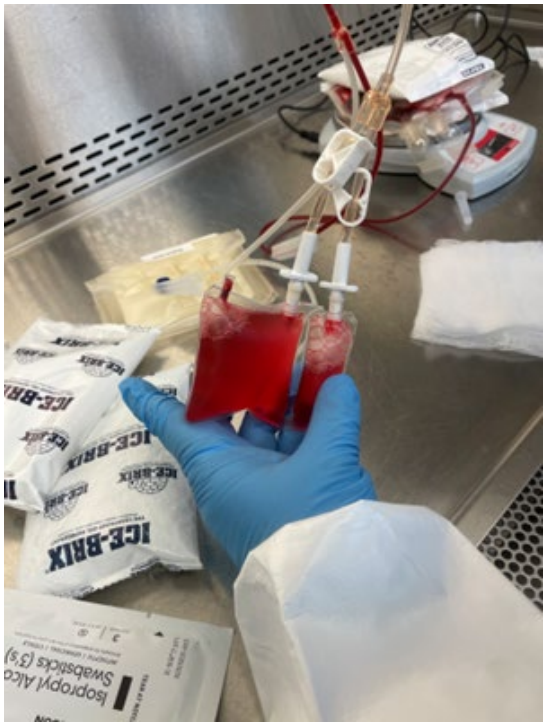


4.2.4 Ensure the spike ends connections are secured and slowly transfer the thawed unit into the “Cell Bag” of the Cell Wash kit.

4.2.5 Close off the “Cell Bag” using the pinch clamp and open the pinch clamp on the “Wash Bag” containing the wash buffer.

4.2.6 Transfer the wash buffer into the cryobag with the residual cord blood. Transfer approximately weighed 25 mL of the wash buffer from the “Wash Bag” on the digital scale into the cryobag (**Figure 15**).

Figure 15



4.2.7 Close the pinch clamp on the “Wash Bag” to stop the wash buffer transfer to the cryobag.

4.2.8 Gently mix the cryobag and open the pinch clamp on the “Cell Bag” to transfer the contents of the cryobag to the “Cell Bag.”

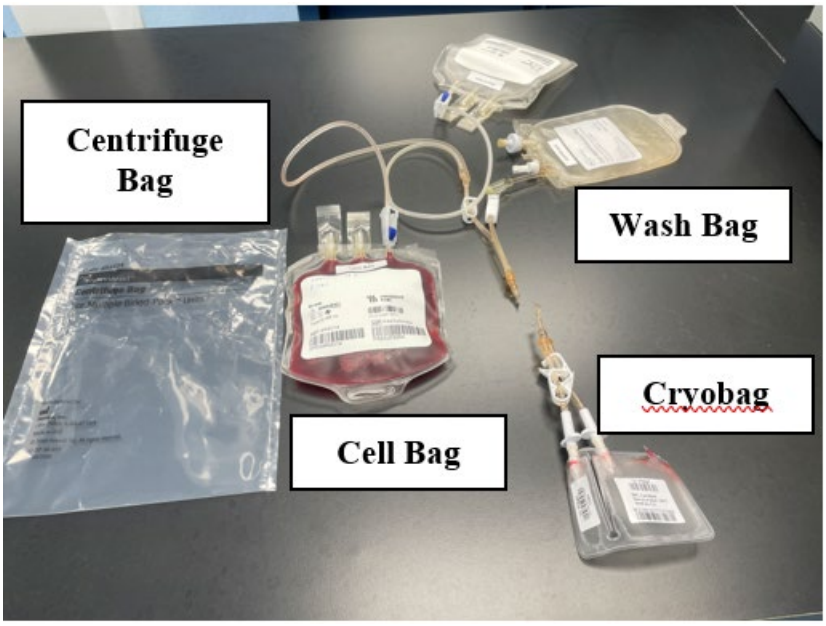
4.2.9 Close the pinch clamp of the “Cell Bag” when the transfer is complete.

4.2.10 The “Cell Bag” should contain approximately 50 mL total volume (25 mL of thawed cord blood and 25 mL of wash buffer containing residual cord blood). The volume can be checked using the scale and approximate the density of the solution as 1 g/mL.

4.2.11 Repeat the wash step 4.2.5 to 4.2.10 four more times until the total volume of diluted REGENECYTE reaches approximately 150 mL

4.2.12 When complete, strip the line clean and heat seal off the cryobag and discard (**Figure 16**).

Figure 16



4.2.13 Acquire a centrifuge bag for the wash step.

4.3 Washing

4.3.1 Verify the centrifuge is set at 2-8 °C and programmed at 880 × g for 20 minutes with the **brakes off**.

4.3.2 Acquire the centrifuge insert and centrifuge bucket.

4.3.3 Place the "Cell Bag" containing the diluted cord blood into the sterile centrifuge bag as a preventative measure should the "Cell Bag" burst during the centrifugation.

4.3.4 Place the "Cell Bag" into the centrifuge insert and the centrifuge insert into the centrifuge bucket as shown in **Figure 17**.

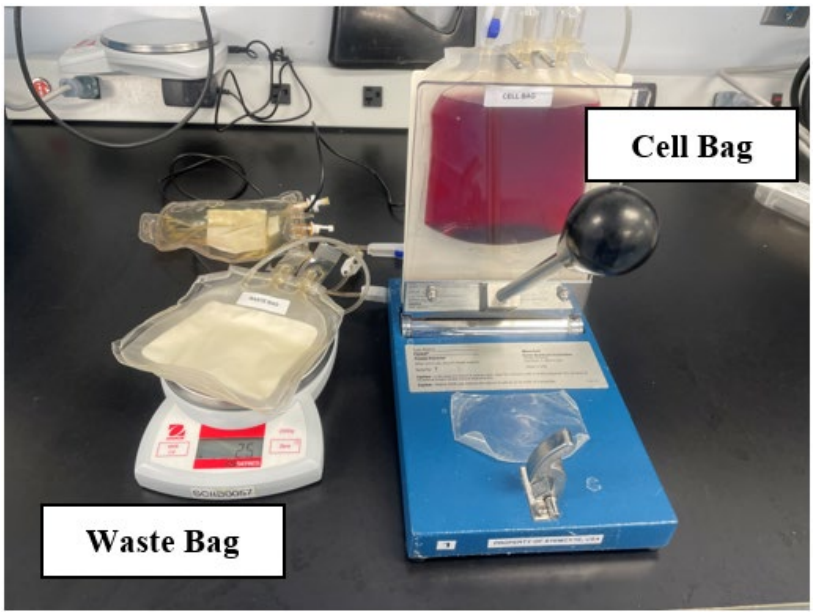
Figure 17

4.3.5 Place the bucket into the centrifuge. Ensure that the opposite bucket is balanced before centrifugation.

4.3.6 Start the centrifuge program for 880 × g for 20 minutes with the **brakes off**.

4.3.7 After the completion of the centrifugation, carefully remove the pelleted "Cell Bag" and place it on the plasma extractor and place the "Waste Bag" on the scale as shown in **Figure 18**.

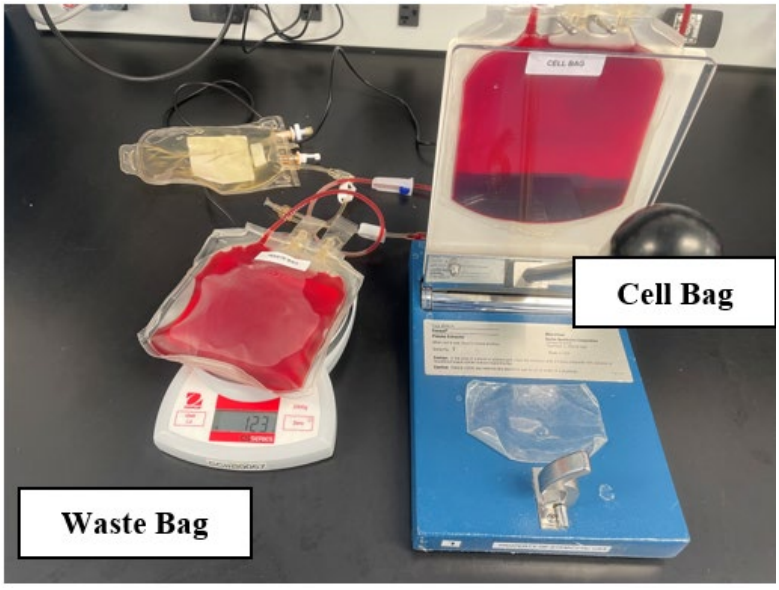
Figure 18



4.3.8 Open the pinch clamp on the "Waste Bag" and the "Cell Bag."

4.3.9 Allow the supernatant from the "Cell Bag" to flow into the "Waste Bag" until only the dark cell pellet remains as shown in **Figure 19**.

Figure 19



4.3.10 Close the pinch clamp on the “Cell Bag” when the transfer is complete.
4.3.11 Strip the tubing line from the “Cell Bag” to the “Waste Bag” and close the pinch clamp.
4.3.12 The final volume in the “Waste Bag” may be greater than 125 mL.
4.3.13 This volume should be subtracted from the total volume of approximately 150 mL to determine the appropriate volume to resuspend the cell pellet to the original volume of 25 mL.
4.3.14 Place the “Cell Bag” on the scale and open the pinch clamp. Open the pinch clamp on the “Wash Bag” containing the Wash Buffer and transfer the appropriate amount as calculated in 4.3.13 to resuspend the cell pellet to obtain a final volume of 25 mL.
4.3.15 Close the pinch clamp on the “Wash Bag” and “Cell Bag” when complete.
4.3.16 Heat seal off the “Cell Bag” for the washed product for infusion.

5. Emergency Product Recovery in the Event of a Container Failure

If the Cryobag is compromised, move further handling into the BSC after thawing. Call StemCyte at 626-646-2485 as soon as possible. Notify the transplant physician and the laboratory director immediately. The transplant physician or (designee) will determine whether to use or discard the product and whether any additional REGENECYTE should be requested. If the product is accepted for use, recovery of the product may be attempted as described below.

5.1 Prepare an empty transfer bag with a sampling site coupler.
5.2 Use a long (3-5 inch) blunt needle (a sterile spinal needle with trochar removed, if available).
5.3 Attach the blunt needle to a sterile 60 mL syringe.
5.4 Aspirate the product, replace the blunt needle with a standard needle and inject it into a sterile transfer bag via a sampling site coupler.
5.5 Continue processing of the transferred product from the point container failure was identified.
5.6 Perform sterility testing on the product sample after final preparation step.

CONTACT INFORMATION

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Cord Blood Services
13800 Live Oak Ave
Baldwin Park, CA 91706
Phone Number: 626-646-2485
Hours: 8:00-17:00 Pacific Standard Time