Full Title: A Phase II Single-Center, Open-Label, Safety and Efficacy Study of Propylene Glycol-Free Melphalan (Evomela) in AL amyloidosis Patients Undergoing Autologous Stem Cell Transplantation

Simple Title: Propylene Glycol-Free Melphalan (Evomela) in AL Amyloidosis Patients

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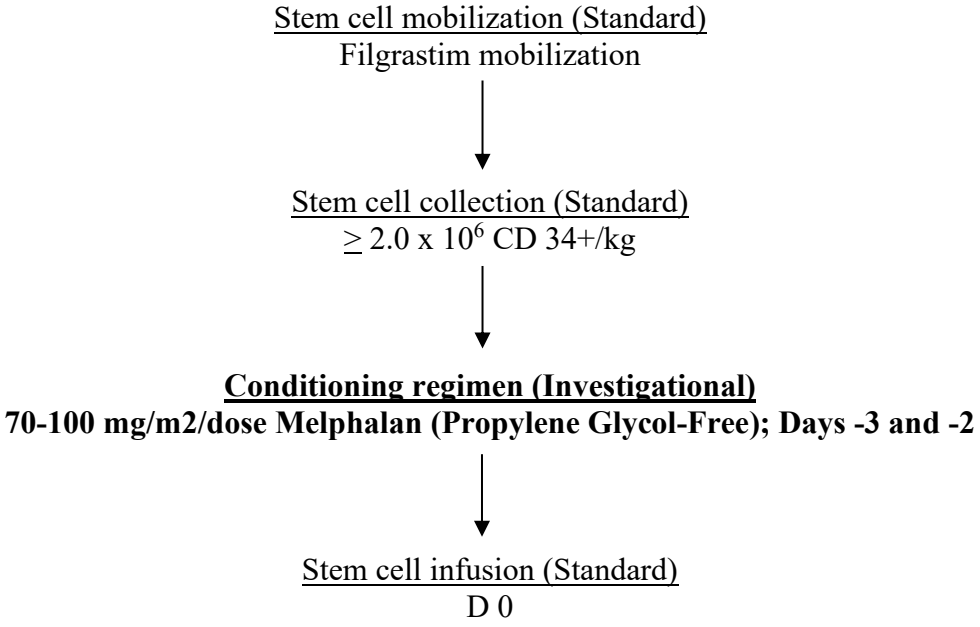

1. OBJECTIVES

1.1 Title: A Phase II Single-Center, Open-Label, Safety and Efficacy Study of Melphalan (Propylene Glycol-Free) in AL Amyloidosis Patients Undergoing Autologous Stem Cell Transplantation

1.2 Study Design:

This is a single arm, open label study designed to evaluate the safety and efficacy of melphalan (propylene glycol-free) in patients with AL amyloidosis. Treatment will be comprised of melphalan (propylene glycol-free) administered intravenously at a dose of 70-100 mg/m2/day on Days -3 and -2 as conditioning prior to autologous stem cell transplantation.

After giving written informed consent, subjects will be evaluated for eligibility for enrollment in the study. Baseline evaluations will be performed as outlined in Section 7. Subjects who satisfy all inclusion and exclusion criteria will begin the study drug. Subjects will be monitored from the time of the medication administration until discharge from the transplant program for safety. Organ function and hematologic status will also be measured at 6 and 12 month follow-up visits.

Standard response criteria for AL amyloidosis hematologic and organ response will be used (Gertz et al. 2005, Palladini et al 2012). Overall response rate will be measured and participants will be categorized into complete response, very good partial response, partial response and progressive disease. Progression free survival, organ response, and safety and tolerability of Melphalan (Propylene Glycol-Free) will be assessed.

1.3 Patient population: (Specific inclusion and exclusion criteria are detailed in section 3)

1.4 Number of sites: One (Boston Medical Center, 820 Harrison Ave, FGH-2, Boston, MA 02118)

1.5 Number of patients: 43 patients

1.6 Primary Objective:

- To determine the safety profile of melphalan (propylene glycol-free) in the conditioning regimen prior to autologous stem cell transplantation in AL amyloidosis patients, including adverse events related to renal dysfunction (was acute renal failure is defined as either a >/=1 mg/dL increase in serum creatinine or a doubling of serum creatinine to >/=1.5 mg/dL for at least 2 days.), cardiac dysfunction (new arrhythmia), or autonomic dysfunction (decline in sitting systolic blood pressure of ≥20mm Hg compared to baseline)

1.7 Secondary Objectives:

- To assess time until neutrophil and platelet engraftment
- To assess treatment related mortality at 100 days
- To assess hematologic overall response rate at 6 months after autologous stem cell transplantation
- To evaluate organ response at 12 months after autologous stem cell transplantation
- To monitor for number of hospitalizations

2. BACKGROUND

2.1 Study Agent

2.1.1. Melphalan (propylene glycol-free)

Melphalan (propylene glycol-free) is an alkylating agent of the bischloroethylamine type. The chemical name is 4-[bis(2-chloroehtyl)amino]-L-phenylalanine hydrochloride. Its molecular formula is $C_{13}H_{18}Cl_2N_2O_2$ and the molecular weight is 341.67. Cytotoxicity of the drug is related to interstrand cross-linking with DNA. It is active against both resting and rapidly dividing tumor cells.

2.1.2. Clinical experience with melphalan (propylene glycol-free)

From 2010 to 2011 a phase IIa, open-label, randomized cross-over trial was performed evaluating propylene glycol-free melphalan and melphalan hydrochloride (Alkeran) in multiple myeloma patients undergoing treatment with autologous stem cell transplantation. In this trial, 24 patients with multiple myeloma were treated with 100 mg/m^2 of melphalan in two doses prior to autologous stem cell transplantation. Patients received one dose of melphalan hydrochloride (Alkeran) and one dose of melphalan (propylene glycol-free) on alternate days. All patients achieved myeloablation. Pharmacokinetic studies demonstrated that propylene-glycol free melphalan was bioequivalent to previously marketed melphalan hydrochloride. Pharmacokinetic studies demonstrated a maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) were approximately 10% higher after propylene-glycol free melphalan when compared with melphalan hydrochloride.

The safety and efficacy of melphalan (propylene glycol-free) was evaluated in a phase IIb, open-label, multicenter study which enrolled 61 multiple myeloma patients (Hari). Melphalan (propylene glycol-free) was administered over approximately 30 minutes intravenously as 2 doses of 100mg/m^2 as conditioning prior to autologous stem cell transplantation on Days -3 and -2. Data from this trial demonstrated an overall response rate of 100%, with a complete response rate of 21% and overall partial response rate of 79%. Based on this data the efficacy and safety of this new formulation was demonstrated.

2.1.3. Summary of Safety Data

All patients in the phase IIb, open-label trial had at least 1 grade 4 hematologic adverse event, which was indicative of myeloablation. Hematologic adverse events are depicted in the figures below.

Hematologic Adverse Events

ADVERSE EVENT (AE)	GRADE 3	GRADE 4	ALL
All hematologic AEs	61 (100%)	61 (100%)	61 (100%)
Neutropenia	3 (5%)	58 (95%)	61 (100%)
Leukopenia	1 (2%)	60 (98%)	61 (100%)
Lymphopenia	0 (0%)	60 (98%)	60 (98%)
Thrombocytopenia	0 (0%)	60 (98%)	60 (98%)
Anemia	31 (51%)	0 (0%)	40 (66%)
Febrile Neutropenia	17 (28%)	0 (0%)	25 (41%)

Nonhematologic adverse events were mostly grade 1 or 2. No treatment-related deaths occurred. The incidence of grade 3 oral mucositis was 13% with no grade 4 events. Side effects occurring in more than 50% of patients included diarrhea, nausea, fatigue, hypokalemia, and vomiting.

Nonhematologic Adverse Events experienced by ≥25% of patients

Adverse Event	No. of patients
Diarrhea	57 (93%)
Nausea	55 (90%)
Fatigue	47 (77%)
Hypokalemia	45 (74%)
Vomiting	39 (64%)
Hypophosphatemia	30 (49%)
Decreased appetite	30 (49%)
Pyrexia	29 (48%)
Constipation	29 (48%)
Mucosal Inflammation	23 (38%)
Dizziness	23 (38%)
Peripheral Edema	20 (33%)
Stomatitis	17 (28%)
Abdominal Pain	17 (28%)
Dysgeusia	17 (28%)
Dyspepsia	16 (26%)

Twelve patients (20%) had serious adverse events (SAEs) and all of these events resolved. Ten of these SAEs were considered possibly related to the study treatment. Serious adverse events included pyrexia (8%); febrile neutropenia, hematochezia, and acute renal failure (3% each); and atrial fibrillation, cellulitis, dehydration, mucosal inflammation, oral pain, presyncope, and staphylococcal infection (2% each). One event, pyrexia, was the only Grade 4 SAE.

2.1.4. Clinical Pharmacokinetic Data

After intravenous administration, melphalan (propylene glycol-free) plasma concentrations rapidly decline in a biexponential manner with distribution and terminal elimination phase half-lives of approximately 10 and 75 minutes, respectively. Typical values for average total body clearance range between approximately 7 to 9 mL/min/kg (250 to 325 mL/min/m^2). Mean (±SD) peak melphalan plasma concentrations in myeloma patients given intravenous melphalan at doses of 10 or 20 mg/m^2 were 1.2 ± 0.4 and 2.8 ± 1.9 mcg/mL, respectively.

The steady-state volume of distribution of melphalan is 0.5 L/kg. Melphalan penetrates into cerebrospinal fluid. Average melphalan binding to plasma proteins ranges from approximately 50 to 90%. Serum albumin is the major binding protein, accounting for approximately 40 to 60% of the plasma protein binding, while α1-acid glycoprotein accounts for about 20% of the plasma protein binding. Approximately 30% of melphalan is (covalently) irreversibly bound to plasma proteins.

Melphalan is eliminated from plasma primarily by chemical hydrolysis to inactive monohydroxymelphalan and dihydroxymelphalan. The contribution of renal excretion to melphalan clearance appears to be low.

2.2 Study Disease and Rationale

Immunoglobulin light-chain (AL) amyloidosis is a disease in which amyloid fibrils derived from monoclonal light-chains are deposited in organs throughout the body resulting in multi-organ dysfunction. The kidneys, heart, gastrointestinal tract, liver and nervous system are most commonly involved. Historically, treatment with high-dose melphalan and autologous stem cell transplantation (HDM/ASCT) has been chosen as first-line treatment in qualifying AL amyloidosis patients due to durable hematologic responses, as well as organ responses, and improved overall survival(Mahmood, Palladini).

HDM/ASCT is recommended in select patients with AL amyloidosis based on measures of cardiac function, pulmonary function and hemodynamic stability(Gertz). Despite rigorous evaluation, some patients with AL amyloidosis develop significant morbidity or mortality during the peri-transplant period related to renal, autonomic nervous system, or cardiac dysfunction. Data from our center demonstrates that 21% of AL amyloidosis patients receiving treatment with high dose melphalan and autologous stem cell transplantation develop acute renal injury during the peri-transplant setting, with 5% of patients requiring initiation of dialysis(Fadia). The rate of atrial fibrillation in the peri-transplant period is approximately 13%, which is higher than reported in other patient populations undergoing treatment with high dose melphalan and autologous stem cell transplantation(Arun). Treatment related mortality in this population of patients has improved from ~17% in the late 1990's, but remains ~4% with many of these deaths related to cardiac events during or after stem cell infusion(Tsai).

The standard protocol for high-dose conditioning prior to ASCT uses melphalan hydrochloride with propylene glycol as a co-solvent. Propylene glycol has been reported to cause metabolic acidosis, sepsis-like syndrome, hyperosmolality, and renal dysfunction, as well as cardiac arrhythmias(Wilson, Zar, Yaucher). Propylene glycol-free melphalan was recently studied in a phase IIb trial that confirmed the efficacy and safety profile of this new formulation(Hari). Based on this clinical trial, propylene glycol-free melphalan was approved by the Food and Drug Administration for use as a high-dose conditioning regimen prior to autologous stem cell transplantation in patients with multiple myeloma.

Due to the known risk of renal and cardiac dysfunction in AL amyloidosis patients during the peri-transplant period, it is hypothesized that the newer formulation of propylene glycol-free melphalan may have decreased risk of toxicity in AL amyloidosis patients.

3. PARTICIPANT SELECTION

3.1 Screening and Recruitment and Consenting

The investigators will recruit for participants from within their own practice. It is standard of care that patients scheduled for visits within the hematology/oncology clinics are "pre-screened" to determine if they may be "potentially eligible" for any available clinical trials. This is not specific for this study. A screening consent is not obtained, as the pre-screening review is conducted prior to their first appointment.

No data will be collected. The medical records are reviewed and a screening note is placed in the medical record to indicate that the patient may or may not be "potentially eligible" for a clinical trial. If the patient is potentially eligible, the physician will discuss the study at the visit. No procedures are performed for screening until after consent is obtained.

No data will be retained prior to obtaining consent. No data is collected during the "pre-screening". During the pre-screen, if a patient is determined to be not potentially eligible for any available clinical trials, the patient would not be considered as a "screen fail" as they have not undergone a full screening.

If potentially eligible, the investigator will inform the potential participant within his/her practice that he/she may be eligible for the research study. If the patient agrees to discuss and receive information about the study, an IRB-approved Informed Consent Form will be presented to the patient by a member of the research staff who will verbally outline the details of the procedures, risks, benefits, alternatives, costs, etc. The patient will be given the opportunity to bring the consent home and discuss with family members and/or other physicians and to ask any and all questions of the investigator and/or research staff. Once the patient is satisfied that all questions have been answered, if he/she wishes to participate, the consent form will be signed and dated by the patient and the person obtaining consent. Copies of the signed Informed Consent Form will be given to the patient, placed in the appropriate medical record, and placed in the research chart.

Potential participants who are non-English speaking will be consented using the Short Form (if IRB approved). A hospital translator, or a translator on the phone line, will be used throughout the consent process and throughout their participation in the study.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process will be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files. Participants will be enrolled following stem cell collection and prior to receiving the investigational agent.

3.2 Inclusion Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

- Age 18 years or older
- Histologic diagnosis of primary systemic (AL) amyloidosis based on:
    - Deposition of amyloid material by Congo red stain showing characteristic apple green birefringence AND/OR characteristic appearance of fibrils on electron microscopy

  AND
    - Evidence of a clonal plasma cell dyscrasia with monoclonal protein in the serum or urine by immunofixation electrophoresis AND/OR abnormal serum free light chain assay AND/OR clonal plasma cells in the bone marrow exam demonstrated by immunohistochemistry, flow cytometry, or in situ hybridization

  AND
    - Evidence of organ involvement

- Eligible for treatment with high dose melphalan and stem cell transplantation per institutional guidelines
- Ability to understand and willingness to sign informed consent
- Pulmonary Function Test demonstrating a DLCO ≥ 50%
- Left ventricular ejection fraction ≥40%
- Systolic blood pressure >90 mm Hg (supine position)
- Eastern Cooperative Oncology Group Performance status of 2 or better (unless patient is diagnosed with AL amyloidosis involving the gastrointestinal and peripheral/autonomic nervous systems, then performance status of 3 is acceptable)

3.3 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study:

- Previous HDM/SCT
- Previous total cumulative dose of oral melphalan > 300 mg
- Cytotoxic chemotherapy within the previous 28 days
- New York Heart Association ≥3
- Decompensated or uncontrolled heart failure
- Oxygen dependence
- eGFR < 30 ml/min
- Active infection (i.e HIV, Hepatitis B or C)
- Pregnancy or breastfeeding
- Exposure to another investigational drug within 3-4 weeks prior to start of study treatment or planned during the course of the trial.
- No plans for anticancer agents other than the study medication during the course of the study. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Ongoing alcohol or drug addiction
- Unable or unwilling to comply with the protocol

4. TREATMENT REGIMEN

The investigational agent will be utilized as the conditioning regimen prior to autologous stem cell transplantation. Expected toxicities and potential risks as well as dose modifications for melphalan (propylene glycol-free) are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's AL amyloidosis.

4.1 Stem cell mobilization (Standard): Filgrastim mobilization

Mobilization regimen will follow transplant program standard.
Filgrastim 16 mcg/kg/day SQ will begin 3 days before first stem cell collection through the day before the final day of collection. For example, first day of stem cell collection begins after filgrastim has been administered for 3 days in a row. The use of plerixafor 0.24 mg/kg is permitted for stem cell collection.

• Central venous catheter placement: A pheresis catheter will be placed in all patients prior to stem cell collection.

4.2 Stem Cell Collection (Standard): ≥2.0 x 10^6 CD 34+/kg

Stem cell collection will begin after three consecutive days of filgrastim and will continue daily for up to 5 days, until a yield of ≥ 2.0 x 106 CD 34+ cells/kg is achieved.

Stem Cell collection and storage will be performed utilizing standard institutional guidelines.

4.3 Conditioning Regimen (Investigational): Evomela 70-100 mg/m^2/dose on Days -3 and -2

Melphalan (propylene glycol-free) (Evomela) will be administered as conditioning treatment prior to autologous stem cell transplantation. The recommended dose is 100 mg/m2/day* by intravenous infusion on two consecutive days (Day -3 and Day -2) prior to autologous stem cell transplantation (Day 0). Dose reductions to 70 mg/m2/day will be will be permitted at Investigator discretion due to patient functional status, age, and quantity of stem cells collected during mobilization.

* For patients > 130% of their ideal body weight, Adjusted Ideal Body Weight will be used to calculate dose.

Melphalan (propylene glycol-free) will be provided by Spectrum Pharmaceuticals, Inc. Melphalan (propylene glycol-free) is provided in 50mg vials which will be reconstituted for intravenous administration.

Hydration and antiemetic administration will follow transplant program standard, as outlined below. Minor deviations may be considered if necessary for treatment if they do not impact patient safety in the clinical judgment of the treating physician and the transplant team.

4.4 Stem cell infusion (Standard): Day 0

4.5 General Concomitant Medication and Supportive Care Guidelines

Participants will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the participant about any new medications he/she is or has taken after the start of the study drug.

Standard supportive care medications are permitted. Institution guidelines are as outlined below. Minor adjustments may be made at the treating physician's discretion based on individual clinical situations. Rationale for such adjustments will be documented in the medical record:

Hydration Guidelines:
Beginning 2 hours before propylene glycol-free melphalan and ending 2 hours after propylene glycol-free melphalan, IV hydration with D5 0.5NS + KCl 20 mEq/L. Rate and composition of IV fluid hydration will be modified to meet individual patient needs.

Antiemetic (prophylactic) Guidelines:
To be given 30 minutes before propylene glycol-free melphalan:
Granisetron 2mg PO
Dexamethasone 10mg PO
Lorazepam 0.5mg PO

For Nausea/Vomiting:
Lorazepam 0.5-1mg PO q3 hours prn and QHS
Compazine 10 mg PO prn nausea/vomiting

The following restrictions apply during the entire duration of the study:

- No other investigational therapy should be given to participants.
- No anticancer agents other than the study medication should be given to participants. If such agents are required for a patient then the patient must first be withdrawn from the study.

Infection prophylaxis:
Propylene glycol-free melphalan is used as a myeloablative treatment prior to autologous stem cell transplantation. Leukopenia with compromised immune function is expected with myeloablative therapy and for this reason the following infection prophylaxis will be applied, which is standard for patients undergoing stem cell transplant. Strengths, routes and durations will be determined as per standard of care:

- Levofloxacin for bacterial infection prophylaxis. This will be continued until neutrophil engraftment or until replacement by additional anti-infectives that may be required for treatment of fever or infection.
- Acyclovir for prophylaxis of herpes zoster infection. This will be continued until one year after autologous stem cell transplantation.
- Fluconazole for fungal infection prophylaxis. This will be continued until neutrophil engraftment.

**Anti-infective medications can be adjusted as needed based on individual patient's organ function or allergy history.

Growth factors:
Filgrastim 300 mcg or 480 mcg will be administered SQ once daily from Day +1 until neutrophil engraftment

Medications to avoid:
IV medications that are known to contain higher levels of propylene glycol will be avoided (including diazepam, lorazepam, phenobarbital, phenytoin, nitroglycerin, and digoxin) while participating in the study. If those medications are determine to be clinically necessary, then the details regarding dosage, frequency, and duration of use will be well-documented and considered in regards to patient outcomes.

4.6 Duration of Participation

Participants will receive two doses of melphalan (propylene glycol-free) prior to autologous stem cell transplantation. Side effects of treatment will be monitored regularly until discharge from the stem cell transplantation program. Participants will be followed for one year after transplantation, with hematologic and organ responses evaluated at 6 and 12 months after transplantation. We anticipate 1 year duration for individual subjects. We anticipate the study will remain active for a total of 4 years including enrollment, treatment, follow-up and data analysis.

4.7 Criteria For Removal From Protocol Treatment:

- Inadequate stem cell yield
- The patient may withdraw from the study at any time for any reason.
- Completion of all protocol therapy.

5. EXPECTED TOXICITIES

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.). All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through 30 days after administration of the last dose of study drug or "discharge" from the stem cell transplant program, whichever comes first.

5.1 Toxicity Management

Participants who have an adverse event or abnormal laboratory value suspected to be related to melphalan (propylene glycol-free) will be followed until the adverse event or abnormal laboratory resolves or returns to grade 1.

It will be documented whether or not each participant completed the clinical study. The reason either study treatment or observations were discontinued will be recorded. Reasons that a participant may discontinue participation in a clinical study are considered to constitute one of the following:
1. Adverse event(s)
2. Abnormal laboratory value(s)
3. Abnormal test procedure result(s)
4. Disease progression (including initiation of new therapy)

5. Protocol violation
6. Participant withdrew consent
7. Lost to follow-up
8. Administrative problems (including study-related issues, IRB and other regulatory issues, and drug administration issues)
9. Death
10. General or specific changes in the participant's condition that render the participant unacceptable for further treatment in the opinion of the treating investigator.

6. DRUG FORMULATION AND ADMINISTRATION

6.1 Melphalan (propylene glycol-free) Formulation

Melphalan (propylene glycol-free) is provided as a white to off-white lyophilized powder in single-dose vial for reconstitution. After reconstitution the solution is clear and colorless to light yellow. Each vial contains 50mg melphalan free base equivalent to 56 mg melphalan hydrochloride.

6.2 Melphalan (propylene glycol-free) Package, Storage and Handling

Melphalan (propylene glycol-free) is supplied in a single carton containing one vial. The medication should be stored at room temperature 25° C (77° F). Temperature excursions are permitted between 15-30° C (59-86° F). The medication is light sensitive and should be retained in the original carton until time of use. This is a cytotoxic drug and should be handled using special handling and disposal procedures.

Medication labels will comply with US legal requirement and be printed in English. The storage conditions for the study drug will be described on the medication label.

6.3 Melphalan (propylene glycol-free) Availability

Melphalan (propylene glycol-free) is commercially available, but will be supplied free-of-charge from Spectrum Pharmaceuticals, Inc with labeling for investigational use.

Drug supplies must be requested using Spectrum's Investigator-Initiated Study Drug Product Request Form. The completed form should be sent to Spectrum Pharmaceuticals at IISdrugsupply@sppirx, leaving at least 2 weeks between request and delivery.

6.4 Melphalan (propylene glycol-free) Administration

Melphalan (propylene glycol-free) will be administered over 30 minutes via dual lumen apheresis catheter as part of the Conditioning Regimen on Days -3 and -2 prior to autologous stem cell transplantation (Day 0). Treatment may be administered inpatient or outpatient. This will be at the discretion of the investigator and will be discussed at the weekly Autologous Stem Cell Transplantation Team Meeting based on the patient's functional status and organ function.

6.5 Melphalan (propylene glycol-free) Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record of another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.) This will be conducted by the BMC Investigational Pharmacy Services office. Unused melphalan (propylene glycol-free) will be destroyed per institutional policy. Destruction will be documented in the Drug Accountability Record Form.

7. STUDY CALENDAR

The following testing will be performed per institutional standard for transplant patients.

REQUIRED STUDIES	Pre-Treatment *	Stem Cell Mobilization & Collection[b]	Study Drug (chemotherapy) Days -3 & -2	Stem Cell Infusion Day 0	Days +1 through engraftment [f]	F/U [#]
PHYSICAL						
History & Physical Exam	X	X	X	X	X	X
Height	X					
Weight, Vital Signs & Performance Status	X	X	X	X	X	X
Toxicity Notation		X	X	X	X	X
LABORATORY-Serum						
CBC with Differential	X	X	X	X	X	X
BUN / Serum Creatinine / Glucose / Mg / Phos	X	X	X	X	X	X
Bili / Alb / Alp / SGOT / SGPT	X	X	X		X	X
Na / K / Cl / CO2	X	X	X		X	X
COR / CRP / LD / Amy / TP/ chol / CK / Ca	X					X
IRON / Uric/ TSH / D-DIMER / Factor X	X					X
β-2 Microglobulin / C-reactive protein	X					X
SPEP / / SIFE / BNP	X					X
VITB12 / FOL / ESR / RETIC / Troponin I	X					X
PT/ PTT/ INR	X	X				X
FLC	X				X[c]	X
HCG (for women of childbearing potential)	X		X[a]			
Hep B Surface AG, Hep B Core AB, Hep C AB	X					
HIV - 1+2	X					
Type & Screen[d]		X	X	X	X	
LABORATORY-Urine						
UA	X					X
UTP24 / UCR24 / UKAP / ULAM	X					X
UPEP / UIFE / TV	X					X
PATHOLOGY						
BM aspiration / biopsy	X					X[≠]
Fat aspirate	X					
X-RAYS AND SCANS						
EKG	X			X		X
CXR	X					X
Echocardiogram	X					X
PFT's	X					
CPST ♥	X					
TREATMENT						
Stem Cell Mobilization and collection		X				
High-Dose Melphalan (propylene glycol-free)			X			
Stem Cell Infusion				X		

f Testing during pre-treatment, during treatment and at follow-up should be done per institutional standard and as clinically indicated, including toxicity evaluations.

\# Follow-up evaluations for disease response will take place at 6 months and one year.

a Pregnancy test to be done within 7 days prior to initiation of chemotherapy for women of childbearing potential

b Dates are not specific as stem cell mobilization may take place any time prior to high dose chemotherapy and stem cell transplant.

c FLC's to be drawn weekly

d Type & Screen to be done on Mondays and Thursdays (or at least twice weekly depending on patient schedule)

* Tests are recommended for good medical practice and only those listed in the eligibility criteria are required by the protocol.

♥ If clinically indicated at physician's discretion

≠ If needed to evaluate response.

8. MEASUREMENT OF EFFECT

8.1 Definitions

Evaluable for toxicity: All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response: Only those participants who have received at least one dose of melphalan (propylene glycol-free) and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to 100 days will also be considered evaluable.)

8.2 AL Amyloidosis Hematologic Response Criteria (Gertz, Palladini)

CATEGORY	RESPONSE CRITERIA
Complete response (CR)	• Normal serum free light chain ratio • Negative serum and urine immunofixation electrophoresis
Very good partial response (VGPR)	• Difference in serum free light chains less than 40 mg/L
Partial Response (PR)	• >50% Reduction in the difference in serum free light chains
Stable Disease (SD)	• Meets neither criteria for CR, VGPR, PR or PD
Progressive Disease (PD)	• From CR, an increase in serum M-protein to > 0.5 g/dL, an increase in the urine M-protein to > 200 mg/day, or an increase in the serum monoclonal free light chain by > 10 mg/dL (100 mg/L). From VGPR, PR or SD, an increase in the serum M-protein from the lowest level by > 50%, as long as the absolute magnitude of this increase is > 0.5 g/dL; or an increase in the urine M-protein from the lowest level by 50%, as long as the absolute magnitude of this increase is > 200 mg/day; or an increase in the serum or urine monoclonal free light chain by > 50% from the lowest level, as long as the absolute magnitude is > 10 mg/dL (100 mg/L).

8.3 Organ Response Criteria (Gertz)

A subject will be said to have had an organ response in an involved organ if any of the following criteria are met.

- Kidney: 50% reduction in 24-hour urine protein excretion in the absence of progressive renal insufficiency (defined as a 25% increase in serum creatinine, as long as that is > to an absolute increase of 0.5 mg/dL). In the case of nephrotic syndrome: a decrease in proteinuria to < 1g/24h and an improvement in one of 2 extrarenal features – normalization of serum albumin or resolution of edema and/or discontinuation of diuretics in response to improvement in edema.
- Heart: ≥ 2 mm reduction in the interventricular septal (IVS) thickness by echocardiogram, improvement of ejection fraction by ≥ 20% (echocardiogram must be performed at the same institution), or decrease in 2 NYHA classes without increase in diuretic need.
- Liver: ≥ 50% decrease in normalization of an initially elevated alkaline phosphatase level or reduction in the size of the liver by at least 3 cm if assessed by imaging.
- Neuropathy: While neurotoxicity is acceptable for determining organ involvement, it will not be adequate for assessing organ response; organ response will be indeterminable for subjects in which neurotoxicity is the only site of organ involvement.
- Gastrointestinal Tract: While GI involvement is acceptable for determining organ involvement, it will not be adequate for assessing organ response: organ response will be indeterminable for subjects in which GI is the only site of organ involvement.

9. ADVERSE EVENTS

9.1 Adverse Event Definition

An adverse event is any untoward or unfavorable physical or psychological occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

9.2 Serious Adverse Event Definition

Serious Adverse Event: According to the FDA's Code of Federal Regulations Title 21 Part 314.80, a SAE is any untoward medical occurrence that results in any of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of an existing hospitalization
- A persistent or significant disability / incapacity
- A congenital anomaly / birth defect
- Important medical events based upon appropriate medical judgment that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of serious.

Expectedness: Unexpected events include any adverse drug experience that is not listed in the current Investigator Brochure (IB) for the drug product (e.g., all previously unobserved or undocumented events).

Relatedness: Indicates that a determination has been made that an event had a reasonable possibility of being related to exposure to the product. Examples of causality include not related, unlikely, possibly, probable, definitely related and unable to be determined.
Unexpected fatal or life-threatening and related experiences associated with the use of the study treatment will be reported to Spectrum Pharmaceuticals, Inc within three business days of awareness of the event.

Upon request from the FDA or Spectrum Pharmaceuticals additional data or information that the agency or Spectrum Pharmaceuticals deems necessary, must be reported as soon as possible but no later than 15 calendar days.

Reporting of AEs and SAEs to the IRB will take place according to institutional IRB policy.

9.3 Adverse Drug Reaction Reporting

An investigator or other study personnel must forward information related to Serious Adverse Events (SAEs) to Spectrum Pharmaceuticals, the manufacturer, via facsimile or e-mail using the MedWatch form, whether the SAE is unexpected or not based on the product investigator's brochure, and whether drug-related or not based on clinical investigator's assessment, within 24 hours of becoming aware of the event. Every effort should be made to provide complete and accurate information on the MedWatch form.

Forms should be e-mailed or faxed to:
pharmacovigilance@aurobindo.com

Toxicity will be scored using CTCAE Version 4.03 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.03 can be downloaded from the CTEP homepage (HTTP://CTEP.INFO.NIH.GOV). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.03. All adverse clinical experiences, whether observed by the investigator or reported by the subject, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the subject's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the subject's outcome.

AEs and SAEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug or "discharge" from the stem cell transplant program, whichever is later. All SAEs should continue to be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

9.4 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of Grade 2 or higher AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

10. DATA MANAGEMENT

10.1 Analyses and Reporting

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. Data may be transcribed legibly on CRFs supplied for each subject or directly inputted into an electronic system or any combination thereof. Data will be analyzed and reported after study is completed or meaningful endpoints are reached. All subsequent data collected will be analyzed and reported in a follow-up clinical report.

10.2 Data Safety Monitoring

Toxicity and accrual monitoring will be performed on a routine basis by the study investigators as well as the multidisciplinary members of the Amyloid Center at Boston University, which has over 40 years' experience in the treatment of AL amyloidosis. Subjects will undergo toxicity assessment, performance status assessment and laboratory tests according to the study calendar in Section 7. Organ response assessment will be conducted at the six-month and one year follow-up appointments. The clinical status and laboratory reports of the study participants will be reviewed routinely by the co-investigators at the weekly meetings of the Autologous Stem Cell Transplantation Team.

In addition, a medical monitor, to be assigned prior to study activation, will review the protocol as outlined below. The Medical Monitor will be a qualified clinician with relevant expertise, but no direct connection with the research, whose primary responsibility is to provide independent safety monitoring in a timely fashion. The PI will submit a report to the Medical Monitor, at a minimum of once every 6 months, including a list of all adverse events and serious adverse events (regardless of relatedness). In addition, any unanticipated problems involving risks to participants or others and participant deaths within 100 days of study intervention will be reported to the Medical Monitor within 24 hours of the PI's knowledge of the event. The Medical Monitor is expected to provide a formal, unbiased written report evaluating individual and cumulative participant safety data when making recommendations regarding needed changes or continuation of the study. Although the PI is responsible for assigning causality and expectedness, the medical monitor will comment on whether or not (s)he is in agreement. Medical Monitor reports will be submitted to the PI following each review (at a minimum of once every 6 months), which the PI will, in turn, submit to the IRB.

10.3 Study monitoring and auditing

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations (CFR).

Investigators must enter study data onto CRFs or other data collection system. The Investigator will permit study-related monitoring visits and audits by Spectrum or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

11. REGULATORY CONSIDERATIONS

11.1 Protocol Amendments

Any amendment to this protocol must be agreed to by the Principal Investigator and reviewed and approved by Spectrum. Amendments should only be submitted to IRB/EC after consideration of Spectrum review. Written verification of IRB approval will be obtained before any amendment is implemented.

11.2 Protocol deviations

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation. In addition, the Investigator will notify the IRB in writing of such deviation from protocol. Non-emergency minor deviations from the protocol will be permitted with approval of the Principal Investigator.

11.3 Institutional Review Board/Ethics Committee approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.
The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

11.4 Study Records Requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

12. STATISTICAL CONSIDERATIONS

This is a single arm, open label study designed to evaluate the safety and efficacy of melphalan (propylene glycol-free) as a conditioning regimen in AL amyloidosis patients undergoing treatment with autologous stem cell transplantation. Patients will receive treatment with 70-100 mg/m2/day on Days -3 and -2 prior to autologous stem cell transplantation.

12.1 Study Design/Endpoints

The primary endpoint of the current study is:

- To determine the safety profile of melphalan (propylene glycol-free) in the conditioning regimen prior to autologous stem cell transplantation in AL amyloidosis patients

The secondary endpoints are:

- To assess the time until neutrophil and platelet engraftment
- To evaluate organ response
- To assess treatment related mortality at 100 days
- To assess hematologic overall response rate at 6 months after autologous stem cell transplantation
- To assess hospitalizations

12.2 Sample Size/Accrual Rate

Using an optimal 2-stage design, we assume a total of 30 patients per year for 3 years meeting inclusion/exclusion criteria, with approximately 50% enrollment with a target of 43 patients enrolled. Using an optimal 2-stage design, we assume p0 = 60% and p1 = 80%, with these values representing the patients free of unacceptable toxicity. We would have a 5% bound on the type I error and 80% power to detect a statistically significant toxicity rate with 11 patients enrolled in Stage 1 and proceeding to an additional 32 patients enrolled in Stage 2 if the toxicity rate is acceptable in Stage 1. Using this design the treatment would be declared successful if at least 30 of the 43 patients did not have unacceptable toxicity during the study period. A transplant related mortality (determined by the stem cell transplant committee to be related to the study drug) of 20% or greater would be cause for study termination at stage 1. Transplant related mortality is defined as mortality that occurs within 100 days of stem cell transplantation.

12.3 Reporting and Exclusions

All participants who met the eligibility criteria and were enrolled in the trial will be included in the main analysis of the response rate. All conclusions will be based on all eligible participants.

13. REFERENCES

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14. APPENDICES

14.1 APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.