Cedars Sinai

CANCER

IIT2023-03-Vescio-ColdCap

Scalp Cooling to Prevent Hair Loss in Patients Undergoing Stem Cell Transplantation for Multiple Myeloma

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Signature	**Date**

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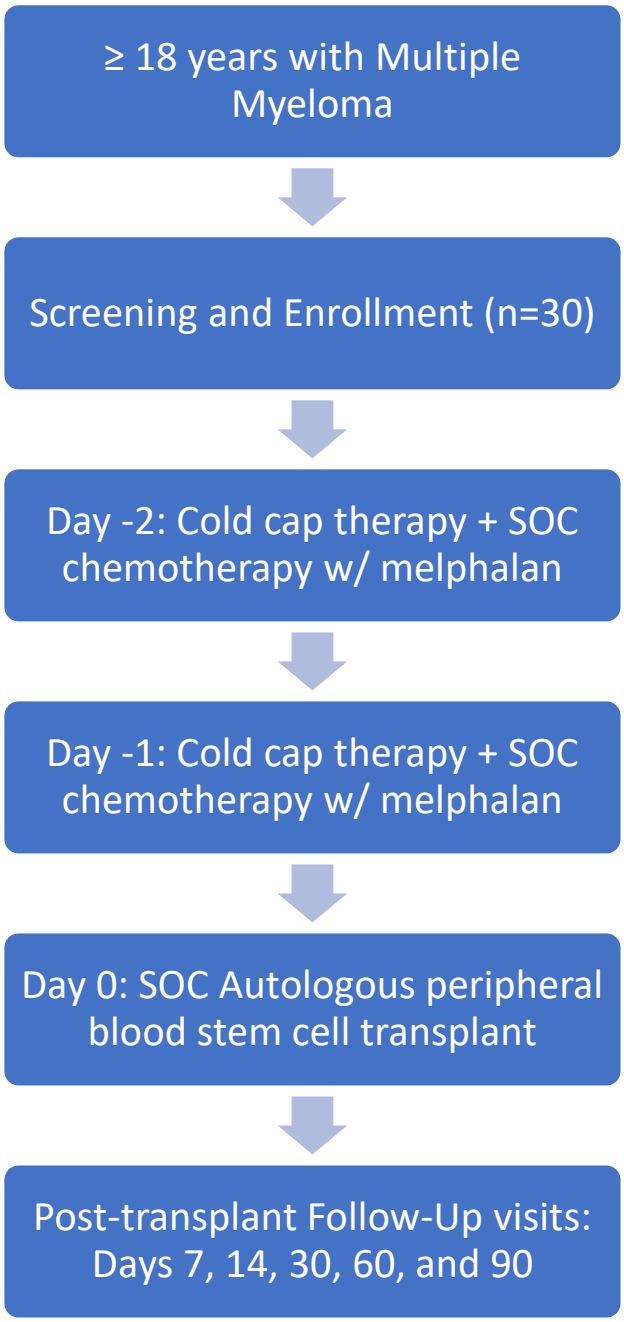
LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
p.o.	per os/by mouth/orally
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SOC	Standard of Care
SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

STUDY SCHEMA



Primary endpoint: Reduced development of hair loss will be defined as < 50% hair loss in 75% of patients treated

STUDY SUMMARY

Title	Scalp Cooling to Prevent Hair Loss in Patients Undergoing Stem Cell Transplantation for Multiple Myeloma
Protocol Number	IIT2023-03-Vescio-ColdCap
Phase	Pilot
Methodology	Single arm, open label
Study Duration	22 months (18 months accrual, 4 months study duration)
Study Center(s)	Cedars-Sinai Medical Center: CS Cancer at the SOCC
Objectives	**Primary objective:** • To assess the effectiveness of a scalp cooling intervention to reduce hair loss in patients with multiple myeloma undergoing an autologous peripheral blood stem cell transplant after high-dose melphalan **Secondary objective:** • To assess the potential impact of hair loss versus the discomfort and inconvenience of the scalp cooling procedure
Number of Subjects	30
Diagnosis and Main Inclusion Criteria	Patients with multiple myeloma planning to undergo high-dose chemotherapy with melphalan and autologous peripheral blood stem cell transplant.
Study Product(s), Dose, Route, Regimen	Subjects will receive Penguin cold cap for 60 minutes prior to melphalan infusion and continue for up to 5 hours (+/- 30 minutes) after melphalan infusion start time, for a total of 6 hours (+/- 30 minutes). Penguin cold cap and melphalan infusion will occur on Days -2 and -1, prior to SOC transplant procedure. Subjects will be followed up for 90 days after transplant. Subjects will have images taken to record hair length and status prior to intervention on Day -2, and after intervention on days 7, 14, 30, 60, and 90. Questionnaires will be taken at Day 0 and 90.
Duration of administration	Penguin cold cap: 60 minutes prior to melphalan infusion and continue for 5 hours (+/- 30 minutes) after melphalan infusion start time, for a total of 6 hours (+/- 30 minutes), on Days -2 and -1.
Reference therapy	Reference is no use of a scalp cooling device which leads to > 50% hair loss in all patients undergoing this procedure historically.
Statistical Methodology	80% power to detect a minimum detectable difference of 17.25% based on the exact binomial test at 5% significance level. The actual significance level is 3.7%

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Multiple myeloma is a malignant plasma cell cancer that is currently incurable but treatable. The cancer is treated with medications such as lenalidomide, bortezomib and corticosteroids to get initial control of the disease. To improve remission rates and survival, high-dose chemotherapy using melphalan followed by an autologous stem cell transplantation as a rescue is often done. During the transplant process, patients are given high doses of melphalan (140 – 200 mg/m2) divided into two days over 20 minutes. Melphalan causes hair loss in essentially all patients, (CTCAE v5 Grade 2), at the doses used for this procedure. Hair typically falls out after 10-15 days and doesn't begin to grow back for 10-12 weeks. This outcome is widely expected and leads some patients to avoid doing an otherwise life sustaining procedure. In those that do proceed with the transplant, the hair loss can be emotionally harmful.

Cryotherapy is commonly used to reduce side effects of the melphalan on the GI tract. Melphalan typically will cause diarrhea, nausea, and mouth sores yet a randomized trial done in 2006 showed that swallowing ice chips for 6 hours starting 30 minutes before the melphalan is given can reduce these unpleasant and potentially dangerous side effects by 60% (Lilleby et. al. 2006). We at Cedars-Sinai routinely have patients do oral cryotherapy for 3.5 hours starting 30 minutes prior to each dose of melphalan. This has reduced patient side effects substantially in our experience and is considered standard of care. The briefer period of administration seems adequate to prevent most problems.

Scalp cooling has been used to prevent hair loss in many patients undergoing chemotherapy for solid tumors. For some women with breast cancer, this hair loss was reported to be more traumatizing than losing a breast to mastectomy (Zhang et. al. 2022). Certainly, the sudden development of alopecia can impact a patient's self- image, and quality of life. Chemotherapy drugs, such as melphalan, typically injure bone marrow, intestinal lining and other cells with high metabolism and rapid cell division. Hair follicles also have these properties and is likely why many chemotherapeutics cause hair loss when used. The use of cold caps during the time of chemotherapy exposure has helped reduce hair loss, presumably by causing vasoconstriction and reducing distribution of the drug to the hair follicle. This intervention has been effective even when drugs which have longer durations of circulation have been given. While there is a theoretical risk that scalp cooling may impair the killing of malignant cells in the scalp by the chemotherapy, there is no evidence of a heightened risk in studies. The penetration of the cold should not reach the skull bone where myeloma cells may reside and is generally to a depth of only a few millimeters. The toxicity of scalp cooling is minimal. In a study of 27 participants using scalp cooling for solid tumors, 96% reported that the procedure was worth the time, effort, cost and discomfort and would recommend usage to others undergoing the same chemotherapy treatment (Sitarz et al). In a randomized trial comparing scalp cooling to placebo in women undergoing chemotherapy for breast cancer, successful hair preservation occurred in 48 of 95 women using cooling versus 0 of 47 women in the control group. The study was closed at the interim analysis due to efficacy (Nangia et. al. 2017). Fifty-four adverse events occurred in the group undergoing cooling, all grade 1 or 2.

Scalp cooling may especially be effective in our patients using high-dose melphalan prior to stem cell transplantation. Melphalan has a much shorter half-life than most of the other chemotherapy drugs used for breast and other solid cancers. Because of melphalan's 70-minute half-life, it is anticipated that in 5 hours the concentration of melphalan will be only 5% of that immediately after administration.

Melphalan concentration at 5 hours (300 minutes) with a $t_{1/2}$ of 70 minutes = 4.2 half-lives.
Melphalan concentration predicted at 5 hours = $0.5^{4.2} = 0.054$ or 5.4%

Melphalan when given orally at doses of 7 mg/m2 daily for non-transplant patients does not cause hair loss. A 95% reduction in the typical 100 mg/m2 dose of melphalan would be only 5 mg/m2. From a literature review by me and by others, this process has not been used for patients with hematologic malignancies. Anecdotally, there are reports of positive outcomes, but these have not been published.

The hope is that by using scalp cooling, patients would not lose as much hair after the stem cell transplant. Since the hair-loss is so universally attained without cold caps, a control arm is not felt to be necessary to demonstrate a difference in outcome. A positive outcome may improve the percentage of people willing to undergo this life-sustaining procedure and improve the quality of life of those who go through with it.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To assess the effectiveness of a scalp cooling intervention to reduce hair loss in patients with multiple myeloma undergoing an autologous peripheral blood stem cell transplant after high-dose melphalan.

2.2 Secondary Objectives

2.2.1 To assess the potential impact of hair loss versus the discomfort and inconvenience of the scalp cooling procedure.

2.3 Endpoints

2.3.1 **Primary Efficacy Endpoint**

Reduced development of hair loss will be defined as < 50% hair loss (CTCAE v5 Grade 0 or 1) in 75% of patients treated.

2.3.2 **Secondary Efficacy Endpoints**

Patient determined decision of scalp cooling benefit

3.0 STUDY DESIGN

We will conduct a pilot study of scalp cooling with Penguin cold caps to examine the feasibility of scalp cooling to reduce the development of hair loss in 30 patients with multiple myeloma undergoing high-dose chemotherapy with melphalan and autologous peripheral blood stem cell transplant at Cedars-Sinai Medical Center.

For this trial 30 patients will be enrolled to receive scalp cooling with Penguin cold caps prior to their stem cell transplant. This device has been used routinely in the Samuel Oschin Cancer Center Infusion center at Cedars-Sinai and also on the 4 South ward where stem cell transplants are done. The cold cap will be used starting 60 minutes prior to and continued for 5 hours (+/- 30

minutes) after melphalan has been started, for a total of 6 hours (+/- 30 minutes). The procedure will be done for both days of melphalan infusion, on Days -2 and -1. The remainder of the transplant procedure will be performed as is routine and part of standard of care on Day 0.

The patient will have photographs taken on the day of their first administration of melphalan. Photographs of the patient's hair will occur again at Day 7, Day 14, Day 30, Day 60 and Day 90 after the stem cell transplant was given. Scalp Cooling questionnaire will be administered on Day 0 and 90.

Every effort will be made to coordinate research study appointments/interventions so that they do not interfere with the pre-planned, standard of care treatment arrangements.

See Study Schema and Time & Events Table for reference.

3.1 Inclusion of Women and Underrepresented Minorities

The total number of subjects involved in the study will be 30. Of those, we estimate that approximately 45% will be cisgender women. The estimated racial/ethnic breakdown of the study may approximately be that 20% may be Black or African American, 10% may be Asian, and 3% may be Native Hawaiian-Pacific Islander. Approximately 30% of the subjects may be Hispanic. While this provides only an estimated breakdown of the study population, efforts should be made to ensure equitable recruitment of individuals that meet the above eligibility requirements.

4.0 PATIENT ELIGIBILITY

4.1 Inclusion Criteria

4.1.1 Age ≥18 years

4.1.2 ECOG performance status ≤2

4.1.3 Confirmed multiple myeloma diagnosis

4.1.4 Planning to undergo SOC high-dose chemotherapy with melphalan (dose to be used = 140 – 200 mg/m^2 (with rounding per CSMC guidelines)) followed by an autologous peripheral blood stem cell transplant.

4.1.5 Written informed consent obtained from subject and ability for subject to comply with the requirements of the study.

4.2 Exclusion Criteria

4.2.1 Prior or current use of any scalp cooling treatment

4.2.2 Medical History and Concurrent Diseases:

- Reynaud's disease
- Cold sensitivity
- Cold agglutinin disease
- Cryoglobulinemia

- Cryofibrinogenemia

4.2.3 Current spinal or neck injury that may interfere with the subject's participation for the full duration of the study, in the opinion of the treating investigator

4.2.4 Skin conditions such as psoriasis, eczema, malignancy, or other condition on the scalp that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

4.2.5 Current use of any other investigational agents

4.2.6 Contraindication to melphalan

5.0 TREATMENT PLAN

5.1 Penguin Cold Cap

The Penguin cold cap is not FDA cleared and is a nonsignificant risk (NSR) medical device that is:

- NOT intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- NOT purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- NOT for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Does NOT otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

The cold cap or immediate package will be labeled in accordance with all applicable federal guidelines. As the Penguin technician will administer the cold cap to subjects and packaging will not be provided, the research team will provide a copy of the package label in accordance with applicable federal guidelines to the subject.

Manufacturer: Penguin Cold Caps: support@penguincoldcaps.com +44 (0)20 8004 4683

5.2 Treatment Administration

Eligible subjects will receive study intervention Penguin Cold Cap for scalp cooling therapy for 60 minutes prior to melphalan infusion and continue for 5 hours (+/- 30 minutes) after melphalan infusion start time, for a total of 6 hours (+/- 30 minutes). Penguin cold cap and melphalan infusion will occur on Days -2 and -1, prior to SOC transplant procedure.

The Penguin cold cap will be supplied by the Penguin manufacturer and will be administered by Penguin approved technicians only. The technician will provide all necessary supplies on the day of scalp cooling procedure.

5.2.1 Penguin Cold Cap Procedure

The Penguin Scalp Cooling device has been used by more than 20,000 patients since the company was founded in 1992.

Prior to the Cold Cap procedure date, patients will be instructed: Hair should be dry when wearing the Cold Cap - The user of the Caps must NOT wet or dampen the hair, or put conditioner or oil on your hair or scalp during the Day -2 and Day -1 scalp cooling procedure.

1. The patient will be provided with the Penguin cold cap free of charge by the study.
2. Dry ice will be used to cool the gel material within the cap and used per product instructions.
3. A Penguin approved technician will be with the patient and help administer the cold cap safely.
4. The approved technician will stay with the patient for the entire procedure.
5. Clinic administration and in hospital administration are both expected (Day -2 in clinic and Day -1 in the hospital on the 4SW).
6. The approved technician will not be asked to do other patient care outside of hair care and will not interfere with the administration of the chemotherapy or other medical care for the patient.
7. The responsibility of the Penguin Cold Cap application will reside solely with the approved technician and no clinic/hospital staff will be asked to assist.
8. The procedure will begin 60 minutes prior to the first administration of melphalan (+/- 15 minutes)
9. The cold cap procedure will end approximately 5 hours (+/- 30 minutes) after the start of the melphalan infusion.
10. The process will be done on Day -2 and Day -1 (for both days of melphalan infusion) of the transplant procedure.

Note: Cold Cap start/end times must be documented by the technician and/or research staff.

5.3 Toxicities and Dosing Delays/Dose Modifications

The cold cap may be interrupted and/or removed for side effects of discomfort, skin irritation, or at the request of the patient and/or at the investigator's discretion for any reason. This information will be recorded and will not change the follow up procedures (photography and questionnaire).

5.3.1 Expected Toxicities (Penguin Cold Cap)

The primary toxicity of the treatment is discomfort from the coldness of the device. Skin irritation is rare but could occur.

5.4 Photography of Hair

A single camera will be used with a SIM card to record hair length and status. The front, 2 sides, and back views (4 total images) of patient hair will be taken at each time point as specified in the study procedures. The images will be captured by the PI and designated research staff. The photographs will be stored with labels using the Subject ID as identification. The images will be stored in a secure research file in accordance with all

applicable federal guidelines and local guidelines. If published, censorship/black out bars will be used to disidentify the patient such that only the hair is visible prior to submission.

5.5 Concomitant Medications/Treatments

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. Concomitant medications will NOT be collected and recorded on a case report form (CRF).

Excluded Concomitant Medications

- No topical creams/ointments to be applied to the scalp only during the Day -2 and Day -1 scalp cooling procedure.
- No conditioner or oil on the hair or scalp during the Day -2 and Day -1 scalp cooling procedure
- Oxaliplatin may not be used while on study.

5.6 Other Modalities or Procedures/ Research vs. Standard of Care Procedures

SOC: High-dose chemotherapy with melphalan, autologous stem cell transplantation, ECOG performance status
Research: Penguin cold cap, Hair imaging

5.7 Duration of Study Participation

The study duration per subject will be up to 4 months, with up to 28 days of screening, 2 days of treatment and up to 90 (±14) days for follow up.

5.8 Removal of Patients from Protocol

Patients will be removed from the study when any of the criteria listed in *Section 6.5* apply. Notify the Principal Investigator and document the reason for study removal and the date the patient was removed on the Case Report Form. The patient should be followed-up per protocol.

5.9 Subject Replacement

Subjects who withdraw from the study treatment prior to starting study intervention (Cold Cap use) will be replaced.

5.10 Evaluable for toxicity

Any patient who begins use of the Cold Cap is evaluable for toxicity and will be included in the safety analysis.

6.0 STUDY PROCEDURES

6.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 28 days prior to enrollment unless otherwise stated. The screening procedures include:

6.1.1 Informed Consent

6.1.2 Medical history and record review

Relevant medical history, including history of current disease, and information regarding underlying diseases will be recorded at Screening.

6.1.3 Demographics

- Age
- Sex
- Race
- Ethnicity

Patients may be offered the Inclusive Demographics Questionnaire, which is a standard, non-study-specific document, available on the IRB Intranet. Study team to record responses in the subject's OnCore record. Completion is voluntary; patients may decline to complete the Inclusive Demographics Questionnaire.

6.1.4 Review subject eligibility criteria

6.1.5 ECOG Performance Status

6.1.6 Hair loss assessment

Hair loss (alopecia) will be assessed using CTCAE v5.

6.1.7 Baseline Adverse Event (AE) assessment

Baseline adverse events, including duration (start and stop dates and times), severity/grade, outcome, treatment, and relation to device will be assessed. See section 7.0 for AE monitoring and reporting.

6.2 Procedures During Treatment

6.2.1 Day -2, Cold Cap

- Prior to Cold Cap and chemotherapy:
  - ECOG Performance Status
  - Hair loss assessment
  - Hair imaging
- Penguin cold cap application
- SOC chemotherapy with melphalan
- Adverse Events (AE) assessment. Only AEs of interest (per Section 7.2.3) to be entered into the EDC.

6.2.2 Day -1, Cold Cap

- Penguin cold cap application
- SOC chemotherapy with melphalan
- Adverse Events (AE) assessment. Only AEs of interest (per Section 7.2.3) to be entered into the EDC.

6.2.3 Day 0, Stem Cell Transplant

- Scalp Cooling Questionnaire
- Adverse Events (AE) assessment. Only AEs of interest (per Section 7.2.3) to be entered into the EDC.
- SOC autologous stem cell transplant

6.3 Follow-up Procedures

Post-stem cell transplant follow-up visits will occur at:

- Day 7 (± 2 days)
- Day 14 (± 2 days)
- Day 30 (± 7 days)
- Day 60 (± 7 days)
- Day 90 (± 14 days)

The following procedures will be performed during each visit:

6.3.1 Hair loss assessment

6.3.2 Hair imaging

The scalp will be imaged at the above days with photography done of each side of the head (four images total).

6.3.3 Adverse Events (AE) assessment

Only AEs of interest (per Section 7.2.3) to be entered into the EDC.

6.3.4 Scalp Cooling Questionnaire (Day 90 only)

6.4 Time and Events Table

	Screening (within 28 days)	**Day -2**	**Day -1**	**Day 0**	**Follow-up visits: Days 7 (± 2), 14 (± 2), 30 (± 7), 60 (± 7), & 90 (± 14)**
Informed Consent	X				
Medical history and record review	X				
Demographics	X				
Review subject eligibility criteria	X				
Registration	X				
ECOG Performance Status	X	X[1]			
Hair loss assessment	X	X[1]			X
Hair imaging		X[1]			X
Penguin cold cap		X	X		
SOC chemotherapy w/ melphalan		X	X		
Scalp Cooling Questionnaire				X	X (Day 90 only)
SOC autologous stem cell transplant				X	
Adverse Events (AE) assessment		X	X	X	X

1. Must be completed prior to Cold Cap and chemotherapy.

6.5 Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

6.5.1 Patient voluntarily withdraws (follow-up permitted).

6.5.2 Patient withdraws consent (termination of treatment and follow-up).

6.5.3 Patient is unable to comply with protocol requirements.

6.5.4 Patient experiences toxicity that makes continuation in the protocol unsafe;

6.5.5 Treating physician determines continuation on the study would not be in the patient's best interest;

6.5.6 Lost to follow-up. *If a research subject cannot be located to document survival after a period of 2 months, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two months must be documented. This will be reviewed during an interim data monitoring visit.*

7.0 ADVERSE EVENTS (AE), UNANTICIPATED ADVERSE DEVICE EFFECT (UADE), SERIOUS ADVERSE EVENTS (SAE), AND UNANTICIPATED PROBLEMS INVOLVING RISK TO SUBJECTS OR OTHERS (UPIRSO)

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence associated with the use of a drug/device in humans, whether or not considered drug/device related.

Planned hospital admissions or procedures for an illness or disease that existed before the subject was screened in the study and progression of underlying disease are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (e.g., surgery was performed earlier than planned).

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgeries, must not be reported as AEs. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an AE.

7.1.1.1 Laboratory test abnormalities

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, result in a delay or dose modification of study treatment, or judged relevant by the investigator), is considered an adverse event.

7.1.2 Serious Adverse Event (SAE)

An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.1.3 Unanticipated adverse device effect (UADE)

An unanticipated adverse device effect (UADE) is defined as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects”.

7.1.4 Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO)

UPIRSOs include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

7.2 Principal Investigator Responsibilities for Safety Monitoring

7.2.1 AE Reporting Period

The investigator or designee is responsible for ensuring that all AEs (that are at least possibly related to the study intervention) and UADEs (both serious and non-serious) observed by the clinical team or reported by the subject which occur from start of study, and until 90 days following stem cell transplant, are fully recorded in the subject’s medical records.

7.2.2 AE Documentation

The investigator, sub-investigator (treating physician if applicable), or study team (according to the responsibilities delegated per the DOA) will document the following for all AEs (both serious and non-serious):

- Event term, according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version (current). The CTCAE current version is available at http://ctep.cancer.gov/reporting/ctc.html
- Description of the event
- Date of onset and resolution
- Expectedness of the toxicity
    - Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
        - the current known adverse events listed in this protocol;
        - the drug package insert; and/or
        - the current Investigator's Brochure
- Grade of toxicity, as per CTCAE criteria
- Attribution of relatedness to the investigational agent- (this must be assigned by an Investigator, sub-investigator, or treating physician)
    - Attribution categories are as follows:
        - Definite: The AE is clearly related to the study treatment.
        - Probable: The AE is likely related to the study treatment.
        - Possible: The AE may be related to the study treatment.
        - Unlikely: The AE is doubtfully related to the study treatment.
        - Unrelated: The AE is clearly NOT related to the study treatment.
- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received conmed or other intervention, etc.
- Outcome of event

Source documentation must be available to support all AEs.

7.2.3 Protocol-specific Adverse Event Monitoring / EDC Guidelines

In this protocol, patients receiving the study intervention (Penguin Cold Cap) will also receive concomitant standard of care chemotherapy and autologous stem cell transplant.

Only AEs of interest, as outlined below, will be recorded in the EDC.

- All AEs that are at least possibly related to the study intervention will be collected.

7.2.4 Duration of AE monitoring

All patients experiencing an AE, regardless of its relationship to study intervention, will be monitored until:

- the AE resolves or the symptoms or signs that constitute the AE return to baseline
- any abnormal laboratory values deemed an AE, has returned to baseline
- there is a satisfactory explanation other than the study device for the changes observed
- death, or

- until 90 (±14) days following the stem cell transplant

7.3 Safety Reporting Requirements

7.3.1 Reporting to the Principal Investigator

The Principal Investigator (PI) must be notified by study staff or co-investigators within 24 hours of learning of any SAEs and UADEs, regardless of attribution and expectedness, occurring during the study or within 90 days following the stem cell transplant

Contact for Expedited Reporting:
Robert Vescio, MD, (310) 423-1825, Robert.Vescio@cshs.org

Alternate Contact for Expedited Reporting:
David Oveisi, MD, (310) 423-3720, David.Oveisi@cshs.org

7.3.2 Reporting to DSMC [for interventional cancer IITs]:

Serious Adverse Events deemed to be related to the protocol and on-study deaths, including death of a research subject unless the death is expected (e.g. due to disease progression) are to be reported to the DSMC within 24 hours of awareness. Hardcopies or electronic versions of the MedWatch Form 3500A (Mandatory Reporting) or a narrative report, along with any other supporting documentation available, should be submitted to the DSMC Coordinator. The DSMC Coordinator will forward the information to the DSMC Chair, and/or medical monitor. The DSMC Chair will review all documentation upon receipt from the DSMC Coordinator and determination of whether the following actions are required: 1) takes action immediately, 2) convenes a special DSMC session (physical or electronic), or 3) defers the action until a regularly scheduled DSMC meeting. Reports are to be emailed to the DSMC team at GroupSOCCICCTODSMCAdmin@cshs.org.

7.3.3 Reporting to the Institutional Review Board (IRB)

As per the Cedars-Sinai IRB Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy, the IRB must be notified of all UPIRSOs as soon as possible, but no later than 10 business days from when the study team learned of any of the following events:

1. Any internal SAE, AE or Research-Related Subject Injury (RRSI), which in the opinion of the Principal Investigator was unanticipated or unexpected, and has a reasonable possibility of relationship to the research.
2. Any actionable external SAE, AE, SUSAR, development safety update report (DSUR), or FDA MEDWATCH report deemed to be a UPIRSO. An event is considered “actionable” if it warrants a change to the conduct of the study.
3. Any internal or external UADE.
4. Any accidental, unintentional protocol or consent/HIPAA related deviation that may impact subjects’ rights, safety, or welfare. See section 10.8.3.
5. Any planned protocol exception or eligibility waiver. See sections 10.8.2 and 10.8.3.

6. Changes to the research or protocol deviations made without prior IRB approval in order to eliminate apparent immediate hazard to a research subject. (Note: These must be reported to the IRB within 5 business days.)
7. Problems, events, unanticipated incidental findings, billing problems, or other events, outcomes, or new information related to the research (e.g., publication, safety monitoring report, interim findings, product labeling changes, findings generated from preclinical, animal studies) that may adversely affect the rights, safety, or welfare of the subjects or others, put subjects or others at increased risk, compromise the research data, or require/recommend changes to the study conduct.
8. Subject complaints or concerns that cannot be resolved by the research staff to the subject's satisfaction.
9. Breach or potential breach of confidential or sensitive information.
10. Incarceration of a subject who is enrolled in a study that is not approved by the IRB to include prisoners.

7.3.4 *For Sponsor-Investigator IDE trials:* Reporting to the Food and Drug Administration

The sponsor-investigator of the IDE must submit all reported UADEs to the FDA as soon as possible but no later than 10 working days after the investigator first learns of the effect.

Copies of IDE Safety Reports will be kept in the Trial Master File in the SOCCI CCTO.

8.0 STATISTICAL CONSIDERATIONS

8.1 Sample Size

The PI judges that a proportion of 75% or less of patients treated to reduce the development of hair loss (defined as <50% hair loss using the CTCAE v5 Grade 0 or 1 at 30 days after the transplant) is not worthy of further investigation. Therefore, a test of hypothesis H0: $p < 0.75$ vs H1: $p > 0.75$ with 30 patients will have 80% power to detect a minimum detectable difference of 17.25% based on the exact binomial test at 5% significance level. The actual significance level is 3.7%.

8.2 Data Sets Analyzed

All eligible patients who are randomized into the study and receive at least one dose of the study intervention (the Safety Population) will be included in the safety analysis.

8.3 Analysis of Primary Endpoint

We will test the null hypothesis that the proportion of patients treated to reduce the development of hair loss (<50% using the CTCAE v5 Grade 0 or 1 at 30 days after the transplant) is no more than 75% using an exact Binomial test at 5% nominal significance level with 3.7% as actual significance level. If the number of patients with reduced development of hair loss is greater or equal to 27 patients, then we will reject the null

hypothesis and declare the study as feasible. Otherwise, we will revise and adapt out intervention to improve feasibility in subsequent trials.

8.4 Analysis of Secondary Endpoint

The secondary objective is to assess the potential impact of hair loss versus the discomfort and inconvenience of the scalp cooling procedure. Scalp cooling questionnaire will be administered on Day 0 and 90. Descriptive statistics will be presented as counts and percentages for qualitative variables and as means with standard deviations, medians with interquartile ranges for quantitative variables.

9.0 STUDY MANAGEMENT

9.1 Conflict of Interest

Any reportable conflict of interest will be disclosed to the local IRB and will be outlined in the Informed Consent Form.

9.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated and prior to the shipment of study supplies to participating sites, if applicable. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.3 Registration/Enrollment Procedures

All patients will be tracked following written informed consent. Those patients who are consented to participate in the clinical trial but do not meet one or more criteria required for participation during the screening phase will be listed as screen failures on the master list of consented subjects. Eligible subjects, as determined by screening procedures and

verified by a treating investigator, will be registered on study at Cedars Sinai Medical Center by the Study Coordinator.

Issues that would cause treatment delays after registration should be discussed with the Principal Investigator (PI). If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Assignment of Subject ID: The study teams will track all subjects who sign consent using OnCore. Subjects found to be ineligible will be recorded as screen failures. Subjects found to be eligible will be registered using a three-digit numeric ID that follows the standard SOCCI format (001, 002, etc.).

A) Eligibility Verification

Prior to registration/enrollment, all subjects must undergo an eligibility verification by the study-specific research staff. Minimal risk studies are exempt from SOCCI Quality Management Core (QMC) central eligibility checklist review and eligibility verification. QMC central eligibility checklist review and eligibility verification for all subjects enrolled is performed only if requested by the PI at any time during the life of the study.

For patients requiring a protocol exception request and/or waiver due to eligibility concerns, refer to Section 9.7.2, Protocol Exceptions and Eligibility Waivers for instructions.

B) Registration

After eligibility is verified, each site will assign the subject a study number and site staff will then register the patient in OnCore®.

Registration is completed as follows:

- Assignment of a patient study number
- Assignment to the patient a dose/treatment arm
- Enter the patient in OnCore
- Notify the investigational pharmacy and treating physicians that a subject has gone on study and anticipated treatment start date

Oversight by the principal investigator is required throughout the entire registration process.

9.4 Data Management, Quality Assurance, and Quality Control and Reporting

REDCap is the Cedars-Sinai Cancer institutional choice for the electronic data capture of case report forms for SOCCI Investigator Initiated Trials. REDCap, a HIPAA-compliant database, will be used for electronic case report forms in accordance with institutional requirements, as appropriate for the project. The Study Staff will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed. See also Section 9.5.2, Monitoring.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

9.5 Data and Safety Monitoring

9.5.1 Safety Oversight

Adherence to the protocol, Good Clinical Practices (GCP), and institutional policy will be monitored by the PI during the course of the study through routine Disease Research Group (DRG) meetings (or equivalent). The PI will maintain continuous safety monitoring for the duration of the study by reviewing subject/study data. It is the responsibility of the principal investigator to adhere to the Data Safety Monitoring Plan throughout the life of the study.

In addition, safety oversight and efficacy data will be reviewed by the SOCC Data and Safety Monitoring Committee (DSMC). The DSMC will review this trial commensurate with the assigned risk class as categorized by the PRMC. The DSMC membership and responsibilities are governed by the committee charter. The DSMC findings and recommendations will be reported in writing to the Principal Investigator as a summary letter which will be forwarded by the Principal Investigator or designee to the CS-IRB. The DSMC outcome letters will be furnished to the FDA, as applicable. Refer to the DSMC Charter for details of the DSMC review.

9.5.2 Monitoring

The SOCC Cancer Clinical Trials Office (CCTO) Quality Management Core (QMC) will conduct internal monitoring visits and audits to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Refer to the DSMP for details pertaining to the type, frequency, and extent of monitoring that will be performed

9.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, monitoring/auditing logs/letters, records of study drug receipt, dispensation, destruction, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. Study documents should be kept on file in accordance with all applicable federal guidelines and local guidelines.

Investigators must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB, and Regulatory Agency (e.g., FDA) inspectors upon request.

9.7 Adherence to Protocol

It is the responsibility of the Investigator-sponsor to ensure that patient recruitment and enrollment, treatment, follow-up for toxicities and response, and documentation and reporting at SOCCI are all performed as specified in the protocol. Except for an emergency situation in which proper care for the protection, safety, and well-being of the

study patient requires alternative treatment, or a protocol exception request approved by the IRB of record, the study shall be conducted exactly as described in the approved protocol.

9.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. For any such emergency modification implemented, the IRB must be notified as soon as possible, but no more than 72 hours from the investigator's awareness of the event.

9.7.2 Protocol Exceptions and Eligibility Waivers

Minimal Risk

A protocol exception is an anticipated or planned deviation from the IRB-approved research protocol, as described in the CSMC IRB Policy*, Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement.* A protocol exception most often involves a single subject and is not a permanent revision to the research protocol. Protocol exceptions that extend beyond a single subject should result in a protocol amendment to avoid serial violations.

Planned exceptions to the protocol that are more than logistical in nature and/or impact an eligibility criterion, affect timing of study drug administration, or the investigator assesses the event may impact subject safety and/or study integrity, may not be implemented without prior IRB approval. The PI or her/his designee is responsible for submitting a protocol exception request and its supporting documents to the CSMC IRB if it meets the CS-IRB UPIRSO policy guidelines of a reportable exception/waiver. Study team should also refer to the IRB *Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement* guidelines to determine which deviations and exception requests require IRB reporting. Once IRB approved, the deviation or exception can be implemented.

Special considerations for Eligibility Waivers (EW)

In general, subjects who do not meet the eligibility requirements should not be enrolled. In the rare event that it is appropriate for subject inclusion, the rationale/justification and subject case history should be submitted to the IRB for approval. Such requests for minimal risk studies do not require prior review by the CCTO Medical Director.

9.7.3 Other Protocol Deviations

Logistical deviations from the protocol (e.g., minor changes to the study schedule for an individual subject) do not require prior IRB approval unless the deviation has the potential to affect the subject's safety or study integrity. Such planned deviations that do meet this definition and do not affect the subject's safety or study integrity should be noted in the subject's research record or deviation log as described in the SOCCI CCTO's Standard Operating Procedure 12: Deviation and Noncompliance Reporting.

Unintentional deviations from the protocol that might affect subject safety or study integrity should be reported to the IRB within 10 days from when the investigator becomes aware that such a deviation has occurred, as outlined in the SOCCI CCTO's Standard Operating Procedure 12: *Deviation and Noncompliance Reporting* (or local policy, for multi-site studies). In this case, a Protocol Deviation report must be submitted in CS-IRB, per CSMC IRB policy, *Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research*

Compliance and Quality Improvement. All submissions should include a description of the plan to avoid similar deviations or exceptions in the future.

9.7.4 **Amendments to the Protocol**

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation. Repeat exceptions or deviations to the protocol may suggest a protocol amendment is needed.

9.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms and/or into a HIPAA-compliant study database. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

9.9 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the sponsor-investigator and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

10.0 REFERENCES

1. Lilleby, K, et. al., A prospective, randomized study of cryotherapy during administration of high-dose melphalan to decrease the severity and duration of oral mucositis in patients with multiple myeloma undergoing autologous peripheral blood stem cell transplantation. Bone Marrow Transplant (2006): 37(11), 1031-5
2. Zhang, Xin-Yu, et. al., Effectiveness, Safety, and Tolerance of Scalp Cooling for Chemotherapy-Induced Alopecia. Oncology Nursing Forum, (2022): 49(4) 369-384.
3. Sitarz, Jamie, and Spencer, Cara, Chemotherapy-Induced Alopecia: Examining Patient Perceptions and Adherence to Home Haircare Recommendations. Clinical Journal of Oncology Nursing (2022); 26 (2), 190-197.
4. Nangia, Julie et. al, Effect of a Scalp Cooling Device on Alopecia in Women Undergoing Chemotherapy for Breast Cancer: The SCALP Randomized Clinical Trial. JAMA (2017) 317(6):596-605.

11.0 APPENDICES

11.1 APPENDIX A: SUMMARY OF CHANGES

Protocol Amendment 1 (Protocol version 2, dated 31OCT2023)

- Sec. 3.0 clarification of imaging timepoints and removal of stopping rule reference.
- Sec. 4.1.4 removal of hair covering percentage inclusion criterion
- Sec. 4.2.2 removal of duplicative exclusion criterion
- Sec. 4.2.6 removal of exclusion criterion for current use of oxaliplatin

Protocol Amendment 2 (Protocol version 3, dated 20NOV2023)

- Sec. 3.0 addition of cold cap administration window of +/- 30 minutes
- Sec. 5.2 addition of cold cap administration window of +/- 30 minutes

11.2 APPENDIX B: QUESTIONNAIRE

Days 0 and 90 Scalp Cooling Questionnaire will be attached as a separate file.

11.3 APPENDIX C: ECOG Performance Status Scale

ECOG PERFORMANCE STATUS SCALE GRADE	DESCRIPTION
0	Fully active, able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activities and able to carry out work of a light or sedentary nature, e.g. light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

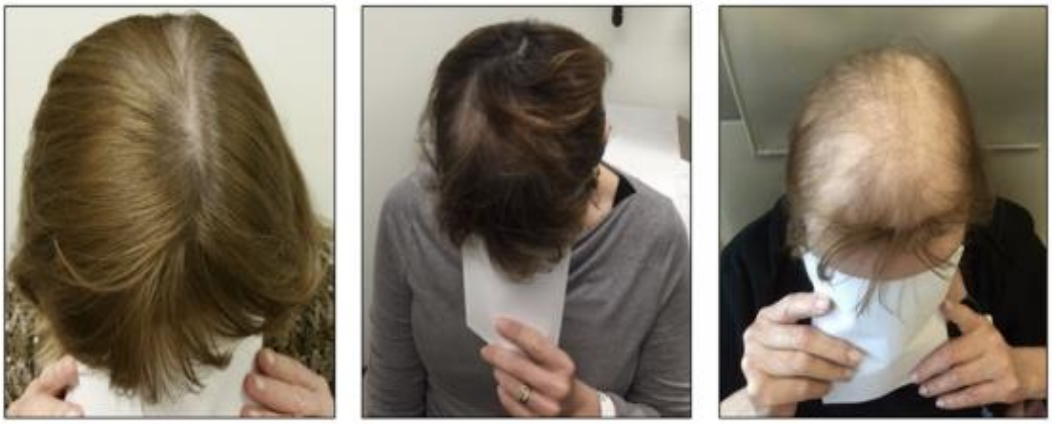
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

11.4 APPENDIX D: HAIR LOSS ASSESSMENT

Grading of Hair Loss (Alopecia) to be assessed by treating investigator or designee.

These will be completed at Screening, Days -2, 7 (± 2), 14 (± 2), 30 (± 7), 60 (± 7), & 90 (± 14).

Alopecia as defined by Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. CTCAE version 5.0 defines alopecia only through Grade 2.



Grade 0
No hair loss

Grade 1
Hair loss of up to 50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage.

Grade 2
Hair loss of > 50% of normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact.