Clinical Study Protocol

Title:	A Phase 2 study to assess the Safety and Efficacy of Scalp Cooling using Penguin™ Cold Caps for the Prevention or Reduction of Chemotherapy-induced Alopecia in Stage I-III Breast Cancer Protocol: Penguin™ cold-cap study 2017
Investigational Product:	Penguin™ Cold Cap
Date:	7/11/19
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Investigator Agreement

I have read and approved this protocol. My signature confirms my agreement that **the clinical study will be conducted in full compliance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonization Guideline for Good Clinical Practice (GCP)**, the Code of Federal Regulations (CFR), the ethical principles that have their origins in the Declaration of Helsinki and all applicable Federal and local regulations. All required study information will be archived as required by regulatory authorities.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

This document is confidential. It contains proprietary information of Penguin™ Cold Caps. Any disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. This document must be used solely for the purpose of reviewing or performing this study.

Investigator: _____ **Date:** _____

David Page, MD

_____ _____

Institution: Providence Portland Medical Center

_____ _____

Protocol Synopsis Penguin™ cold-cap Study 2017

Name of Investigational agent: Penguin™ cold-caps

Title of Study: A Phase 2 study to assess the Safety and Efficacy of Scalp Cooling using Penguin™ Cold Caps for the prevention or reduction of Chemotherapy-induced Alopecia in Stage I-III Breast Cancer

Study Center(s): Providence Portland Medical Center (PPMC); Providence St. Vincent Medical Center (PSVMC)

Study Period: 2 years

Phase of Development: Phase II

Objectives:

Primary objective:

- To estimate the efficacy of Penguin™ cold caps in preventing or reducing hair loss in patients receiving (neo)adjuvant chemotherapy (one of four common regimens) for early stage breast cancer.

Secondary objectives:

- To assess the safety of Penguin™ cold-caps for scalp cooling therapy.
- To assess patient-reported outcomes using the "was it worth it scale", the EORTC QLQ-C30 quality of life scale and the body image scale (BIS).
- To assess outcomes by alternative measures such as serial photography with a dedicated digital research camera, CTCAE v4.0 alopecia scale, and by patient-reported wig/head cover use.
- To assess variations in efficacy due to variables such as treatment site (PPMC versus PSVMC), compliance with technique, or caretaker type (volunteer versus non-volunteer).

Exploratory objective:

- To evaluate the feasibility of implementing scalp cooling therapy in Providence facilities.

Study Design:

This will be a phase II prospective, open label, non-randomized study conducted to determine the safety and efficacy of Penguin™ cold cap system in the prevention or reduction of

chemotherapy-induced alopecia in patients with early stage breast cancer undergoing chemotherapy.

Eligible subjects will be enrolled to one of 4 study arms (Table 1) determined by type of chemotherapy. Subjects will have early stage breast cancer of any receptor subtype, for which standard of care chemotherapy is planned. Eligible subjects will be enrolled at Providence Portland Medical Center (PPMC) and Providence St. Vincent Medical Center (PSVMC).

The Penguin™ cold cap therapy will be administered to all enrolled subjects according to the dosing schedule specified by the study arms. Penguin™ cold caps is a portable scalp cooling system which uses gel-filled cold caps that are cooled on dry ice and exchanged every 30 minutes to maintain optimum temperature. No scalp preparation is required before use.

Cold-cap therapy will commence at least 50 minutes prior to infusion, and will continue for at least 4 hours following completion of chemotherapy. Participants will be provided cold-caps in a personal cooler (cooled by dry ice). Participants and their caretakers will undergo training to ensure appropriate handling and fitting of cold-caps.

Subjects enrolled in the study will have a photograph of the head and scalp taken on day 1 (prior to first infusion), at selected times during chemotherapy treatment, as well as day 30 post-treatment visit using a dedicated research camera. The treating physician investigator or trained study personnel will score participants for alopecia on the day 30 post-treatment visit, using the Dean's scale for the primary outcome measure. As a secondary outcome measure, adverse effects will be evaluated routinely using the NCI-CTCAE v4.0 alopecia scale. In addition, the Dean's scale as scored using photographs by an independent investigator will be reported.

Table 1: Chemotherapy regimen according to study arm

Arm	**Regimen**	**Cytotoxic Drugs + Dose**
Arm 1 n = 20	ACT/HP	Doxorubicin 60 mg/m^2 x 4 Cyclophosphamide 600 mg/m^2 x4 Paclitaxel 175 mg/m2 x 4 (or) 80 mg/m^2 x 12 +/- trastuzumab/pertuzumab
Arm 2 n = 20	TCH/P	Docetaxel 75 mg/m^2 x 6 Carboplatin AUC =6 x 6 +/- trastuzumab/pertuzumab
Arm 3 n = 20	TC	Docetaxel 75 mg/m^2 x 4 Cyclophosphamide 600 mg/m^2 x 4
Arm 4 n = 20	T/H	Paclitaxel 80 mg/m^2 x 12 +/- trastuzumab

- Participants will be monitored for toxicity at the time of treatment and prior to chemotherapy at scheduled standard-of-care physician/NP assessments. Toxicities will be reported using CTCAE v4.0 definitions.

- Participants will be provided a written diary to capture variables that may influence study results including: cold-cap down time (i.e. time during treatment when cold cap is not applied or exchanged), number of post-chemotherapy cold-cap exchanges.

Inclusion Criteria

To be enrolled in the study, subjects must meet the following inclusion criteria.

1. At least ≥ 18 years of age
2. Diagnosis of stage I-III breast cancer for whom neoadjuvant or adjuvant cytotoxic chemotherapy (ACT/HP, TCH/P, TC, or T/H) is planned.
3. Willing and able to provide informed consent.
4. Availability of caretaker(s) to accompany participant and facilitate cold-cap placement/exchanges using the recommended technique.
5. Women of childbearing potential must use acceptable measures to avoid becoming pregnant during study period and for 30 days after last dose of chemotherapy.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study.

1. Pre-existing alopecia (Dean's scale ≥ 1)
2. Another malignancy that required active treatment with systemic chemotherapy within 2 years of study recruitment.
3. Prior radiotherapy treatment involving head.
4. Pre-existing chronic severe headaches or migraines.
5. Skin conditions that in the opinion of PI would be at risk of worsening with study.
6. Cold sensitivity or cold agglutinin disease
7. Cryoglobulinemia
8. Cryofibrogenemia
9. History of current evidence of any condition, therapy or abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, such that trial participation is not in the best interest of the subject.

Number of Subjects: up to 80 anticipated

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List of Definitions and Abbreviations

ACT	Doxorubicin, Cyclophosphamide, Paclitaxel
ACT/HP	Doxorubicin, Cyclophosphamide, Paclitaxel +/- Trastuzumab or Pertuzumab
AE	adverse event
ANR	Anthracyclines
BIS	body image scale
CC	cold cap
CI	confidence interval
CIA	Chemotherapy-induced alopecia
CFR	Code of Federal Regulations
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
EC	Epirubicin, Cylophosphamide
EC/Doc	Epirubicin, Cyclophosphamide, followed by Docetaxel
FEC	5-fluourouracil, Epirubicin, Cyclophosphamide
FEC/Doc	5-fluourouracil, Epirubicin, Cyclophosphamide followed by Docetaxel
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
ESBC	Early stage breast cancer
ET	Etoposide
FDA	Food and Drug Administration
GCP	Good Clinical Practices
IB	Investigator's brochure
ICH	International conference on harmonization
IRB	Institutional Review Board
ITT	Intention-to-treat
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NP	nurse practitioner
PCS	Paxman cooling system
PI	Principal investigator
PPMC	Providence Portland Medical Center
PSVMC	Providence St. Vincent Medical Center
QLQ	Quality of Life Questionnaire
SAE	Serious adverse event
SCALP trial	Scalp Cooling Alopecia Prevention trial
SQ	Subcutaneous

TAC	Taxotere, adriamycin, cyclophosphamide
TC	Docetaxel, cyclophosphamide
TCH/P	Docetaxel, carboplatin +/- trastuzumab/pertuzumab
T/H	Paclitaxel +/- trastuzumab
TM	Trademark
TX	Taxanes
US	United states
v	Version
VAS	Visual analog scale
WIWI	Was-it-worth-it

1 INTRODUCTION

1.1 BACKGROUND

1.1.1 Breast Cancer

The American Cancer Society estimates that about 1 in 8 women will develop invasive breast cancer over the course of her lifetime [American Cancer Society, 2012]. In 2017, an estimated 252,710 new cases of invasive breast cancer are expected to be diagnosed in women in the U.S., along with 63,410 new cases of non-invasive (in-situ) breast cancer. About 2,470 new cases of invasive breast cancer are expected to be diagnosed in men in 2017. A man's lifetime risk of breast cancer is about 1 in 1,000.

As of March 2017, there are more than 3.1 million women with a history of breast cancer in the U.S. This includes women currently being treated and women who have finished treatment.

1.1.2 The Role of Chemotherapy in the Treatment of Breast Cancer and Chemotherapy-induced Alopecia (CIA)

The use of cytotoxic chemotherapy remains a mainstay in the treatment of a majority of both advanced and early stage breast cancer cases with numerous landmark studies identifying clear survival benefits. Despite this finding, the use of chemotherapy incurs substantial burden to patients in the form of toxicities, untoward side effects, economic strain and psychological ramifications.

Chemotherapy-induced alopecia (CIA) is a common and emotionally distressing side effect of breast cancer therapy. Hair loss frequently ranks as highly as nausea and fatigue as an ominous side effect of cancer treatment. In fact, patients have been known to refuse potentially lifesaving chemotherapy due to concerns about hair loss. A survey conducted 25 years ago found that slightly less than 10% of women diagnosed with cancer, in the 24 to 66 age group, were actually ready to forego chemotherapy due to the impending threat of losing their hair. A more recent study in newly diagnosed cancer patients found that a little over 15% of participants refused cancer treatment partially or completely, and of those, a majority were women refusing adjuvant chemotherapy for their breast cancer. Without their hair, many women find their identity and femininity altered, and experience difficulty in maintaining the sense of optimism necessary to cope with the challenging journey of a cancer diagnosis.

1.1.3 Therapeutic significance of Scalp Cooling in the Prevention or Reduction of Chemotherapy-induced Alopecia

To date, there is no currently accepted standard of care for the treatment of chemotherapy-induced alopecia. However, a number of methods -including scalp tourniquets, pulsed electrostatic fields, topical medications such as minoxidil, and cold caps -have been tested for the reduction of CIA. Of these methods, scalp cooling has proven effective in Europe though it has been slow to gain popularity in the U.S.

1.1.4 Scalp Cooling Methods

Modes of delivery for scalp cooling therapy occur via continuously cooling machine based systems or manual cold caps. Machine based systems which are currently FDA approved include the Paxman® scalp cooling system (PCS-1 and 2, Orbis) and the DigniCap® system (Dignitana Corp). Manual scalp cooling has been practiced with several methods such as simple bags with crushed ice and frozen cryogel packs. Examples of commercially manufactured manual caps include ChemoCap™ (ChemoCap, Canada), Elasto-Gel™ Cold Caps (Southwest Technologies, Akromed Inc.) and Penguin™ Cold Caps (Medical Specialties of California). These manual caps require frequent cap changes due to thaw-effects and are labor intensive for caretakers. They can also be uncomfortable for patients due to the cap's heavy weight. However, they appear to be effective in preliminary trials, and cost/labor considerations may be mitigated by a hospital-based service.

It is believed that the continuously cooling machine based systems are more convenient because no cap changes are needed. However, the continuously cooling machines have the disadvantage of limiting physical capacity in infusion centers and restricting patient mobility during scalp cooling since patients have to be connected to the machines.

1.1.5 Potential mechanism of action of Scalp Cooling Therapy in the Prevention or Reduction of CIA

Scalp cooling is thought to work by inducing vasoconstriction and the reduction of metabolism in hair follicles during chemotherapy. Vasoconstriction may lead to reduced blood flow to hair follicles in the period of peak plasma concentration of the relevant chemotherapy agent. The reduced blood flow may translate to reduced biochemical activity which makes hair follicles less vulnerable to the damage of chemotherapy agents. Theoretically, the end result of reduced blood flow and reduced metabolism in the hair follicles is ultimately a decrease in hair loss.

1.1.6 Rationale for the use of Penguin™ Cold Caps

Penguin™ cold caps represent a drug-free and relatively non-invasive technique of scalp cooling that has been shown to be successful in minimizing hair loss in patients undergoing chemotherapy for the treatment of cancer. Scalp cooling with Penguin™ cold caps involves applying specially designed caps onto the head to cool the scalp, and maintaining the correct optimum temperature for a period of time dependent on treatment specific parameters. Other manual precooled cold caps such as Arctic cold caps are also available for use in the U.S. However, Arctic cold caps have been involved in fewer studies and is less well known.

1.2 Nonclinical Studies with Scalp Cooling Therapy

To date there are no published studies of Penguin™ cold caps in animal models.

1.3 Clinical Experience with Scalp Cooling Therapy

1.3.1 Phase 2 trials

1.3.1.1 Studies assessing Safety and Efficacy of Scalp Cooling for Prevention or Reduction of CIA

A number of studies have been performed in Europe to study the safety and efficacy of scalp cooling therapy for the prevention and reduction of CIA. The largest published series of 1411 scalp-cooled patients from the Dutch Scalp Cooling Registry demonstrated an efficacy rate of 50% based on non-use of wigs among scalp-cooled patients using the Paxman® scalp cooling system. The Dutch study showed that the prevention or reduction of CIA with scalp cooling may be better with certain types of chemotherapy (taxanes), decreased doses of chemotherapeutic agents and longer scalp cooling times. However, when anthracyclines and taxanes are combined and given together (simultaneously) with cyclophosphamide (a schedule commonly called TAC; taxotere, adriamycin, cyclophosphamide), the results are typically poor despite the use of machine-based scalp cooling therapy.

A German study (Friedrichs et. al) of 83 breast cancer patients receiving adjuvant chemotherapy with anthracycline and taxane based regimen reported a mean success rate of >52.6% for less than 50% hair loss and no use of head covering (wigs). The study used the DigniCap® scalp cooling system with a feedback-controlled feature that allowed direct measurement of scalp temperatures. Patient satisfaction scores directly linked to hair preservation was assessed throughout the study and was reportedly between VAS 70-80; with 100 being the highest and representing complete satisfaction. Even though epirubicin was used in the study, ACT chemotherapy regimen was not studied. The (neo)adjuvant chemotherapeutic regimens used in the study were FEC, FEC/Doc, EC, and EC/Doc.

The Scalp Cooling Alopecia Prevention (SCALP) trial is a multicenter, randomized, non-blinded study conducted in the U.S. from December 9, 2013 to September 30, 2016 for women planning to undergo taxane- and/or anthracycline-based neoadjuvant or adjuvant chemotherapy for breast cancer. Successful hair preservation was found in 48 of 95 women with scalp cooling (50.5%; 95% CI, 40.7%-60.4%) compared with 0 of 47 women in the control group (0%; 95% CI, 0%-7.6%) after the fourth chemotherapy cycle. There were no statistically significant differences in changes in scales for quality of life measures from baseline to chemotherapy cycle 4 among the scalp cooling and control groups. The scalp cooling device used was the Paxman® scalp cooling system which was well tolerated with no serious adverse events reported. The trial was stopped early due to demonstration of superiority in the treatment group.

In another U.S. prospective cohort trial (Rugo et. al) of stage I-II breast cancer female patients receiving adjuvant chemotherapy, hair loss of 50% or less was observed in 67 of 101 patients at 4 weeks after last chemotherapy. Of patients who underwent scalp cooling, 27.3% (95% CI, 18%-36.6%) reported feeling less physically attractive compared with 56.3% (95% CI, 31.9%-80.6%) of patients in the control group (P=.02). It is important to note that this study involved non-anthracycline based chemotherapy. The study utilized the DigniCap® scalp cooling system. Annual follow-up is ongoing and will last for 5 years to determine the incidence of scalp metastases.

1.3.1.2 Studies assessing Safety and Efficacy of Penguin™ cold caps in Europe

A European study of the Penguin™ cold cap system for the prevention of CIA (Katsimbri et. al) in 70 patients receiving chemotherapy from multiple causes of cancer demonstrated positive findings. Specifically, patients were enrolled into one of four study arms: Group A, taxane-based regimen without anthracyclines (TX); Group B, taxane + anthracycline based regimens (TX + ANR); Group C, anthracycline-based regimens (without taxanes; ANR); Group D, etoposide based regimens (without taxanes or anthracyclines; ET). The main tumor types treated were lung cancer (20 patients, 30%), cancer of unknown primary (11 patients, 16%), and breast cancer (9 patients, 13%). Scalp cooling was achieved by maintaining scalp temperatures below 15^{o}C before, during and after chemotherapy. Assessment of hair loss was performed using the Dean's scale grading system. Grades 0-2 were considered as satisfactory hair protection while grades 3-4 were considered failures. 57 patients were evaluable for assessment. In groups C and D, 11 of 12 patients (92%) had no alopecia. In group A, 30 of 34 patients (88%) treated with taxanes had adequate hair protection. In group B, only 4 of 11 patients (36%) had adequate hair protection. The system was well tolerated and demonstrated efficacy for protection from hair loss caused by TX, ANR and ET based on study findings.

1.3.1.3 Studies assessing Safety and Efficacy of Penguin™ cold caps in the U.S.

A prospective U.S. study of 20 patients (Cigler at.al) to assess the efficacy of Penguin™ cold caps for scalp cooling in prevention of CIA was conducted in women receiving adjuvant TC chemotherapy for breast cancer. The TC (docetaxel [Taxotere] and cyclophosphamide) chemotherapy regimen is typically associated with severe alopecia. All the patients independently elected to use scalp cooling with cold caps. Degree of hair loss was assessed by a single practitioner using Dean's alopecia scale (grade 1/excellent [< 25% hair loss], grade 2/good [25%-50% hair loss], grade 3/moderate [50%-75% hair loss], grade 4/poor [> 75% hair loss]), digital photographs, and patient self-report of hair thinning or the need to wear a wig/head covering. Assessment of hair loss was made at baseline, before each chemotherapy treatment, and at follow-up (3 weeks to 3 months after the fourth chemotherapy treatment). At the follow-up visit, 18 (90%) patients did not feel the need to wear a wig or head covering. Only 2 (10%) patients reported the need to wear a wig or head covering at the follow-up visit. These 2 patients were assessed as having grade 3 and grade 4 hair loss by Dean's scale, respectively. Of the 5 patients assessed as having grade 2 hair loss by Dean's scale, none reported the need to wear a wig or head covering. Despite not wearing a wig, or head covering, the majority of patients reported hair thinning at each visit. Scalp cooling was generally well tolerated. No patient discontinued cold therapy due to side effects from the cold caps.

1.3.2 Adverse Effects and Tolerability of Scalp Cooling

In general, scalp cooling is well tolerated. The most common reported side effects are headaches, unpleasant feelings due to the heaviness of the cap and coldness, dizziness and transient lightheadedness. Headaches are usually not severe and can often be prevented by Tylenol. Freezing has never been reported. Toxicity data from U.S and European studies are tabulated below.

Table 2. Summary of Adverse Device Effects in the SCALP trial

	Participants by Chemotherapy Cycle, No. (%)			
Adverse Device Event	1 (n = 101)	2 (n = 84)	3 (n = 66)	4 (n = 62)
Headache	12 (11.9)	9 (10.7)	1 (1.5)	4 (6.5)
Nausea	4 (4.0)	2 (2.4)	1 (1.5)	1 (1.6)
Dizziness	3 (3.0)	1 (1.2)	0	0
Chills	1 (1.0)	0	0	0
Paresthesia	1 (1.0)	0	0	0
Pruritus	1 (1.0)	0	0	0
Sinus pain	0	0	1 (1.5)	0
Skin and SQ tissue				

disorders	1 (1.0)	0	0	0
Skin ulceration	1 (1.0)	0	0	0
Dry skin	1 (1.0)	1 (1.2)	1 (1.5)	0
Scalp pain	1 (1.0)	2 (2.4)	1 (1.5)	1 (1.6)

All adverse device events were graded using the Common Technology Criteria for Adverse Events (CTCAE) version 4.0. A total of 54 adverse events were reported: 44 patient-cycles had 46 anticipated adverse device effects and 8 patient-cycles had 8 unanticipated adverse device effects. There were no serious adverse events or serious adverse device events.

Table 3. Summary of Adverse Effects reported in German Study (Friedrichs et. al)

Adverse Effect ≥ 50%	Patients with adjuvant chemotherapy (n = 58)	Patients with palliative chemotherapy (n = 6)
Feeling cold	22 (37.9%)	2 (33.3%)
Headache	14 (24.1%)	0
Heaviness of head	11 (18.9%)	0
Scalp pain	6 (10.3%)	1 (16.7%)

Only 2 out of 19 patients who stopped scalp cooling therapy stopped due to physical side effects (one due to feeling cold and one due to headache). The frequency of side effects was generally higher in patients with neo-adjuvant chemotherapy compared to patients in palliative chemotherapy regimens.

Table 4. Summary of Adverse Effects reported in U.S. study (Rugo et.al)

Adverse Effect	Patients in Scalp Cooling group (n = 101)	Patients in control group (n = 16)
Headache	4 (0.04%)	0
Pruritus	1 (0.01%)	0
Skin pain	1 (0.01%)	0
Head discomfort	1 (0.01%)	0

None of these events were rated severe. One patient had a headache that was rated as moderate using CTCAE v4.0. No patient has developed scalp metastases with a median follow-up from the last chemotherapy administration of 29.5 months (range 24.4-34.8 months). Patient follow up will continue for 5 years.

1.3.2.1 Adverse Effect of Scalp Metastases with Scalp Cooling

Scalp cooling has been slow to gain popularity in the United States partly because of concerns that limiting chemotherapeutic activity in the scalp by virtue of scalp cooling may increase the

risk of scalp metastasis. However studies to date indicate that rates of scalp metastasis between scalp-cooled and non–scalp-cooled patients with solid tumor malignancies are virtually identical.

In a retrospective cohort study of the incidence of scalp metastases by Lemieux J. et.al, women with breast carcinoma undergoing chemotherapy were assigned to one of two groups; the scalp cooling group (n = 553) and the non-scalp cooling group (n = 87). The median follow-up was 5.8 years (+/- 1.7) for the scalp-cooling group and 5.4 years (+/- 1.7) for the non-scalp cooling group. The incidence of scalp metastases was 1.1% (6 cases out of 553 patients) among women who used scalp cooling in the neoadjuvant or adjuvant setting and 1.2% (1 case out of 87 patients) among women who did not use scalp cooling in the neoadjuvant or adjuvant setting. These findings suggest that the incidence of scalp metastases is quite rare following the use of scalp cooling therapy.

However, there have been isolated cases of scalp metastasis after scalp cooling reported in the literature. In a case report by Lemieux J, two cases of occurrence of scalp metastases occur after 7- and 9-year follow-up respectively. The first patient presented with a scalp metastasis as first metastatic site 9 years following breast cancer chemotherapy; she used scalp cooling for adjuvant treatment in 2 of 4 cycles of doxorubicin and cyclophosphamide. The second case presented a scalp metastasis as first metastatic site 7 years following chemotherapy for her first cancer; she used scalp cooling in only one of six cycles of adjuvant cyclophosphamide, methotrexate, and 5-fluorouracil and then was treated for a local recurrence 5 years later with surgery and 6 cycles of epirubicin 100 mg/m^2 without scalp cooling. It is deemed unlikely that scalp cooling used in one out of 12 chemotherapy cycles in this patient with high risk of recurrent disease contributed to the finding of a scalp metastasis 7 years after her initial diagnosis.

Additionally, in a robust systematic review and meta-analysis of 10 studies by Rugo et.al, the incidence of scalp metastasis following scalp cooling was assessed. 1959 patients who received scalp cooling were evaluated over an estimated mean time frame of 43.1 months and compared to 1238 patients over an estimated mean time frame of 87.4 months who did not receive scalp cooling therapy with chemotherapy. The incidence rate of scalp metastasis in the scalp cooling group versus the no scalp cooling group was 0.61% (95% CI 0.32-1.1%) versus 0.41% (95% CI 0.13-0.94%); P = 0.43. The findings of this meta-analysis would suggest that scalp cooling does not increase the incidence of scalp metastases.

2 STUDY OBJECTIVES

2.1 Primary Objective

To estimate the efficacy of Penguin™ cold caps in preventing or reducing hair loss in patients receiving (neo)adjuvant chemotherapy (one of four common regimens) for early stage breast cancer.

2.2 Secondary Objective

The secondary objectives include the following:

- To assess patient-reported outcomes using the 5-question "was it worth it" questionnaire, the EORTC QLQ-C30 and QLQ-BR23 quality of life questionnaires, and the body image scale (BIS) questionnaire;
- To assess outcomes by alternative measures such as serial photography using a dedicated research camera (baseline versus 1-month follow-up), CTCAE v4.0 alopecia scale, and by patient-reported wig/head cover use;
- To assess for variations in efficacy according to variables such as treatment site (PPMC v. PSVMC), ethnicity, hair type (straight v. curly), compliance with technique, or caretaker type (volunteer v. non-volunteer).

2.3 Exploratory Objective

Exploratory objective(s) are:

- To evaluate the feasibility of implementing hospital-sponsored scalp cooling services in Providence facilities.

3 INVESTIGATIONAL PLAN

3.1 Study Design

This will be a phase II prospective, open label, non-randomized study conducted to determine the safety and efficacy of Penguin TM cold cap system in preventing or reducing chemotherapy-induced alopecia in patients with early stage breast cancer undergoing chemotherapy.

Eligible subjects will be enrolled to one of 4 study arms (Table 5) determined by type of chemotherapy. Subjects will have early stage breast cancer of any receptor subtype, for which standard of care includes chemotherapy. Eligible subjects will be enrolled at Providence Portland Medical Center (PPMC) and Providence St. Vincent Medical Center (PSVMC).

The Penguin™ cold cap therapy will be administered to all enrolled subjects according to the dosing schedule specified by the study arms. Penguin™ cold caps is a portable scalp cooling system which uses gel-filled cold caps that are cooled on dry ice and exchanged every 30

minutes in order to maintain optimum temperature. Its unique crylon gel formula is specifically created to maintain cold temperatures for much longer periods of time than other conventional cooling gels and foams. No scalp preparation is required before use.

Subjects will designate one or more caretakers (spouse, friend or volunteer) to attend infusion sessions and to assist with proper fitting and exchanging of cold-caps. Prior to commencing infusions, designated caretakers and participants will undergo training by trained staff who certified in the proper use of cold-caps. Training sessions will include: safe handling of dry ice, technique for ensuring proper cooling of cold-caps, and technique for securing and positioning cold-caps to scalp.

Cold-cap therapy will commence at least 50 minutes prior to infusion, and will continue for 4 hours following completion of chemotherapy. Participants will be provided cold-caps in a personal cooler (cooled by dry ice).

Subjects enrolled in the study will have a photograph of the head and scalp taken on one occasion that falls between day -7 to day 1 of chemotherapy initiation. Additional photographs will be taken at selected times during chemotherapy cycles, and on day 30 (+/- 5) post-treatment using a dedicated research camera. The treating physician investigator or designated study personnel will score participants for alopecia on the day 30 post-treatment visit, using the Dean's scale for the primary outcome measure. As a secondary outcome measure, adverse effects will be evaluated routinely using the NCI-CTCAE v4.0 alopecia scale. In addition, the Dean's scale as scored using photographs by an independent investigator will be reported.

Table 5: Chemotherapy regimen according to study arm

Arm	**Regimen**	**Cytotoxic Drugs + Dose**
Arm 1 n = 20	ACT/HP	Doxorubicin 60 mg/m^2 x 4 Cyclophosphamide 600 mg/m^2 x4 Paclitaxel 175 mg/m2 x 4 (or) 80 mg/m^2 x 12 +/- trastuzumab/pertuzumab
Arm 2 n = 20	TCH/P	Docetaxel 75 mg/m^2 x 6 Carboplatin AUC =6 x 6 +/- trastuzumab/pertuzumab
Arm 3 n = 20	TC	Docetaxel 75 mg/m^2 x 4 Cyclophosphamide 600 mg/m^2 x 4
Arm 4 n = 20	T/H	Paclitaxel 80 mg/m^2 x 12 +/- trastuzumab

3.1.1 Rationale for the Primary Objective

Prior studies of scalp cooling therapy involved the use of machine-based systems such as the Paxman® and the DigniCap® scalp cooling systems which are typically more expensive and have the disadvantage of limiting physical capacity in infusion centers. These factors have limited their widespread use. Consequently, there is a need to study the efficacy of more portable scalp cooling systems such as the Penguin™ cold-caps. While there have been some studies of the Penguin™ cold-caps in Europe, few have been conducted in the U.S.

3.1.2 Rationale for the Secondary Objective

The rationale for using the 5-question "was it worth it" scale, the EORTC QLQ-C30 scale and the BIS is to obtain information about the usefulness of scalp cooling therapy using Penguin™ cold-caps by the patient population served at PPMC and PSVMC. This would inform decisions about implementation of Penguin™ cold-caps at our facilities.

3.1.3 Rationale for Exploratory Objective

Prior studies of the Penguin™ cold cap therapy were relatively small and did not provide significant information about the feasibility of implementing scalp cooling therapy in a "real-world" setting. Therefore, this study will attempt to assess the feasibility of implementing scalp cooling therapy among patients undergoing chemotherapy at Providence medical facilities. Furthermore, this trial will attempt to evaluate the efficacy of scalp cooling therapy when participants are involved in the use of cold caps with the help of their caretakers.

3.1.4 Benefit/Risk Assessment

This trial is designed to incorporate scalp cooling therapy with the use of cold caps into the management of early stage breast cancer with chemotherapy. The trial will only enroll subjects for whom standard of care includes the use of adjuvant or neo-adjuvant chemotherapy. The use of Penguin™ cold-caps for scalp cooling has not raised significant safety concerns in previous trials as discussed above. Therefore the risk of significant harm from adverse events is minimal.

One potential risk from the use of Penguin™ cold-caps for scalp cooling is the development of scalp metastases. However, prior studies and case reports have demonstrated that the incidence of scalp metastases arising after the use of scalp cooling is incredibly low, and has not been born out in retrospective and prospective series (Rugo et. al).

3.2 Selection of Study Population

3.2.1 Inclusion Criteria

To be enrolled in the study, subjects must meet the following inclusion criteria.

1. At least ≥ 18 years of age
2. Diagnosis of stage I-III breast cancer for whom neoadjuvant or adjuvant cytotoxic chemotherapy (ACT/HP, TCH/P, TC, or T/H) is planned.
3. Willing and able to provide informed consent.
4. Availability of caretaker(s) to accompany participant and facilitate cold-cap placement/exchanges using the recommended technique.
5. Women of childbearing potential must use acceptable measures to avoid becoming pregnant during study period and for 30 days after last dose of chemotherapy.

3.2.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study.

1. Pre-existing alopecia (Dean's scale ≥ 1)
2. Another malignancy that required active treatment with systemic chemotherapy within 2 years of study recruitment.
3. Prior radiotherapy treatment involving head.
4. Pre-existing chronic severe headaches or migraines.
5. Skin conditions that in the opinion of PI would be at risk of worsening with study.
6. Cold sensitivity or cold agglutinin disease
7. Cryoglobulinemia
8. Cryofibrogenemia
9. History of current evidence of any condition, therapy or abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, such that trial participation is not in the best interest of the subject.

3.3 Termination of Study Treatment

The investigator may stop the study treatment regimen due to intolerable adverse effect to any component of the Penguin™ cold-caps, a clinically significant adverse event or for protocol noncompliance.

3.4 Withdrawal of Consent

Any subject may terminate participation in the study at any time but every effort should be made to continue with study treatment and evaluations. If a subject elects to discontinue study participation at any time for safety, medical or personal reasons, the investigator should make a reasonable effort to determine the reason for the subject's withdrawal and document the reason. Any clinically significant adverse events leading to premature withdrawal are to be followed until resolution.

4 STUDY TREATMENTS

4.1 Study Design

Subjects who meet all eligibility criteria will be treated with scalp cooling therapy using Penguin™ cold-caps as described above (Section 3.2).

4.2 Regimen Medications

Patients will be assigned to one of four study arms according to chemotherapy regimens that constitute standard of care for treatment of breast cancer. However, the respective chemotherapy regimens utilized here are not under direct investigation in this trial.

4.3. Method of Assigning Subject Numbers

After a subject has signed the informed consent form and has been deemed eligible for enrollment, the investigator will assign a unique subject number to that subject. Patients will be assigned a number in the order of study enrollment e.g. CC-01, CC-02 (denoting cold cap #1, cold cap #2). Subjects who withdraw from the study after being assigned a subject number will retain that number.

4.4 Treatment Compliance

The investigator of study personnel will administer Penguin™ cold-cap therapy to enrolled subjects deemed eligible as described in Section 3.1. Patients will be given diaries to monitor compliance and document duration of cold cap therapy throughout the study. These patient diaries will be reviewed and collected at study closure by assigned study staff.

4.5 Prohibited, Prior and Concomitant Treatments

Subjects are advised not to take any medications without discussing with their oncologist. However, any medications given to treat a reported study related adverse event will be documented pursuant to established protocol.

5 STUDY PROCEDURES AND SCHEDULE

5.1 Study Schedule

The schedule of study events is outlined in table 5.

Table 6: Schedule of Study Events

Study Events	Study Period				Post-Treatment Follow-up	Follow-up interview
	Screening	Prior to Day 1	Day 1 (start of chemotherapy)	Days of subsequent chemotherapy cycles	Day 30	(Day 30 to 3000)
Administrative Procedures						
Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Training of caretaker/participant		X				
Study Intervention/Administration						
Chemotherapy			X	X		
Penguin cold-cap used			X	X		
Clinical Evaluations						
Complete history & Physical including baseline scalp/hair assessment	X					
Dean's alopecia scale			X	X	X	
CTCAE v4.0			X		X	
Quality of Life Questionnaires (QLQ-C30; QLQ-BR23)		X			X	X
Body image scale (BIS) Questionnaires		X			X	X
Patient diary			X	X		
W1W1 Questionnaire					X	X
Efficacy Measurements						
Photography of scalp/hair			X (a)	X(b)	X	
Post-treatment exit interview						X (c)

Footnotes for Schedule of Events Table:

a. Photography of scalp/hair will be taken prior to start of chemotherapy to document baseline condition.

b. Photography of scalp/hair will be performed at least four times for serial assessment, which includes cycle 1 (baseline), at least two additional cycles, and at post-treatment. Recommended timepoints are summarized:

ACT regimen - cycle 1 and 3 of AC, cycle 2 of Taxol, and post-treatment

ACT/H regimen - cycle 1 and 3 of AC, cycle 2 of Taxol, and post-treatment

TCH/P regimen - cycle 1, 3 and 5 of TCH/P, and post-treatment

TC regimen - cycle 1, 3 and 4, and post-treatment

TH regimen - cycle 1, 7 and 10 of Taxol, and post-treatment

c. Follow-up in-person or phone interview to be conducted and recorded between days 30 to 3000 to evaluate long-term patient narrative and opinion of cold cap experience

5.2 Study Procedures

5.2.1 Screening

The purpose and procedures of the study will be fully explained to participants. Those wishing to enroll in the study will sign a written informed consent prior to initiating any protocol specific activities or procedures. The following screening evaluations will be performed prior to Day 1:

- Obtain informed consent. No study related testing will be completed prior to completion of a fully executed consent form.
- Medical evaluations including history of present illness, chronic conditions, gender, and history of allergies
- Baseline assessment of scalp to ensure absence of alopecia
- Review pertinent medical history to ensure participant meets study inclusion criteria

5.2.2 Prior to Day 1

The following procedures will be completed at this time:

- Training of caretaker/participant to ensure proper use of cold-caps. Caretaker and participant will be required to demonstrate proficiency in technique prior to initiation of chemotherapy.
- Complete QLQ and BIS questionnaire.

5.2.3 Day 1 (first chemotherapy infusion)

The following procedures will be completed at this visit:

- Photography of hair/scalp prior to initiation of chemotherapy to document baseline condition.
- Administration of chemotherapy regimen indicated by study arm.
- Administration of scalp cooling therapy using Penguin™ cold-cap at least 50 minutes prior to chemotherapy, during chemotherapy and for 4 hours after infusion of chemotherapy.
- Completion of CTCAE v4.0, Dean's alopecia scale and patient diary.

5.2.4 Any day between day 1 and day 30 post-treatment

If nurse or other qualified medical personnel receives information about an adverse event he/she will document the event.

- Administration of chemotherapy cycles and Penguin™ cold cap per study arm.
- Complete Dean's alopecia scale and patient diary.
- Photography of hair and scalp at selected chemotherapy cycles.

5.2.5 Day 30 post-chemotherapy treatment follow-up

The following procedures will be completed at this visit:

- Photography of hair/scalp to obtain post-chemotherapy assessment
- Completion of the QLQ, BIS, CTCAE v4.0, Dean's alopecia scale, and WIWI questionnaire.

5.2.6 Follow-up interview

The following procedures will be completed during a visit between day 30 to 3000

- Follow-up recorded interview whereby subjective narrative of the patient will be obtained
- Completion of the QLQ, BIS, and WIW questionnaire may be repeated at that time

The interviewer will use an interview script to conduct a semi-structured, verbal interview in an attempt to solicit extensive, qualitative assessments of patient experience. Interviews may be conducted in person or by telephone and will be recorded and transcribed. Patients will be asked to sign a consent addendum for this portion of the study. The consent addendum and interview script will be reviewed and approved by the IRB prior to use.

Interview responses and information will be stored in a secure database located on the Providence network and accessible only by using a password-protected Providence computer. Any hard copy notes and materials will be stored in a locked office in a secure medical office suite. Only members of the study team will be given access to the information. Any published or presented results will not contain patient identifying information.

6 ADVERSE EVENTS AND REPORTING REQUIREMENTS

6.1 Adverse Event Definition

An adverse event (AE) is any new undesirable medical occurrence or change (worsening) of an existing condition in a subject that occurs on or after Day 1 until Day 30 post-chemotherapy pursuant to the administration of scalp cooling therapy with Penguin™ cold-caps.

Adverse events reported by the subject or observed by the investigator will be individually listed on an AE case report form (CRF). The signs and symptoms, date of onset, duration, action taken, severity, outcome to date, and relationship to the study use of the Penguin™ cold-caps will be recorded. The severity of AEs will be graded according to the National Cancer Institute Common Technology Criteria for Adverse Events (NCI-CTCAE), version 4.0 toxicity criteria. Severity will be classified as described in Section 6.1.3.

For adverse events of grade 3 or 4, the principal investigator will determine whether to modify or discontinue study treatment.

At each visit, the investigator will be prompted to report AEs as "not", "possibly," or "definitely" related to the administration of scalp cooling therapy with Penguin™ cold-caps.

6.1.1 Definition of Serious and Life Threatening Adverse Events

A serious adverse event (SAE) is one that results in any of the following outcomes:

- Death
- Is life-threatening
  - A life-threatening adverse experience is any AE that places the subject, in view of the Investigator, at immediate risk of death from the reaction as it occurred.
- A persistent or significant disability/incapacity
- Inpatient hospitalization or prolongation of existing hospitalization, except a planned hospitalization during days in clinic, or hospitalization for social reasons or the convenience of the subject or physician shall not be considered a SAE.
- Important medical event
  - Important medical events that may not result in death, be life-threatening, or require hospitalization but may be serious when, based upon appropriate medical judgment, the event may jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed above.

6.1.2 Definition of Relationship to Study Intervention (Administration of Penguin™ cold cap)

Association or relatedness to the study regimen will be graded as either "not", "possibly," or "definitely" related to the study administration of Penguin™ cold-cap therapy. Determination of relatedness includes:

- **Definitely**, characterized as an AE that
  - Follows direct temporal sequence from study intervention.
  - Abates upon discontinuation of the study intervention.
  - Cannot be explained by the known characteristics of the subject's clinical state or by other modes of therapy administered to the subject.
- **Possibly**, characterized as an AE that
  - Follows a reasonable temporal sequence from study intervention.
  - Abates upon discontinuation of the study intervention.
  - Could have been produced by the subject's clinical state or by other modes of therapy administered to the subject.

- **Not Related**, characterized as an AE that
  - Does not follow any temporal sequence from study intervention.
  - Is explained by the subject's clinical state or by other modes of therapy administered to the subject.

6.1.3 Definition of Severity

The severity of adverse changes in physical signs or symptoms will be graded according to the NCI-CTCAE v4.0 as follows:

Grade 1: **Mild** (transient or mild discomfort, no limitation in activity, no medical therapy/intervention required)

Grade 2: **Moderate** (mild to moderate limitation in activity, some assistance may be needed, no or minimal medical intervention/therapy required)

Grade 3: **Severe** (marked limitation in activity, some assistance usually required, medical therapy/intervention required, hospitalization possible)

Grade 4: **Life threatening** (extreme limitation in activity, significant assistance required, significant medical therapy/intervention required, hospitalization or hospice care probable)

Grade 5: **Death**

6.1.4 Definition of Action Taken

None: No action taken with regard to study intervention

Interrupted: The study intervention was stopped but restarted after the subject's symptom abated. The subject was rechallenged with the study intervention.

Discontinued: The study intervention was permanently stopped.

6.1.5 Definition of Outcome to Date

Resolved with sequelae: The subject has recovered from the AE with observable residual effects.

Resolved without sequelae: The subject has fully recovered from the AE with no observable residual effects.

Unresolved: The AE is present and observable.

Death: The subject died as a result of the AE.

Lost to Follow-up: Source documentation confirms that repeated attempts to contact subject have failed. All documents regarding study contact will be logged into the study binder.

6.2 Notification of Serious or Unexpected Adverse Events

The principal investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32). A suspected adverse reaction must be both serious and unexpected in order to meet the reporting requirements.

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed.

An adverse event or suspected adverse reaction is considered "serious" if, in view of the principal investigator, 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, or 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.

Serious adverse events will be reported to the IRB and the FDA. IRB policies for the reporting of adverse events will be followed. Voluntary reporting FDA forms (Form FDA 3500) will be used for reporting of SAEs.

7 STATISTICAL CONSIDERATIONS AND ASSESSMENT OF ENDPOINTS

7.1 Sample Size Considerations

This clinical trial is a proof of concept and safety study but not a "first-in-human" study. The number of subjects is generally consistent with prior studies of similar investigational products. A sample size of 20 subjects per treatment arm was selected due to resource and cost constraints. In addition, it provides sufficient precision in estimating efficacy, as described in the confidence interval tables.

Subjects who are enrolled but withdraw consent prior to administration of the Penguin™ cold-cap therapy will not be evaluable and will be replaced.

7.2 Primary Endpoint: Efficacy of Penguin™ cold-caps for Prevention or Reduction of CIA

Efficacy will be reported as the proportion of evaluable subjects in each arm who achieve a score of 0-2 on the Dean's alopecia scale (i.e. less than 50% hair loss by standardized photography) at the 30-day post-chemotherapy assessment visit. A modified intention-to-treat (ITT) analysis will be followed whereby all subjects receiving at least 75% of prescribed chemotherapy dose will be considered evaluable (those receiving less chemotherapy are excluded to minimize confounding effect of chemotherapy dose).

Subjects who withdraw consent prior to efficacy assessment will constitute treatment failures according to the intention-to-treat principle. Based upon historical experience, it is expected that virtually 0% of patients will retain hair (dean score 0-2) in the absence of cold-cap therapy.

The point estimate and confidence intervals (80%, 95%) of efficacy will be reported for each arm. Table 9 illustrates confidence intervals of efficacy of various scenarios, assuming 75% evaluability. These data will be used to inform prospective chemotherapy patients of the likelihood of success which will aid decision-making.

Table 7: Confidence interval estimates assuming 75% evaluability

x (# successful)	n (# evaluable)	Efficacy estimate (x/n)	80% CI	95% CI
0	15	0	0-.14	0-.22
3	15	0.2	.08-.39	.04-.48
6	15	0.4	.23-.60	.16-.68
9	15	0.6	.40-.77	.32-.84
12	15	0.8	.61-.92	.52-.96

Thresholds for declaring success will not be pre-defined in this preliminary clinical trial. However, if a clinically significant proportion of patients achieve hair retention, and if therapy is feasible, we may expand the trial to enroll more patients and increase statistical precision.

7.2.1 Laboratory values, vital signs, physical findings and other safety data

Any laboratory results, vital signs, physical findings, or outcomes of any other investigations that are conducted during the course of the study that in the opinion of the investigator should be considered an adverse event must be documented.

7.3 Secondary Endpoint: Assessment of Patient-reported Outcomes and variations In Efficacy

The secondary endpoint is to evaluate the effect of Penguin™ cold-cap therapy on patient-reported outcomes such as the "was it worth it" scale, the quality of life scale and the BIS scale. These outcomes will be reported as the proportion of patients (and confidence intervals) reporting the study cold-cap therapy as positive and beneficial for the WIWI scale. For the QLQ, outcomes will be reported as the proportion of patients (and confidence intervals) who report

improvement in quality of life; maintaining same quality of life; or worsening quality of life after study participation.

7.4 Exploratory Endpoints

Exploratory endpoints that will be analyzed include assessment of the feasibility of implementing a scalp-cooling therapy program in Providence facilities in the future. This will be determined by the general consensus of a committee of stakeholders comprised of hospital leadership and clinician providers after study conclusion. In addition, the study will report the subjective experiences of participants and caretakers.

8 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Protection of Human Subjects

This study will be conducted in accordance with the US CFR, Title 21, Part 11, 50, 54, 56 and 312, the Declaration of Helsinki (1964) including all amendments and revisions, the Good Clinical Practices: Consolidated Guideline (E6); International Conference on Harmonization, the Food and Drug Administration Guidance for Industry, Computerized Systems Used in Clinical Trials, the ethical principles that have their origins in the Declaration of Helsinki and all applicable country-specific and local regulations. All required study information will be archived as required by regulatory authorities.

8.2 Informed Consent

Informed consent must be obtained and documented prior to the initiation of study registration and study intervention.

The investigator (or designee) will explain the study procedures, treatments, costs, potential benefits/risks involved, and the alternatives for care or treatment to the patient/legally authorized representative (hereafter referred to as "patient"). Determination of the appropriate person to give legal consent will be done in accordance with ICH/GCP, Providence Health & Services Policy and state law. All study procedures will be explained in terms the patient can understand and an opportunity will be given for the patient to ask questions. Special care will be given to explaining the use and disclosure of a patient's protected health information and if applicable, a patient's rights. This must be done before the informed consent is signed. This discussion will be documented in the patient's chart.

A copy of the signed consent form will be provided to the patient and the original consent form will be kept in the patient chart at the Clinical Trials Office.

9 STUDY ADMINISTRATION

9.1 Monitoring Plan

9.1.1 Site Initiation

The principal investigator and research nurse will conduct an implementation meeting for sub-investigators and applicable research and clinical staff. Attendance at this meeting will be documented.

9.1.2 Interim Monitoring

Interim monitoring will be scheduled at regular intervals throughout the study, with the timing dependent on subject enrollment. Generally, the study monitor will compare the data entered on the CRFs with the hospital or clinic records (primary source documents) and check for protocol compliance, including verification of informed consent, all subject visit dates, all AEs, all concomitant medications, and all key efficacy observations. In addition, the Site Regulatory Binder containing essential documents, study drug accountability, and supporting records will be reviewed. Findings from this review will be summarized in writing and presented to the investigator, and the dates of the monitoring will be recorded by the study monitor in a sign-in log to be kept in the Site regulatory Binder.

9.1.3 Study Close-out

At the study's conclusion close-out monitoring will be performed, including a final review and reconciliation of all study materials and regulatory documents including Penguin™ cold caps and patient diaries.

9.1.4 Site Responsibility

The procedures defined in the protocol and in the CRFs will be carefully reviewed by the investigator and his/her staff prior to study initiation to ensure appropriate interpretation and implementation. No deviations from the protocol should be made. Minor exceptions may be approved on a case-by case basis and must be authorized by the principal investigator and documented in writing. Significant deviations that may impact subject safety or study integrity will be reported to the IRB and may result in termination of study participation. Any changes to the protocol will originate from the principal investigator in the form of an amendment.

9.2 Study Documents and Access to Records

It is the responsibility of the investigator and the study staff to maintain a comprehensive and centralized filing system of all study-related documentation, which is suitable for inspection at any time by the study monitor, the Sponsor or its designee, the FDA and other regulatory agencies. Elements should include, but are not limited to:

- Study files, containing the curriculum vitae of all investigators and his/her designees, FDA form 1572, the protocol with all amendments, the IB, local lab certifications and lab normal ranges, and all correspondence to and from local regulatory authorities.
- Subject files, containing the completed original supporting source documentation and the signed informed consent form(s).
- Dispensing records of test agents.
- In accordance with FDA regulations, the investigator shall retain records for a period of at least 2 years after the investigation is discontinued.

9.3 Quality Assurance

The principal investigator and all designees will ensure the integrity of all data collected and calculations made during the conduct of the study according to their quality assurance standards of operations. Edit checks will be run on the data and queries issued. All data will undergo 100% review.

9.4 Confidentiality and Publication Policy

This trial will be listed in clinical trial databases as appropriate, e.g. www.clinicaltrials.gov.

10 REFERENCES

Cigler T, Isseroff D, Fiederlein B, et al. Efficacy of Scalp Cooling in Preventing Chemotherapy-Induced Alopecia in Breast Cancer Patients receiving Adjuvant Docetaxel and Cyclophosphamide Chemotherapy. Clinical Breast Cancer. 2015;15(5): 332-4.

Borsellino M, Young MM. Anticipatory coping: Taking control of hair loss. Clinical Journal of Oncology Nursing. 2011;15:311-315. doi:10.1188/11.CJON.311-315

Rugo HS, Klein P, Melin SA, et al. Association between Use of a Scalp Cooling Device and Alopecia after Chemotherapy for Breast Cancer. JAMA. 2017;317(6): 606-14.

Van den Hurk CJ, Peerbooms M, Van de Poll-Franse LV, et al. Scalp cooling for hair preservation and associated characteristics in 1411 chemotherapy patients–results of the Dutch Scalp Cooling Registry. Acta Oncol 2012; 51:497-504.

Nangia J, Wang T, Osborne C, 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.

Katsimbri P, Bamias A, Pavlidis N. Prevention of chemotherapy-induced alopecia using an effective scalp cooling system. Eur J Cancer. 2000;36(6):766-71.

Rugo HS, Melin SA, Voigt J. Scalp cooling with adjuvant/neoadjuvant chemotherapy for breast cancer and the risk of scalp metastases: systematic review and meta-analysis. J Breast Cancer Res Treat. 2017 Mar 8. doi: 10.1007/s10549-017-4185-9 [Epub ahead of print].

Friedrichs K, Carstensen MH. Successful reduction of alopecia induced by anthracycline and taxane containing adjuvant chemotherapy in breast cancer - clinical evaluation of sensor-controlled scalp cooling. Springer Plus 2014;3:500.

Lemieux J, Amireault C, Provencher L, Maunsell E. Incidence of scalp metastases in breast cancer: a retrospective cohort study in women who were offered scalp cooling. Breast Cancer Res Treat. 2009; 118(3):547-52.

Lemieux J, Desbiens C, Hogue JC. Breast cancer scalp metastasis as first metastatic site after scalp cooling: two cases of occurrence after 7- and 9-year follow-up. Breast Cancer Res Treat. 2011;128(2):563-6.

Tierney AJ, Taylor J, Closs SJ. Knowledge, expectations and experiences of patients receiving chemotherapy for breast cancer. Scand J Caring Sc*i*. 1992;6(2):75-80. doi: 10.1111/j.1471-6712.1992

Puts MT, Monette J, Girre V, et al. Characteristics of older newly diagnosed cancer

patients refusing cancer treatments. Support Care Cancer. 2010;18(8):969-74. doi: 10.1007/s00520-010-0883-0

APPENDICES

Appendix 1: Dean's Alopecia Scale

- Grade 0 - No hair loss
- Grade 1 - Up to 25% hair loss
- Grade 2 - Greater than 25% hair loss and up to 50% hair loss
- Grade 3 - Greater than 50% hair loss and up to 75% hair loss
- Grade 4 - Greater than 75% hair loss

Appendix 2: Was It Worth It (WIWI) Questionnaire

Patient ID #: _____ Date: _____

1. Was it worthwhile for you to participate in this research?
   a) Yes
   b) No
   c) Unsure

2. If you had to do it over, would you participate in this research?
   a) Yes
   b) No
   c) Unsure

3. Would you recommend participating in this research study?
   a) Yes
   b) No
   c) Unsure

4. Overall, did your quality of life change by participating in this research?
   a) It improved
   b) Stayed the same
   c) Became worse

5. Overall, how was your experience of participating in this research?
   a) Better than I expected
   b) The same as I expected
   c) Worse than I expected

Appendix 3: Body Image Scale (BIS) Questionnaire

Patient ID #: _____ Date: _____

	Not at all	A little	Quite a bit	Very much
Have you been feeling self-conscious about your appearance?	_____	_____	_____	_____
Have you felt less physically attractive as a result of your disease or treatment?	_____	_____	_____	_____
Have you been dissatisfied with your appearance when dressed?	_____	_____	_____	_____
Have you been feeling less feminine as a result of your disease or treatment?	_____	_____	_____	_____
Did you find it difficult to look at yourself naked?	_____	_____	_____	_____
Have you been feeling less sexually attractive as a result of your disease or treatment?	_____	_____	_____	_____
Did you avoid people because of the way you felt about your appearance?	_____	_____	_____	_____
Have you been feeling the treatment has left your whole body less whole?	_____	_____	_____	_____
Have you felt dissatisfied with your body?	_____	_____	_____	_____
Have you been dissatisfied with the appearance of your scar?	_____	_____	_____	_____
	Not applicable			

Appendix 4 **Patient Cold Cap Time Log/Diary**

Patient ID #: _____

Day 1 Cycle: _____

Date: _____

Subsequent Cycle: _____

Date: _____

Penguin™ cold caps should be switched every 30 minutes during these times:
50 minutes prior to start of infusion, during infusion and four hours after infusion completed.

Prior to start of Infusion Record times below	
:	Cold cap initially placed on head
:	Cold cap switched
:	New cold cap on

During Infusion Record times below						
	:	**Treatment began**		Hour 5	:	Cold cap switched
30 minutes	:	Cold cap switched			:	New cold cap on
	:	New cold cap on		Hour 5.5	:	Cold cap switched
Hour 1	:	Cold cap switched			:	New cold cap on
	:	New cold cap on		Hour 6	:	Cold cap switched
Hour 1.5	:	Cold cap switched			:	New cold cap on
	:	New cold cap on			:	**Treatment ended**
Hour 2	:	Cold cap switched				
	:	New cold cap on		**Additional times if needed- Please note below**		
Hour 2.5	:	Cold cap switched			:	Cold cap switched
	:	New cold cap on			:	New cold cap on
Hour 3	:	Cold cap switched			:	Cold cap switched
	:	New cold cap on			:	New cold cap on
Hour 3.5	:	Cold cap switched			:	Cold cap switched
	:	New cold cap on			:	New cold cap on
Hour 4	:	Cold cap switched			:	Cold cap switched
	:	New cold cap on			:	New cold cap on
Hour 4.5	:	Cold cap switched			:	Cold cap switched
	:	New cold cap on			:	New cold cap on

Please note any problems or delays that occurred when changing cold caps during treatment:

Patient/Caretaker Signature and Date: _____

Penguin™ Cold Caps should be switched every 30 minutes after the completion of treatment for up to four hours.

***Reminder to bring this log to your next scheduled treatment visit**

Please note any problems or delays that occurred when changing cold caps after treatment:

Four hours after Infusion complete Record times below						
30 minutes	:	Cold cap switched		**Additional times if needed- Please note below**		
	:	New cold cap on			:	New cold cap on
Hour 1	:	Cold cap switched			:	Cold cap switched
	:	New cold cap on			:	New cold cap on
Hour 1.5	:	Cold cap switched			:	Cold cap switched
	:	New cold cap on			:	New cold cap on
Hour 2	:	Cold cap switched			:	Cold cap switched
	:	New cold cap on			:	New cold cap on
Hour 2.5	:	Cold cap switched			:	Cold cap switched
	:	New cold cap on			:	New cold cap on
Hour 3	:	Cold cap switched			:	Cold cap switched
	:	New cold cap on			:	New cold cap on
Hour 3.5	:	Cold cap switched			:	Cold cap switched
	:	New cold cap on			:	New cold cap on
Hour 4	:	Cold cap switched			:	Cold cap switched
	:	New cold cap on			:	New cold cap on

Patient/Caretaker Signature and Date: _____

Appendix 5: Quality of Life Questionnaires (QLQ)

EORTC QLQ-C30 (version 3)

Please answer all questions by circling the number that best applies to you. There are no "right" or "wrong" answers. The information you provide will remain confidential.

Patient ID #: _____ Today's Date: _____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing Yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17.	Have you had diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ-BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

Patient ID #: _____ Today's Date: _____

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	Did you have a dry mouth:	1	2	3	4
32.	Did food and drink taste different than usual?	1	2	3	4
33.	Were your eyes painful, irritated or watery?	1	2	3	4
34.	Have you lost any hair?	1	2	3	4
35.	Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36.	Did you feel ill or unwell?	1	2	3	4
37.	Did you have hot flushes?	1	2	3	4
38.	Did you have headaches?	1	2	3	4
39.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40.	Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41.	Did you find it difficult to look at yourself naked?	1	2	3	4
42.	Have you been dissatisfied with your body?	1	2	3	4
43.	Were you worried about your health in the future?	1	2	3	4

During the past <u>four</u> weeks:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
44.	To what extent were you interested in sex?	1	2	3	4
45.	To what extent were sexually active? (with or without intercourse)	1	2	3	4
46.	Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
47.	Did you have any pain in your arm or shoulder?	1	2	3	4
48.	Did you have a swollen arm or hand?	1	2	3	4
49.	Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50.	Have you had any pain in the area of your affected breast?	1	2	3	4
51.	Was the area of your affected breast swollen?	1	2	3	4
52.	Was the area of your affected breast oversensitive?	1	2	3	4
53.	Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4