NCT01986140
Scalp Cooling to Prevent Chemo-induced Hair Loss (SCALP)

Unique Protocol ID: H: 33692 SCALP

Statistical Analysis Plan

Scalp Cooling Alopecia Prevention Trial (SCALP)

Protocol Number
BCM: H-33692

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Version: 1.0

Date: November 30, 2015

Scalp Cooling Alopecia Prevention Trial (SCALP)

SAP Revision Record

Revision Number	Details of Revision	Date
1.0	Original SAP	11-30-2015

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List of Abbreviations

AADE	anticipated adverse device effect
AE	adverse event
BIS	Body Image Scale
CI	confidence interval
CMH	Cochran-Mantel-Haenszel test
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EORTC	European Organisation of Research and Treatment of Cancer
HADS	Hospital Anxiety & Depression Scale
ICH	International Conference on Harmonisation
IQR	interquartile range
ITT	intent-to-treat
KM	Kaplan-Meier
NSABP	National Surgical Adjuvant Breast and Bowel Project
OS	overall survival
QLQ-C	Quality of Life Questionnaire-Core
QOL	Quality of Life
SAP	statistical analysis plan
SD	standard deviation
TFR	time to first recurrence

1. Introduction

The purpose of this document is to describe the statistical methods, data derivations and data summaries to be employed for this prospective, multi-center, parallel group (no intervention control), randomized clinical trial to compare success in hair preservation, between the Orbis Paxman Hair Loss Prevention System and control (no cooling) after 4 cycles of chemotherapy.

The preparation of this statistical analysis plan (SAP) has been based on International Conference on Harmonisation (ICH) E3 and E9 Guidelines and in reference to protocol Version 0.9 dated November 5, 2015.

2. Study Objectives

2.1 Primary Objective

Efficacy: To compare success in hair preservation, between the Orbis Paxman Hair Loss Prevention System and control (no cooling) after 4 cycles of chemotherapy. Hair preservation is defined as CTCAE v4.0 grade 0 or 1 alopecia determined by the independent, blinded healthcare professional. All eligible study subjects who receive at least one cycle of chemotherapy will be evaluable for hair preservation response.

Safety: To estimate the rate of significant cold-related anticipated adverse device effects (AADEs).

2.2 Secondary Objectives

Efficacy: To compare the two groups on the basis of subject-perceived hair preservation (assessed by the CTCAE v4.0 and the alopecia pictorial tool), medical oncologist perceived hair preservation (assessed by the CTCAE v4.0), rate of use of wigs and/or head wraps, and change in quality of life as assessed by the EORTC QLQ-C30, Hospital Anxiety & Depression Scale (HADS), and Body Image Scale (BIS).

Safety: To compare the two groups on the basis of subject reported comfort, rate of early scalp metastases and survival.

3. Investigational Plan

3.1 Study Design

This is a prospective, multi-center, parallel group (no intervention control), randomized clinical trial to compare success in hair preservation, between the Orbis Paxman Hair Loss Prevention System and control (no cooling) after 4 cycles of chemotherapy. The study is proposed to conduct in up to 10 centers within the USA that are routinely engaged in the administration of adjuvant or neoadjuvant chemotherapy to women with stage I – II breast cancer.

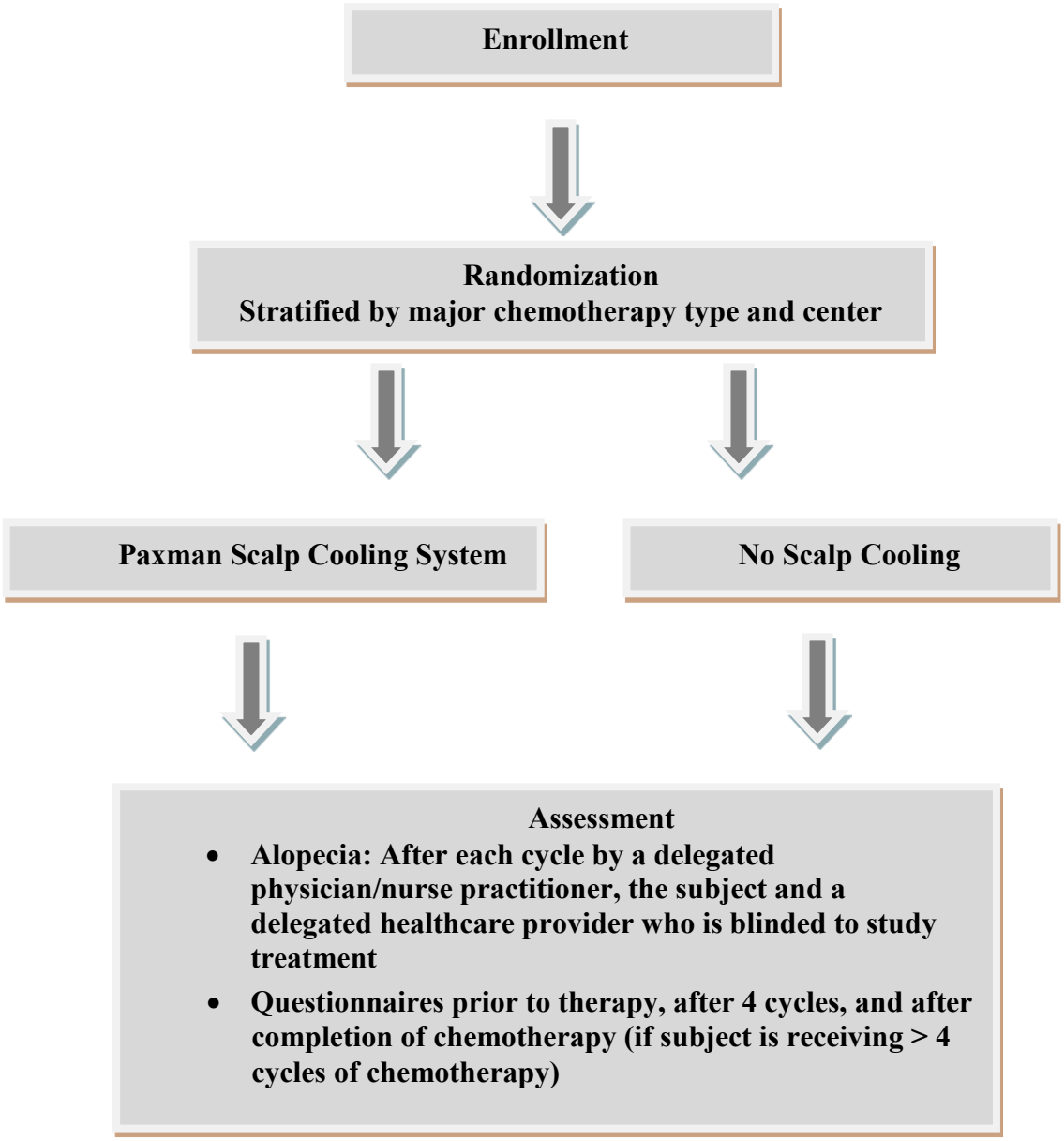
All subjects randomized to scalp cooling will undergo scalp cooling using the Orbis Paxman Hair Loss Prevention System prior to, during and after administration of each chemotherapy session, for 4 complete cycles of full-dose anthracycline or taxane based chemotherapy.

At baseline and after each cycle, subjects will have an alopecia assessment by a delegated physician or nurse practitioner and a second independent healthcare provider who is blinded to study treatment. The independent healthcare provider is a healthcare professional (physician, nurse, medical assistant, or research coordinator) who is trained in alopecia assessment, who is fully independent from the study, and who is completely blinded to the subject's treatment. This alopecia assessment will be made using the CTCAE v4.0 grading system. The alopecia assessment will always be performed prior to subjects receiving their next cycle of chemotherapy. Subjects will also perform their own alopecia assessment and be asked about wig and scarf use after each cycle using the CTCAE v4.0 and the alopecia pictorial tool (Appendix A).

Each subject will be followed up 2-3 weeks after completion of each chemotherapy cycle, and 2-4 weeks after completion of the final chemotherapy cycle. Each subject will also be followed for 5 years after chemotherapy for evaluation of secondary safety endpoints.

Appendix B presents a calendar of study events.

3.2 Study Schema



4. Statistical Consideration

4.1 Sample Size Determination

The trial will require 213 response evaluable subjects and assuming at most 10% drop-outs we expect to accrue at most 235 subjects.

Our primary endpoint is hair preservation. We expect to see very low rates (< 10-15%) of hair preservation in the control group, and propose to use a 2 to 1 randomization in order to gain additional experience with the experimental arm, and to make participation more attractive. An absolute difference of 20% (i.e. 15% vs. 35%) will be deemed a clinically meaningful difference. A total sample size of 213 response evaluable study participants will provide 85% power to detect a difference in preservation of 20% between control (15%) and Paxman (35%) at the 5% level of significance. If, as we expect, the rate of preservation will be lower than 15% in the control group, then the power to detect a 20% improvement will be higher.

	Scenario 1	Scenario 2
Level of Significance	5%	5%
Proportion Alopecia Grade <2		
Control	0.15	0.10
Paxman Scalp Cooling	0.35	0.30
Odds Ratio	3.05	3.86
Power	0.85	0.90
N control	71	71
N Paxman	142	142
Total N	213	213

Assuming at most 10% drop-outs, we expect to accrue at most 235 study participants.

4.2 Interim Analysis

One interim analysis will take place about two-thirds of the way through the study after 95 subjects are enrolled to the cooling group and 47 subjects are enrolled to the no cooling group and have been evaluated for the primary endpoint. The purpose of the interim analysis is to allow the study to stop early for efficacy (superiority). To maintain the overall type 1 error rate, an O'Brien-Fleming spending function has been used to calculate the superiority boundary. Calculations were performed using nQuery Advisor + nTerim 3.0 (Statistical Solutions. Boston, MA).

The following table summarizes the superiority boundary at each of 2 looks when 66% and 100% subjects are enrolled and evaluated, respectively. The superiority boundary on the p-value scale at the interim analysis is calculated as p=0.0061 (or Z=2.509). If the one-tailed p-value from a Fisher's exact test is less than or equal to 0.0061, it will be recommended that the trial stop for efficacy. This interim analysis has minimal effect on the significance level of the final analysis. The power in the final analysis is maintained.

Looks	Accumulated 'Information'	Evaluable N (cooling group)	Evaluable N (no cooling group)	Superiority Boundary (Z value)[1]	Superiority Boundary (One-tailed p-value)
1	66%	95	47	2.509	0.0061
2	100%	142	71	1.993	0.0231

1. For the software, Z-value boundaries are specified assuming that a Z test for proportions (unpooled variance) will be used, however the corresponding p-values apply equally well to Fisher's exact test, which was used in the original sample size calculations, and is still proposed for the analysis.

If the interim analysis does not declare superiority, the study will continue to full accrual as planned. If the interim analysis finds that cooling is superior to placebo, the results will be reported to the DSMB. The DSMB will examine the interim results and provide recommendations to continue the trial or stop the trial early.

4.3 Randomization

Randomization will be performed prior to performing any procedures and will use the permuted block method. Subjects will be randomized to either scalp-cooling or non-scalp cooling (control) on a 2:1 basis. Randomization will be stratified by two major chemotherapy types (anthracycline or taxane) and up to 10 centers with total of up to 20 strata.

5. Analysis Population

5.1 Randomized Population

Includes all subjects registered and randomized. This population will be included in overall subject listings, in the list of treatment discontinuations after enrollment, and also in summary tables of subject demographics and baseline disease characteristics.

5.2 Intent-To-Treat (ITT) Population

Includes all subjects eligible and randomized who undergo at least one cycle of chemotherapy. This population, which is considered response evaluable, will be included in the analysis of efficacy endpoints and secondary safety endpoints.

5.3 Safety Population

Includes all subjects registered and randomized to the scalp cooling arm who begin the first cycle of chemotherapy, regardless of whether subjects are eligible or not or how much treatment cycle the subjects receive. This safety population will be used for the summaries and analysis of the primary safety endpoint (AADEs) and subject reported comfort.

6. Statistical Methods and Analyses

6.1 General Methodology and Technical Consideration

Data for this study will be recorded via an electronic data capture system (EDC) using eCRFs. All the data exported from the EDC will be kept in the final dataset with the original variable names. Any derived data will be assigned to new variables. Original data will not be overwritten.

For statistical analysis throughout this study, for descriptive purposes, categorical (or discrete) variables will be summarized in frequency tables with numbers and percentages, and continuous variables will be summarized showing means, standard deviations (SD), medians, ranges or interquartile range (IQR). The 95% confidence interval (CI) for rate data will be calculated using Wilson method. Standard statistical methods for analyzing categorical data, continuous data, and survival data will be applied whenever appropriate. All statistical tests will be two-sided and conducted at an alpha level of 0.05, unless otherwise stated.

Unless otherwise specified, SAS 9.4 will be used for all data analyses.

6.2 Subject Disposition

Subject enrollment and disposition will be summarized for all randomized subjects. A subject disposition table showing numbers of subjects in different analysis populations by two treatment groups will be provided at the beginning of summary report. Sites and investigators will be presented in table. Two separate tables, one listing subjects who are off study before the treatment and one summarizing the reason of treatment discontinuation, will also be provided.

6.3 Important Protocol Violations

Important protocol violations will be summarized in frequency tables using all randomized subject. These include unacceptable concomitant therapy, eligibility criteria violation, information consent violation, etc. Information collected in the eCRF and information collected at the sites by clinical research associates will be used to determine the protocol deviations. The number and percentage of subjects with important protocol deviation will be summarized by deviation category and treatment group.

6.4 Demographic and Baseline Characteristics

Demographic variables include age (at randomization), race and ethnicity. Baseline clinical characteristics include stage of breast cancer, scheduled chemotherapy regimen, ECOG, menopausal status, history of hormone replacement therapy and oral contraceptive use. Tables of demographic variables and baseline characteristics variables, grouped by overall,

major chemotherapy type, and center will be provided. Data will be summarized as described in Section 5.1 and will be based on the randomized population.

6.5 Efficacy Analysis

6.5.1 Primary Efficacy Endpoint: Success in Hair Preservation by Healthcare Professional

The primary efficacy analysis will be based on the ITT population. The primary efficacy endpoint will be success in hair preservation, defined as CTCAE v4.0 alopecia grade < 2, and will be assessed by a healthcare professional that is blinded to study treatment. Although hair preservation will be assessed at baseline and after each cycle, only the assessment after 4th cycle of chemotherapy will be deemed as the primary efficacy endpoint.

Subjects who stop wearing the scalp cooling system during the study will continue to be evaluated after every chemotherapy cycle. For purposes of estimating treatment success rates, study subjects who cannot be evaluated at the post-cycle 4 time point will be deemed treatment failures. Missing or lost hair preservation evaluations will be deemed treatment failures.

The rates of hair preservation in the scalp cooling group and the control group will be calculated and summarized. Fisher's exact test will be used to test whether there is a difference in the rates of hair preservation. The study will be deemed as success if there is a significant difference in rates of hair preservation between the scalp cooling group and the control group. P value, the difference in rates and its 95% CI will be reported.

Since subjects are randomized with stratification of center, each center will contribute about the same number of subjects to each treatment group. A logistic regression model or a Cochran-Mantel-Haenszel test (CMH) stratified by center will be used to test for interaction between the treatment effect and center to confirm the consistency of the treatment effect.

6.5.2 Success in Hair Preservation by Subject Self and Oncologist

These secondary efficacy analyses will be based on the ITT population. Missing or lost hair preservation evaluations will be deemed treatment failures. Data on hair preservation assessed by subject self and oncologist will be analyzed using descriptive statistics with rates and their 95% CI. Comparison between the scalp cooling group to the control group will not be performed.

6.5.3 Use of Wigs and/or Head Wrap

This secondary efficacy analysis will be based on the ITT population. Data of wigs and/or head wrap use will be analyzed using descriptive statistics with rates and their 95% CI. Comparison between the scalp cooling group to the control group will not be performed.

6.5.4 Quality of Life by EORTC QLQ C-30, HADS, and BIS

These secondary efficacy analyses will be based on the ITT population. Quality of life (QOL) will be assessed at baseline, after 4 cycles of chemotherapy, and after completion of chemotherapy (if receiving more than 4 cycles). Three widely used and validated scales will be used: the EORTC QLQ-C30, HADS and BIS.

The QLQ-C30 is composed of 30 items for both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status/QOL scale, and six single items. Among these, emotional functioning and social functional scores of the QLQ-C30 are deemed as the variables of interest. Calculation of the QLQ scores will follow the scoring procedures described in the EORTC QLQ C-30 manual[1].

The HADS is composed of 14 items. Among them, 7 items are for assessing anxiety and 7 items are for assessing depression. Two summary scores for anxiety and depression of the HADS will be calculated and they are the variables of interest.

The BIS is composed of 10 items. A summary score using the first 9 items and excluding the last item which asks for scars will be calculated and it is the variable of interest.

Any missing questionnaire assessment will be handled as last observation carried forward.

Descriptive statistics will be used to summarize the variables of interest with median and IQR by time points and treatment groups. Changes in the variables of interest from baseline to after 4 cycles of chemotherapy will be summarized by treatment groups with median and IQR, and compared using Wilcoxon rank sum tests. Methods such as the generalized estimating equations and mixed models for analyzing the changes overtime and group comparison will also be applied if appropriate.

6.6 Safety Analyses

6.6.1 Primary Safety Endpoint: Anticipated Adverse Devise Effects (AADEs)

The primary safety analysis will be based on the safety population. The primary safety endpoint is AADE as the following complications are known to be associated with use of the Orbis Paxman Hair Loss Prevention System for the management of chemotherapy-induced alopecia:

- cold discomfort (during scalp cooling) described in the protocol Appendix C
- headache (during and after scalp cooling) described in CTCAE v4.0

- forehead pain (during scalp cooling) caused by pressure and tightness of the cooling cap described in CTCAE v4.0
- dizziness or light-headedness (during scalp cooling) described in CTCAE v4.0
- nausea described in CTCAE v4.0

The primary safety analysis will report incidence rates of these adverse device effects and their exact 95% CI by treatment cycles.

6.6.2 Subject Reported Comfort Scale

This secondary safety analysis will be based on the safety population. Subject-reported comfort is categorized into 5 levels from very comfortable to very uncomfortable. The comfort data will be summarized in frequency tables with number and percentage by treatment cycles. The overall subject reported comfort scale will be summarized using median and range.

6.6.3 Early Scalp Metastases and Survival

This secondary safety analysis will be based on the ITT population. All subjects will be followed yearly for 5 years looking at time to first recurrence (TFR), overall survival (OS), site of first recurrence, and incidence of isolated scalp metastasis. Data will be collected during routine clinical observation. Recurrence is defined as the return of cancer after treatment and after a period of time during which the cancer cannot be detected. TFR is measured from the date of randomization to the date of first recurrence. Patients without recurrence at the last contact date will be considered as censored. OS is measured from the date of randomization to the date of death. If a patient is still alive or is lost to follow up, the patient will be considered as censored at the last contact date. TFR and OS will be estimate using the Kaplan-Meier (KM) survival curve median and 95% CI (using log-log transformation). KM summary table and plots will be provided. Site of first recurrence will be tabulated. Incidence rate of isolated scalp metastasis and its 95% CI will be estimated and will be compared with the scalp metastasis rate and its 95%CI reported in NSABP[2].

6.7 Compliance

Compliance will be assessed by proportion of prescribed time (defined as 30 minutes pre-chemotherapy + duration of chemotherapy + 90 minutes post-chemotherapy) to that the device is worn. Data will be summarized by median and range by treatment cycles and based on the safety population.

7. Tables, Listings and Figures

TABLE 1 SUBJECT DISPOSITION (RANDOMIZED POPULATION)

Population	Arm 1	Arm 2
Randomized	xx	xx
ITT	xx	xx
Safety	xx	xx

TABLE 2 LIST OF SITES AND INVESTIGATOR

Investigator	Site	n
xxx	xxx	xx
---	---	---

TABLE 3 LIST OF RANDOMIZED SUBJECTS WHO WERE NOT TREATED (RANDOMIZED POPULATION)

Subject ID	Site	Reason off Study Treatment	Comments
xxxx	xxx	xxx	xxx
---	---	---	---
---	---	---	---

TABLE 4 SUMMARY OF REASONS FOR TREATMENT DISCONTINUATION (RANDOMIZED POPULATION)

Parameter	Arm 1 N=xx	Arm 2 N=xx
Treatment Discontinuation	xx (xx.x)	xx (xx.x)
Adverse Event	xx (xx.x)	xx (xx.x)
Consent Withdrawn	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)
Treatment Completion	xx (xx.x)	xx (xx.x)

TABLE 5 SUMMARY OF MAJOR POTOCOL VIOLATIONS (RANDOMIZED POPULATION)

Parameter	Arm 1 N=xx	Arm 2 N=xx
At least 1 violation	xx (xx.x)	xx (xx.x)
Concomitant Therapy	xx (xx.x)	xx (xx.x)
Eligibility Criteria	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)
Without any violation	xx (xx.x)	xx (xx.x)

TABLE 6 DEMOGRAPHIC INFORMATION AND BASELINE CHARACTERISTICS (RANDOMIZED POPULATION)

Parameter	Arm 1 N=xx	Arm 2 N=xx
Center [n (%)]		
---	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)
Major Chemotherapy Type [n (%)]		
---	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)
Age (years)		
Mean (SD)	xx.x(xx.x)	xx.x(xx.x)
Median (Min, Max)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Race [n (%)]		
----	xx (xx.x)	xx (xx.x)
----	xx (xx.x)	xx (xx.x)
Ethnicity [n (%)]		
---	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)
Breast Cancer Stage [n (%)]		
---	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)
Scheduled Chemotherapy Regimen [n (%)]		
---	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)
ECOG performance Status [n (%)]		
---	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)
Menopausal Status [n (%)]		
----	xx (xx.x)	xx (xx.x)
----	xx (xx.x)	xx (xx.x)
History of Hormone Replacement [n (%)]		
----	xx (xx.x)	xx (xx.x)
----	xx (xx.x)	xx (xx.x)
History of Oral Conceptive use [n (%)]		
---	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)

TABLE 7 DEMOGRAPHIC INFORMATION AND BASELINE CHARACTERISTICS BY CENTERS (RANDOMIZED POPULATION)

Parameter	Center 1		Center 2		Center ---	
	Arm 1 N=xx (%)	Arm 2 N=xx (%)	Arm 1 N=xx (%)	Arm 2 N=xx (%)	Arm 1 N=xx (%)	Arm 2 N=xx (%)
Age (years)						
Mean (SD)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
(Min, Max)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
Race [n (%)]						
----	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
----	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity [n (%)]						
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Breast Cancer Stage [n (%)]						
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Scheduled Chemotherapy Regimen [n (%)]						
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ECOG performance Status [n (%)]						
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Menopausal Status [n (%)]						
----	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
----	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
History of Hormone Replacement [n (%)]						
----	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
----	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
History of Oral Conceptive use [n (%)]						
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

TABLE 8 DEMOGRAPHIC INFORMATION AND BASELINE CHARACTERISTICS BY MAJOR CHEMOTHERAPY TYPE (RANDOMIZED POPULATION)

Parameter	Anthracycline		Taxane	
	Arm 1 N=xx (%)	Arm 2 N=xx (%)	Arm 1 N=xx (%)	Arm 2 N=xx (%)
Age (years)				
Mean (SD)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Median	xx.x	xx.x	xx.x	xx.x
(Min, Max)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
Race [n (%)]				
----	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
----	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity [n (%)]				
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Breast Cancer Stage [n (%)]				
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Scheduled Chemotherapy Regimen [n (%)]				
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ECOG performance Status [n (%)]				
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Menopausal Status [n (%)]				
----	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
----	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
History of Hormone Replacement [n (%)]				
----	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
----	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
History of Oral Conceptive use [n (%)]				
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

TABLE 9 SUMMARY OF SUCCESS IN HAIR PRESERVATION ASSESSED BY HEALTHCARE PROFESSIONAL (ITT POPULATION)

Parameter	Arm 1 N=xx		Arm 2 N=xx	
	n	% (95% CI)	n	% (95% CI)
Hair Preservation				
Success	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)
Failure	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)
By Center:				
Hair Preservation in Center 1				
Success	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)
Failure	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)
Hair Preservation in Center ---				
Success	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)
Failure	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)

TABLE 10 SUMMARY OF SUCCESS IN HAIR PRESERVATION ASSESSED BY SUBJECT SELF AND ONCOLOGIST (ITT POPULATION)

Parameter	Arm 1 N=xx		Arm 2 N=xx	
	n	% (95% CI)	n	% (95% CI)
Hair Preservation by Subject self				
Success	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)
Failure	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)
Hair Preservation by Oncologist				
Success	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)
Failure	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)

TABLE 11 USE OF WIGS AND/OR HEAD WRAP (ITT POPULATION)

Parameter	Arm 1 N=xx		Arm 2 N=xx	
	n	% (95% CI)	n	% (95% CI)
Wigs and/or Head Wrap Use				
Yes	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)
No	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)

TABLE 12 SUMMARY OF QOL (ITT POPULATION)

Parameter	Arm 1 N=xx			Arm 2 N=xx		
	Baseline n=xx (%)	**Post-Cycle 4 n=xx (%)**	**End of Chemotherapy n=xx (%)**	**Baseline n=xx (%)**	**Post-Cycle 4 n=xx (%)**	**End of Chemotherapy n=xx (%)**
EORTC QLQ-C30						
Emotional Functioning Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Social Functioning Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
HADS						
Anxiety Summary Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Depression Summary Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
BIS						
1-9 items Summary Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

TABLE 13 SUMMARY OF CHANGES IN QOL (ITT POPULATION)

Changes from Baseline to Post Cycle 4	**Arm 1 N=xx**	**Arm 2 N=xx**
EORTC QLQ-C30		
Emotional Functioning Median (IQR)	xx.x (xx.x)	xx.x (xx.x)
Social Functioning Median (IQR)	xx.x (xx.x)	xx.x (xx.x)
HADS		
Anxiety Summary Median (IQR)	xx.x (xx.x)	xx.x (xx.x)
Depression Summary Median (IQR)	xx.x (xx.x)	xx.x (xx.x)
BIS		
1-9 items Summary Median (IQR)	xx.x (xx.x)	xx.x (xx.x)

TABLE 14 SUMMARY OF ANTICIPATED ADVERSE DEVISE EFFECTS (SAFETY PULATION)

AADEs	**Arm 1 N=xx**					
	Cycle 1 n=xx (%)		**Cycle 2 n=xx (%)**		**Cycle --- n=xx (%)**	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Cold Discomfort	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)
Headache	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)
Forehead Pain	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)
Dizziness or Light-Headedness	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)
Nausea	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)

TABLE 15 SUMMARY OF SUBJECT REPORTED COMFORT SCALE (SAFETY PULATION)

Comfort Scale	**Arm 1 N=xx**		
	Cycle 1 n=xx (%)	**Cycle 2 n=xx (%)**	**Cycle --- n=xx (%)**
	n (%)	n (%)	n (%)
Very Comfortable	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reasonable Comfortable	xx (xx.x)	xx (xx.x)	xx (xx.x)
Comfortable	xx (xx.x)	xx (xx.x)	xx (xx.x)
Uncomfortable	xx (xx.x)	xx (xx.x)	xx (xx.x)
Very Uncomfortable	xx (xx.x)	xx (xx.x)	xx (xx.x)

TABLE 16 SUMMARY OF SURVIVAL (ITT POPULATION)

Parameter	Arm 1 N=xx	Arm 2 N=xx
First Recurrence		
25% Percentile (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Median (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
75% Percentile (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Overall Survival		
25% Percentile (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Median (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
75% Percentile (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)

TABLE 17 SUMMARY OF SITE OF FIRST RECURRENCE (ITT POPULATION)

Parameter	Arm 1 N=xx	Arm 2 N=xx
Site of First Recurrence [n (%)]		
Site 1	xx (xx.x)	xx (xx.x)
Site 2	xx (xx.x)	xx (xx.x)
Site 3	xx (xx.x)	xx (xx.x)
---	xx (xx.x)	xx (xx.x)
Isolated Scalp Metastasis [n (%)]		
n	xx	xx
% (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)

TABLE 18 COMPLIANCE (SAFETY PULATION)

Compliance	Arm 1 N=xx		
	Cycle 1 n=xx (%)	**Cycle 2 n=xx (%)**	**Cycle --- n=xx (%)**
Median (Min, Max)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)

FIGURE 1 KAPLAN-MEIER CURVES OF TIME TO FIRST RECURRENCE (ITT POPULATION)

FIGURE 2 KAPLAN-MEIER CURVES OF OVERALL SURVIVAL (ITT POPULATION)

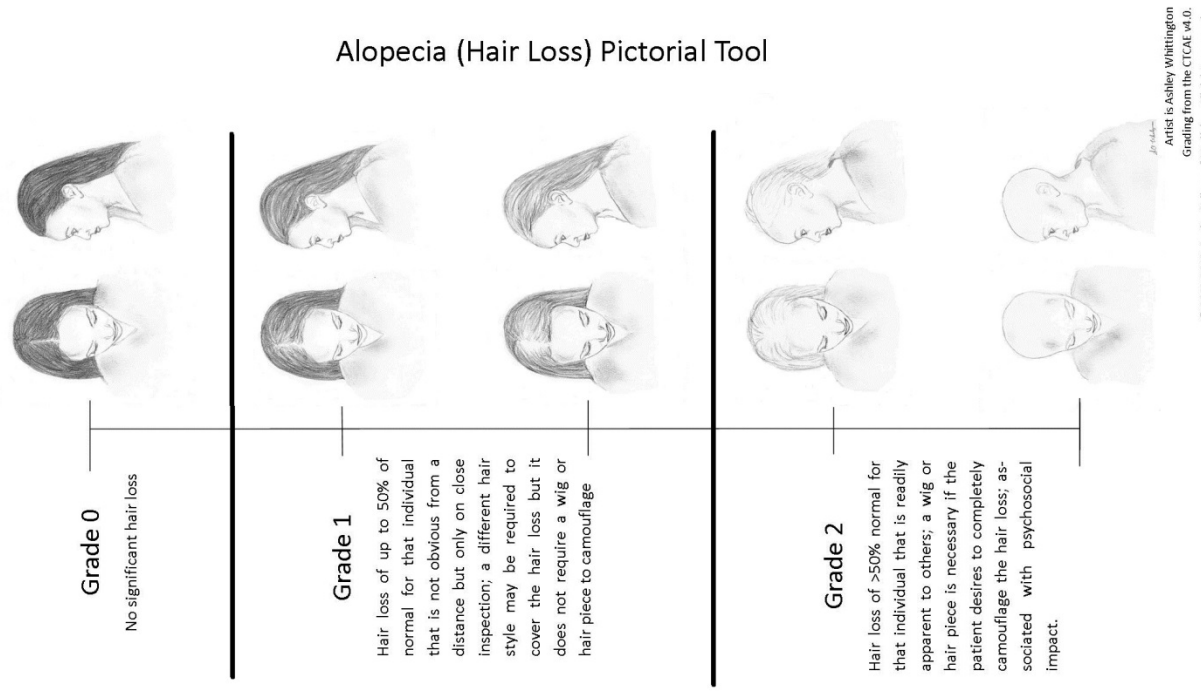
8. References

1. QL coordinator. “EORTC QLQ C30 scoring manual”. Quality of Life Unit, EORTC Date Center. 2001.

2. Rugo, H. M., SA. Expert statement on scalp cooling with adjuvant/neoadjuvant chemotherapy for breast cancer and the risk of scalp metastases. 2010.

9. Appendix A: CTCAE v4.0 Grading Scale and Alopecia Pictorial Tool

CTCAE v4.0 Alopecia	(Hair Loss)
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% 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.



10. Appendix B: Study Calendar

Parameter		**Pre-Study**[1]	**Day 1 of each chemotherapy cycle**					**2-3 weeks AFTER each chemotherapy cycle**[2, 9]					**Year 1, 2, 3, 4, 5**
			1	**2**	**3**	**4**	**5-8**[3]	**1**	**2**	**3**	**4**[10]	**5-8**[3, 10]	
History & Physical and Demographics		X											
Physician/nurse practitioner and blinded provider: Alopecia Assessment[8]		X						X	X	X	X	X	
Patient: Alopecia Assessment and Wig/Scarf Use Questions[8]								X	X	X	X	X	
Photographs[7, 8]		X						X	X	X	X	X	
Laboratory Assessments (TSH[1]*, Hgb A1c[1]*, CBC, CMP)		X											
Questionnaires: EORTC QLQ-C30, HADS, BIS		X									X	X[6]	
Subjects Randomized to Cooling Arm Only	Cooling Cap Fitting	X											
	Paxman Cooling System Administration[4]		X	X	X	X	X						
	Comfort Scale[5]		X	X	X	X	X						
Long Term Follow-Up: Survival, Recurrence, Site of First Recurrence (if applicable)													X

1. Within 4 weeks prior to starting treatment, unless otherwise specified: *TSH within 1 year prior to treatment, Hgb A1c within 3 months prior to treatment (if history of diabetes).
2. If chemotherapy is delayed due to toxicities from chemotherapy, this will be done with the next cycle once chemotherapy is resumed.
3. If the subject is receiving more than 4 cycles.
4. The Orbis Paxman Hair Loss Prevention System will be used with each dose of chemotherapy. The pre-cooling time is at least 30 minutes and the post-cooling time is at least 90 minutes.
5. A comfort scale will be administered after the device is removed with each cycle (see Appendix C).
6. Only after last cycle of chemotherapy if receiving more than 4 cycles.
7. Photographs will be taken of ALL subjects at baseline, after 4 cycles, and after completion of chemotherapy (if receiving more than 4 cycles). Additionally, photographs of the first 25 subjects enrolled from each site who complete at least 1 cycle will be taken at each Alopecia Assessment.
8. Alopecia Assessments and photographs should be discontinued after a subject is determined to have Grade 2 alopecia by the clinician, the blinded provider AND the subject. All assessments and photographs will be done on the day of determining Grade 2 alopecia, but should not be done at subsequent visits.
9. This visit typically occurs on Day 1 of each cycle (e.g. Post-Cycle 2 visit = Cycle 3 visit).
10. If subject is only receiving 4 cycles, Post-Cycle 4 visit should occur 2-4 weeks after Cycle 4. If subject is receiving more than 4 cycles, the End of Treatment visit should occur 2-4 weeks after the final cycle of chemotherapy.