

## Scalp Cooling Alopecia Prevention Trial (SCALP)

---

Julie Nangia, MD  
Assistant Professor  
Lester & Sue Smith Breast Center at  
Baylor College of Medicine  
660 MB, One Baylor Plaza  
Houston, TX 77030  
USA

## Scalp Cooling Alopecia Prevention Trial (SCALP)

***Principal Investigator/  
Sponsor:***

Julie Nangia, MD  
Assistant Professor  
Lester & Sue Smith Breast Center at  
Baylor College of Medicine  
660 MB, One Baylor Plaza  
Houston, TX 77030  
USA

Phone: 713-798-1311  
Fax: 713-798-8884  
Email: [nangia@bcm.edu](mailto:nangia@bcm.edu)

***Co-Investigators***

**Baylor College of Medicine**  
Mari Rude, NP  
Susan Hilsenbeck, PhD  
Mothaffar Rimawi, MD  
Kent Osborne, MD  
Polly Niravath, MD  
Sao Jiralerspong, MD  
Matthew Ellis, MD

US Oncology / Texas Oncology – Memorial City  
Houston, TX 77024  
Site PI: Frankie Holmes, MD  
Phone: 713-467-1722  
Email: [frankie.holmes@usoncology.com](mailto:frankie.holmes@usoncology.com)

Texas Oncology – Baylor Charles A. Sammons Cancer Center  
Dallas, TX 75246  
Site PI: Cynthia Osborne, MD  
Phone: 214-370-1000  
Email: [cynthia.osborne@usoncology.com](mailto:cynthia.osborne@usoncology.com)

Hematology & Oncology Associates of Northern New Jersey  
Morristown, NJ 07962  
Site PI: Steven Papish, MD  
Phone: 973-538-3593 x 2338  
Email: [spapish@hoannj.com](mailto:spapish@hoannj.com)

Texas Oncology – Medical City Dallas  
Dallas, TX 75230

Site PI: Jay Courtright, MD  
Phone: 972-566-7790  
Email: [jay.courtright@usoncology.com](mailto:jay.courtright@usoncology.com)

Cleveland Clinic  
Cleveland, OH 44195  
Site PI: Jame Abraham, MD  
Phone: 216-445-0150  
Email: c/o Justina Vigluicci [vigluij@ccf.org](mailto:vigluij@ccf.org)

Memorial Sloan Kettering Cancer Center  
1275 York Avenue, New York, New York 10065  
Site PI: Shari B. Goldfarb, M.D.  
Email: [goldfars@mskcc.org](mailto:goldfars@mskcc.org)

*Coordinating Center*

Baylor College of Medicine

**Research Coordinator**

Claudette Foreman  
Phone: 713-798-7315  
Email: [caforema@bcm.edu](mailto:caforema@bcm.edu)

**Study Monitor**

Kristen Otte  
Phone: 713-798-8874  
Email: [otte@bcm.edu](mailto:otte@bcm.edu)

### Scalp Cooling Alopecia Prevention Trial (SCALP)

#### - Protocol Revision Record -

<b>Revision Number</b>	<b>Details of Amendment</b>	<b>Date</b>
0.1	Original Protocol	1-3-12
0.2	FDA recommendation changes	5-3-13
0.3	Added new sponsor details	5-29-13
0.4	FDA recommendation changes	8-1-13
0.5	PRMC recommendation changes	9-5-13
0.6	DSMB, FDA and other site recommendation changes	11-19-13
0.6 - Update 1	Minor amendments associated with change to 5-year post-study follow-up, change to use of up to 5 centers, use of Orbis 1 device only and correction of device software version	12-22-13
0.6 - Update 2	Clarification of regimens allowed (allowing pertuzumab use) and adding baseline photographs of all subjects	1-9-14
0.7	Photography guidelines, clarification of acceptable baseline labs windows, change to exclusion criterion re: abnormal TSH (option to assess T3 and free T4 levels), Taxotere dosing with pertuzumab	9-19-14
0.8	Change in number of possible participating sites from 5 to 10, addition of paclitaxel with carboplatin as an allowable chemotherapy regimen (inclusion criterion), administrative changes and clarifications throughout	2-3-15
0.9	Addition of weekly paclitaxel with weekly carboplatin as an allowable chemotherapy regimen (inclusion criterion), clarification to definition of “blinded healthcare provider,” addition of interim analysis, addition of Dignity Health as participating site	11-5-15
10	Addition of Memorial Sloan Kettering Cancer Center as a participating site, clarification re: allowing subjects to remain on study if they have an allergic reaction to taxane-based chemotherapy and must switch to paclitaxel protein-bound chemotherapy (Abraxane), increasing number of enrolled subjects due to a higher than anticipated drop out rate	7-1-16

## Table of Contents

<i>Synopsis</i> .....	8
A.1    TITLE .....	8
A.2    DESIGN .....	8
A.3    BRIEF DESCRIPTION .....	8
A.4    STUDY POPULATION .....	8
A.5    PURPOSE.....	8
A.6    ENROLLMENT.....	8
A.7    CLINICAL SITES.....	8
A.8    PRIMARY ENDPOINTS .....	8
A.9    FOLLOW-UP.....	8
<i>B) Schema</i> .....	9
<i>C) Background</i> .....	10
C.1    BREAST CANCER AND CHEMOTHERAPY-INDUCED ALOPECIA .....	10
C.2    METHODS FOR MANAGEMENT OF CHEMOTHERAPY-INDUCED ALOPECIA .....	10
C.3    EFFECTIVENESS OF SCALP COOLING IN THE PREVENTION OF CHEMOTHERAPY-INDUCED ALOPECIA.....	11
C.4    SCALP METASTASES CONCERN.....	13
C.5    OTHER SIDE EFFECTS WITH SCALP COOLING .....	15
C.6    PSYCHOSOCIAL EFFECTS OF SCALP COOLING SYSTEM FOR ALOPECIA PREVENTION IN PATIENTS WITH CANCER UNDERGOING CHEMOTHERAPY .....	17
<i>D) Investigational Device Information</i> .....	17
D.1    IDENTIFICATION OF THE DEVICE .....	17
D.2    DESCRIPTION OF THE DEVICE .....	18
D.3    INTENDED USE OF THE DEVICE .....	18
D.4    TRAINING AND EXPERIENCE NECESSARY FOR USE OF THE DEVICE .....	18
D.5    DEVICE TRACEABILITY .....	19
<i>E) Risk Benefit Analysis</i> .....	19
E.1    ANTICIPATED RISKS AND ADVERSE DEVICE EFFECTS .....	19
E.2    ADDITIONAL STUDY MEASURES TO MINIMIZE RISK .....	21
E.3    RISK BENEFIT CONCLUSION .....	21
<i>F) Purpose</i> .....	22
<i>G) Hypothesis</i> .....	22
<i>H) Endpoints</i> .....	22
H.1    PRIMARY ENDPOINTS .....	22
H.2    SECONDARY ENDPOINTS .....	22
<i>I) Participant Selection</i> .....	23
I.1    INCLUSION CRITERIA.....	23
I.2    EXCLUSION CRITERIA.....	24
I.3    INCLUSION OF UNDERREPRESENTED POPULATIONS .....	24
<i>J) Study Design</i> .....	24
J.1    GENERAL ASPECTS OF STUDY DESIGN.....	24

J.2	CENTER SELECTION .....	25
J.3	LEAD CENTER .....	25
J.4	OTHER PARTICIPATING CENTERS .....	25
J.5	STUDY POPULATION .....	25
J.6	SUBJECT SCREENING & ENROLLMENT .....	26
J.7	SUBJECT IDENTIFICATION .....	26
<b>K)</b>	<b><i>Study Procedures</i></b> .....	<b>26</b>
K.1	RANDOMIZATION PROCEDURE .....	26
K.2	BASELINE ASSESSMENT .....	27
K.3	PROCEDURES .....	27
K.4	CONCOMITANT TREATMENT AND SUPPORTIVE CARE GUIDELINES .....	31
K.5	DURATION OF FOLLOW-UP .....	31
K.6	CRITERIA FOR REMOVAL FROM STUDY .....	32
K.7	CRITERIA AND PROCEDURES FOR DISCONTINUATION OF TREATMENT .....	32
K.8	DELAYS .....	33
<b>L)</b>	<b><i>Study Calendar</i></b> .....	<b>34</b>
<b>M)</b>	<b><i>Adverse Events</i></b> .....	<b>35</b>
M.1	REPORTABLE ADVERSE EVENTS .....	35
M.2	ADVERSE EVENT REPORTING REQUIREMENTS .....	35
M.3	ADVERSE EVENT DEFINITIONS .....	35
M.4	ADVERSE EVENT REPORTING .....	38
<b>N)</b>	<b><i>Informed Consent</i></b> .....	<b>39</b>
<b>O)</b>	<b><i>Investigation Administration</i></b> .....	<b>40</b>
O.1	ETHICAL CONDUCT .....	40
O.2	REGULATORY REQUIREMENTS .....	40
O.3	RESPONSIBILITIES OF THE SPONSOR .....	41
O.4	RESPONSIBILITIES OF THE INVESTIGATOR .....	42
O.5	STUDY MONITOR .....	43
O.6	INVESTIGATOR SELECTION CRITERIA .....	44
O.7	STUDY INITIATION .....	45
O.8	RECORDS AND REPORTS .....	45
O.9	DATA MONITORING AND QUALITY CONTROL .....	47
O.10	QUALITY ASSURANCE AUDITING AND INSPECTION .....	47
O.11	PATIENT CONFIDENTIALITY .....	48
O.12	INVESTIGATOR/STUDY DISCONTINUATION .....	48
O.13	PROTOCOL MODIFICATIONS .....	48
O.14	SUPPLY AND DISPOSITION OF DEVICES .....	49
O.15	TRAINING .....	49
O.16	MEETINGS .....	49
<b>P)</b>	<b><i>Statistical Considerations</i></b> .....	<b>49</b>
P.1	STUDY DESIGN .....	50
P.2	SAMPLE SIZE/ACCRUAL RATE .....	50
P.3	INTERIM ANALYSIS .....	50
P.4	STRATIFICATION FACTORS .....	51
P.5	ANALYSIS OF PRIMARY ENDPOINTS .....	51
P.6	ANALYSIS OF SECONDARY ENDPOINTS .....	52
P.7	REPORTING AND EXCLUSIONS .....	53
<b>Q)</b>	<b><i>Publication</i></b> .....	<b>53</b>

<b><i>APPENDICES</i></b> .....	56
<i>A) Orbis Paxman Hair Loss Prevention System</i> .....	56
<i>B) CTCAE v4.0 Grading Scale and Alopecia Pictorial Tool</i> .....	56
<i>C) Comfort Scale</i> .....	56
<i>D) QOL Questionnaires</i> .....	56

## Synopsis

### A.1 Title

Scalp Cooling Alopecia Prevention Trial (SCALP)

### A.2 Design

Multi-center randomized non-blinded controlled prospective-trial

### A.3 Brief Description

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 infusion, for 4 complete cycles of full-dose anthracycline- or taxane-based chemotherapy.

Each subject will be followed up  $3 \pm 1$  weeks after completion of chemotherapy.

### A.4 Study Population

Women with stage I-II breast cancer, who will undergo either neoadjuvant or adjuvant chemotherapy.

### A.5 Purpose

Demonstrate that the Orbis Paxman Hair Loss Prevention System is safe and effective in reducing chemotherapy-induced alopecia in woman with breast cancer undergoing neoadjuvant or adjuvant chemotherapy.

### A.6 Enrollment

Up to 325 subjects.

### A.7 Clinical Sites

Up to 10 Sites in the USA. All sites will use the same protocol and undergo the same training on use of the Orbis Paxman Hair Loss Prevention System.

### A.8 Primary Endpoints

**Primary Efficacy Endpoint:** To compare success in hair preservation, between the Orbis Paxman Hair Loss Prevention System and control (no cooling) after 4 cycles of chemotherapy.

**Primary Safety Endpoint:** To estimate the rate of significant anticipated device effects specified in section M.4.

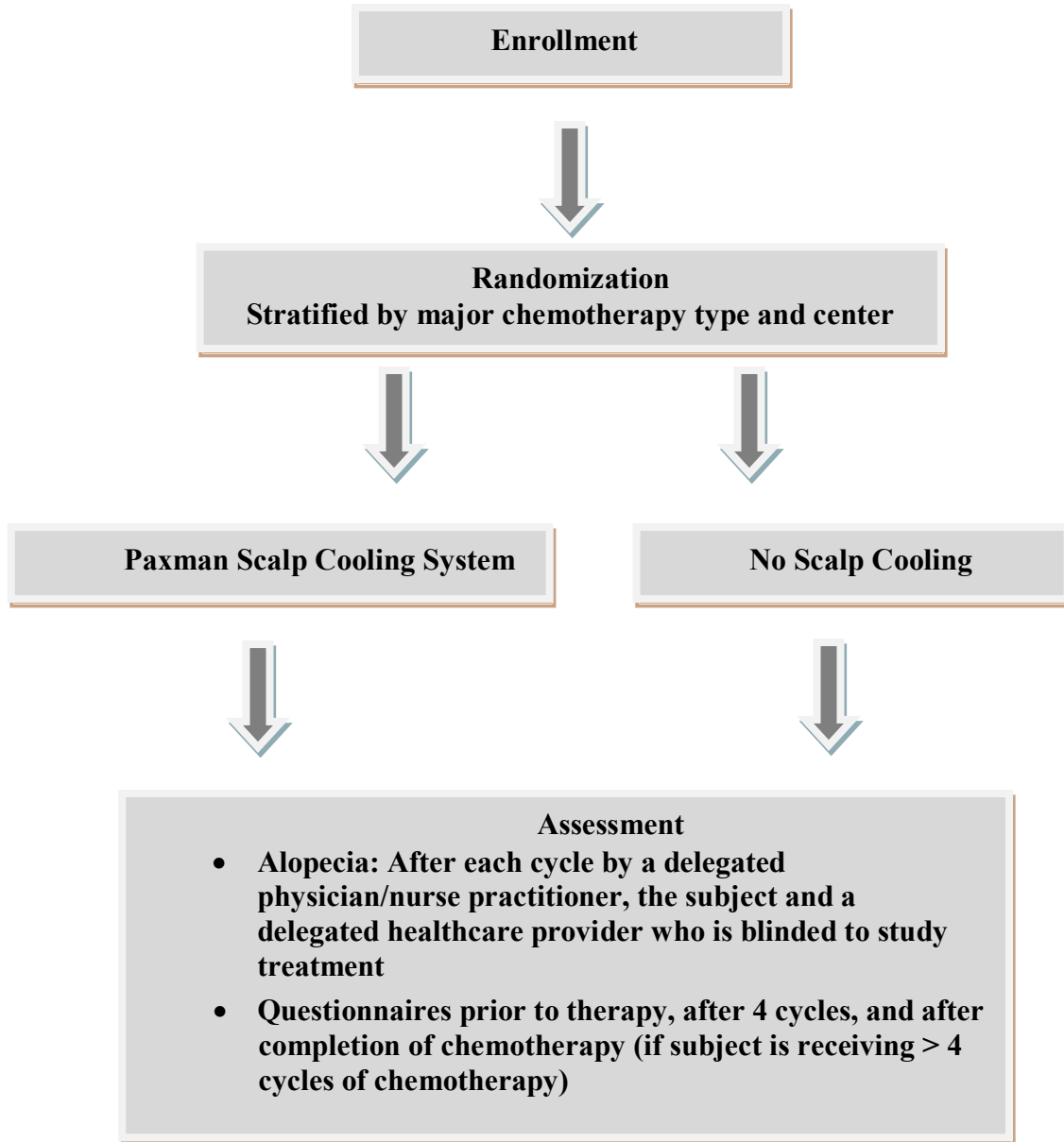
### A.9 Follow-Up

Study subjects will be followed  $3 \pm 1$  weeks after completion of chemotherapy when the final alopecia assessment will occur (if grade 2 alopecia has not been reached) and the questionnaires will be administered. Subjects will be followed post-study for 5 years



during routine clinic follow-up or via phone call for time to first recurrence, overall survival, site of first recurrence, and incidence of isolated scalp metastasis.

**B) Schema**



## **C) Background**

### **C.1 Breast Cancer and Chemotherapy-Induced Alopecia**

In 2011, an estimated 230,480 new cases of invasive breast cancer will be diagnosed in women in the United States (American Cancer Society 2011). Chemotherapy will be part of the treatment planned for many of these women. Neoadjuvant chemotherapy is given prior to surgery to improve surgical options and to increase the chances of cure. Post-surgical or adjuvant chemotherapy, is given after surgery to minimize the risk of local and systemic tumor recurrence and therefore increase the chances of cure.

Chemotherapy treats micro-metastatic disease and decreases the risk of recurrence. However, it may be associated with distressing adverse effects, including alopecia, fatigue, nausea, and potentially life threatening effects such as neutropenia. The most effective and commonly used chemotherapy regimens for breast cancer include the agents anthracyclines (e.g. doxorubicin and epirubicin) and taxanes (e.g. docetaxel and paclitaxel) that cause complete alopecia. Despite improvements in most aspects of supportive care, and newer chemotherapy regimens with less systemic toxicity, alopecia remains universal.

Women with breast cancer rate chemotherapy-induced alopecia as one of the most severe, troublesome and distressing side effects of chemotherapy (Grevelman 2005) (Lemieux 2009). As early as 1984, it was reported that patients who experience hair loss following chemotherapy reported suffering negative body image, anxiety, and depression. Auvinen et al noted that the hair loss acted as a constant reminder to the patient of the underlying cancer and it had an impact not only on the patient, but also on those individuals close to the patient. Among women losing their hair because of breast cancer treatment, many indicate that coping with hair loss is more difficult than the loss of their breast since it is outwardly visible to others, affects their femininity, and is a constant reminder of their cancer (Kaderman 1999; Benjamin 2002). In 2011, Breed et al noted that 13% of women cancer patients surveyed believed they would be rejected by their partner in the event they experienced hair loss resulting from chemotherapy. Trueb reported in 2010 that 47% of women cancer patients considered chemotherapy-induced hair loss the most traumatic aspect of cancer treatment. Furthermore, 8% of women surveyed reported that they would actually decline chemotherapy because of the fear of this side-effect, despite the fact that the hair loss is nearly always temporary. This may lead to women hesitating in taking chemotherapy, which may compromise their outcome. This side effect of chemotherapy is mostly, but not always, reversible (Massey 2004). It takes months to years after the completion of chemotherapy for the hair to recover, and it may be of a different quality, color, and thickness.

### **C.2 Methods for Management of Chemotherapy-Induced Alopecia**

Chemotherapy-induced alopecia is caused by the fact that chemotherapy relies for its effectiveness on the ability of drugs used to inhibit and suppress growth and multiplication of rapidly dividing cancer cells. These drugs are not able to distinguish between cancerous cells & non-cancerous cells i.e. hair follicles. At any one time, approximately 85-90% of human hair follicles are in a state of rapid growth (Massey 2004). Numerous measures to prevent or reduce the effects of chemotherapy-induced alopecia, including mechanical,

pharmacological and physical methods, have been investigated since the 1960s with varying degrees of success (Massey 2004).

Breed reports that in the late 1970s scalp tourniquets were utilized to reduce the blood flow to hair follicles during peak chemotherapy levels (Breed 2011). Hair loss was reduced in patients receiving doxorubicin. This approach was associated with side effects including headache and nerve compression and is no longer utilized. A number of pharmacological agents with different mechanisms of action have been studied over the years for their effects to minimize chemotherapy-induced hair loss. Of the agents that have been evaluated in humans, two – AS101 (an immune modulator) and minoxidil (a hair growth promoter) – were able to reduce the severity and shorten the duration of alopecia, but could not prevent it (Wang 2006). Trueb reported in 2009 that 2% topical minoxidil solution shortened the duration of alopecia in breast cancer patients receiving adjuvant chemotherapy (Trueb 2009). It was not effective in preventing chemotherapy-induced alopecia when doxorubicin was used as part of the treatment.

Physical methods employed to reduce chemotherapy-induced alopecia have included electrotrichiogenesis and scalp cooling. The former was reported in 2002 with promising results in a pilot study, but no further results have been published (Christodoulou 2006). In an increasing number of European countries, scalp cooling has been introduced to prevent or reduce chemotherapy-induced alopecia. Scalp cooling causes cutaneous vasoconstriction, which reduces the blood flow to the hair follicles during peak plasma concentrations of the chemotherapeutic agents and therefore reduces cellular uptake of these agents. It also results in reduced biochemical activity, which makes hair follicles less susceptible to the damage of the chemotherapy agents (Grevelman 2005).

Scalp cooling was at first performed using crushed ice packs that were placed on the patient's head, but with unsatisfactory results. The ice packs were subsequently replaced with cryogel ice caps (ChemoCap, Elasto-Gel, Hypothermia Cap and Penguin Cold Cap). Since the caps are put on freezing cold, and thaw over time, they are uncomfortable for the patient and also very labor-intensive for the nurse. The fluctuation in temperature affects the results of the scalp cooling treatment. This led to the development of cooling systems that could provide a continuous cooling of the scalp.

Continuous scalp cooling relies on circulation of a liquid coolant. Available options include the Orbis and Paxman Scalp Cooling models of scalp cooler manufactured by Paxman Coolers and the DigniCap system manufactured by Digitana.

### **C.3 Effectiveness of Scalp Cooling in the Prevention of Chemotherapy-Induced Alopecia**

The efficacy of scalp cooling depends on several factors: chemotherapy regimen and dose, dose interval, performance status of the patient, scalp cooling temperature, post cooling time, and scalp cooling system (Lemieux 2008). Comfort and ease of use are also factors in success, as discomfort or difficulties with cooling or changing the cap can result in poor compliance. Most studies looking at scalp cooling utilize the WHO Criteria for hair loss to grade alopecia or a variation of this. Hair loss is rated grade 0 (no significant hair loss) through grade 4 (non-reversible alopecia). Success is commonly defined as the patient not requiring a wig (grades 0, 1, and 2).

There are several review articles looking at scalp cooling. One of the first is the review by Grevelman and Breed looking at the efficacy of scalp cooling. Included were 53 studies and 3 personal communications in which over 2,610 patients were treated with scalp cooling. The efficacy in terms of good hair preservation was 56% for studies before 1995 and 73% for studies carried out from 1995 to 2005. The improvement of results is likely due to improved scalp cooling systems and techniques (Grevelman 2005).

In 2011, Breed, et al reported on a review of 60 scalp cooling studies, which used the various techniques described above and were published between 1977 and 2010 (Breed 2011). Included in the review were 7 randomized, controlled studies, 7 non-randomized, controlled studies with statistical analysis, 11 non-randomized, controlled studies without statistical analysis, and 36 non-controlled studies. In six of the seven randomized, controlled studies, which included 111 scalp-cooled patients, scalp cooling resulted in significantly better hair preservation than controls. The proportion of treated patients having good hair preservation (WHO grade 0-2) ranged from 25% to 100%. The non-randomized, controlled studies with statistical analysis resulted in significantly better hair preservation following scalp-cooling in all seven studies. This dataset included a total of 1207 scalp-cooled patients, including 770 from a single study. The proportion of treated patients classified as having good hair preservation ranged from 41 to 97% (compared to 0-38% for controls). In the 11 non-randomized, controlled studies without statistical analysis, an average of 67% of patients had good hair preservation. In the 36 non-controlled studies, positive effects of scalp cooling on hair preservation were seen in all but one study. The median value of good hair preservation in this latter series was approximately 80%. Together, these studies are considered to constitute reasonable clinical evidence that scalp cooling is effective in reducing chemotherapy-induced alopecia.

Many of the studies provide additional detail about the various chemotherapy regimens and include outcome measures other than the severity of hair loss. In a Danish study of 62 evaluable women, several outcomes were considered including: severity of hair loss, burden of hair loss, burden of scalp cooling, wig use, hair regrowth, and body image. Drug regimens included Adriamycin/Cytosar (AC), 5-FU/Epirubicin/Cytosar (FEC), 5-FU/Adriamycin/Cytosar (FAC) and Taxotere/Adriamycin/Cytosar (TAC). Scalp cooling was effective in preventing chemotherapy-induced hair loss in 32 of 62 evaluable patients (Mols 2009). In this study, patients did not perceive scalp cooling as burdensome. In this study and others, the TAC regimen is associated with poor hair preservation even with the use of scalp cooling (likely related to concurrent taxane & anthracycline use).

The effect of alopecia and the effects of scalp cooling on well-being were looked at in a study by van den Hurk (Van den Hurk 2010). This was a prospective multi-center study performed in 13 hospitals. The Paxman system for scalp cooling was utilized. Breast cancer patients receiving chemotherapy combinations including anthracyclines and taxanes were included. This study looked at both the severity of alopecia and at several quality of life measures to assess well-being of patients. Scalp cooling was effective in 52% of the cases. There was a trend toward higher well-being and a better body image in the scalp-cooled patients.

Several additional studies have looked specifically at the Orbis Paxman Hair Loss Prevention System. One of the first was the study by Massey that looked at scalp cooling at 8 centers in United Kingdom with data collection from 1997 to 2000 (Massey 2004). All

patients were women with breast cancer being treated in the adjuvant or palliative setting. Twelve different chemotherapy regimens were utilized. The procedure included application of small amount of conditioner to dampened hair, to allow for closer contact of the PSC with the scalp. A pre-cooling time of 15-20 minutes was recommended, with a post infusion cooling time of 2 hours for most regimens. A variation of the WHO criteria for alopecia was utilized. Nurses graded the alopecia and patients were asked to complete report forms on attitude toward the process and side effects. A total of 94 patients were included in the study, with 66% of patients receiving FEC. Of these patients, 89% had grade 0 alopecia and did not require a wig.

In summary, there are many studies and reviews that have looked at scalp cooling. Many of these studies were small and not well designed. It is also difficult to compare these studies because of differences in patient characteristics, chemotherapy agents, length of cooling, and hair loss assessments. Most of these studies have been done in Europe and more recently Asia. Success rates are variable, but scalp cooling appears to be effective in preventing chemotherapy-induced alopecia especially in more recent studies. The Orbis Paxman Hair Loss Prevention System is widely used to prevent chemotherapy-induced alopecia in Europe, Australia, and Asia. In the United States scalp cooling is rarely used as it is not approved by the Food and Drug Administration.

#### **C.4 Scalp Metastases Concern**

As scalp cooling acts by reducing the effect of chemotherapy in the scalp, a theoretical increased risk of scalp metastases is often discussed. Since breast cancers may metastasize to the scalp, the discussion most often concerns these patients. Published data demonstrate that the incidence of scalp metastasis following adjuvant therapy in breast cancer is inherently low and it is exceedingly rare to have scalp metastases as the first site of metastases as they nearly always occur late in the course of the disease when other metastases are already present. Thus, increasing a woman's chance of dying of breast cancer because she underwent scalp cooling at the time of adjuvant chemotherapy seems remote if possible at all.

Rugo and Melin analyzed all the literature to date in a correspondence (Rugo 2010). This included a study by Browstein and Helwig where metastatic sites were identified in a 1972 study of 167 women with breast cancer and cutaneous metastasis who did not receive chemotherapy. The incidence of scalp involvement in these women with cutaneous metastasis was only 3%. The authors emphasized that the scalp metastasis in women with breast cancer usually occurred late in the disease. Furthermore Rugo and Melin, looked at three studies from 1976 to 2009, involving a total of 2,697 breast cancer patients who received chemotherapy without scalp cooling and who were followed up for around 5 years; the incidence of scalp metastases ranged from 1.2% to 2.5% (while the incidence of all skin metastases ranged from 24% to 30%). When breast cancer is metastatic and involves the skin or scalp, the breast cancer is usually widespread and it would be exceedingly rare to have breast cancer recur with the scalp as the only site of metastatic disease. It is also exceedingly rare for scalp metastases to be the first site of recurrence in breast cancer patients.

In consideration of scalp metastases as the first site of recurrence of cancer, Rugo and Melin looked at reference data from the National Surgical Adjuvant Breast and Bowel

Project (NSABP), involving 7,800 women with breast cancer treated with surgery alone or combined with chemotherapy (Rugo 2010). Of these 7,800 women, only 2 (0.025%) experienced scalp metastasis as their first site of recurrence. Both of these patients had positive lymph nodes and one of them had received adjuvant chemotherapy. It is not mentioned in the correspondence how many of these women had skin metastases or scalp metastases. Rugo & Melin's expert opinion was "that scalp cooling can and should be offered to breast cancer patients who will be treated with adjuvant chemotherapy, and also those who are offered palliative chemotherapy associated with a significant risk of alopecia. The risks involved appear to be extremely small and the potential gain for the large number of women receiving adjuvant chemotherapy for breast cancer in the United States is substantial."

A number of other studies investigating the incidence of scalp skin metastases, and its relationship to scalp cooling, have been published in the literature. In a review of scalp cooling by Grevelman and Breed that included 56 studies and approximately 2,500 patients, scalp metastasis were reported in 9 patients (0.36%) (Grevelman 2005). In a total of 24 of the 56 studies reviewed, specific attention was paid to the risk of scalp skin metastases following the use of scalp cooling. It was reported that no scalp skin metastases were found in 16 of these studies. The follow-up time of the studies included in the review varied from 2 months to 63 months.

In addition to the review by Grevelman and Breed, a number of more recent studies have investigated the incidence of scalp metastases following scalp cooling of women with breast cancer receiving chemotherapy. In 2006, Christodoulou et al reported on a series of 227 breast cancer patients who underwent scalp cooling with a cold cap while receiving chemotherapy (Christodoulou 2006). Two of the breast cancer patients (0.88%) developed scalp metastases. Both patients had advanced cancer with multiple sites of metastases. The follow-up period for this study was not specified. The authors concluded that "the incidence of scalp metastases in patients using scalp cooling methods during chemotherapy is low and it does not seem to influence the clinical outcome."

In a prospective multicenter study by Spaeth and colleagues, 911 cancer patients were included from 2002 to 2006 (Spaeth 2008). 876 of these patients were women, most with localized or advanced breast cancer, whom were treated with adjuvant chemotherapy or palliative chemotherapy. There were 770 cancer patients who chose chemotherapy with scalp cooling and 141 who chose to have chemotherapy without scalp cooling. During the follow-up, a minimum time of at least 2 years, there was one cutaneous scalp metastasis and two subcutaneous scalp metastases occurring among the patients who had scalp cooling, and no scalp metastases among the patients who abstained from scalp cooling. The brief report does not give any indication of what kind of primaries the three patients with scalp metastases had, or if the chemotherapy was given as adjuvant treatment or as palliative treatment for advanced disease.

In 2009, Lemieux et al reported on a retrospective cohort study of women diagnosed with invasive breast cancer between June 1998 and June 2002 at a single institution in Quebec (Lemieux 2009). Scalp cooling was routinely offered to women with breast cancer. Of a total of 640 patients included, 86.4% received scalp cooling during neoadjuvant or adjuvant chemotherapy. Six patients (1.1%) in the scalp cooling group developed scalp metastases (with or after the diagnosis of metastases to multiple other sites), along with

one patient in the control group (1.2%). The rate of scalp metastases in the scalp cooling group and the control group was not statistically different. In this cohort, scalp metastases never presented as the sole metastatic site and these patients with scalp metastasis had widely metastatic disease. See Table 1 below for details of the 7 patients with scalp metastasis.

Table 1

Patient number	Age at diagnostic	Stage	Histology	Grade	LVI	Metastatic sites <sup>b</sup>	Use of scalp cooling in adjuvant/neo adjuvant?
1	57	I	Ductal	Poorly differentiated	No	1,2,3,7	No <sup>a</sup>
2	44	IIIA	Ductal	Poorly differentiated	Yes	1,2,3,4,5,6,7	Yes
3	41	IIIB	Ductal	Well differentiated	No	2,6,7	Yes
4	50	IIB	Ductal	Poorly differentiated	Yes	1,2,3,7	Yes
5	62	IIA	Ductal	Moderately differentiated	No	2,3,4,5,7	Yes
6	38	IIIB	Ductal	Moderately differentiated	Yes	2,6,7	Yes
7	54	IIIB	Adeno-squamous	Unknown	Yes	1,2,3,4,5,6,7,9	Yes

LVI, lymphovascular invasion, <sup>a</sup>scalp cooling used for chemotherapy given at relapse, <sup>b</sup>1 lung, 2 bone, 3 liver, 4 CNS, 5 lymph nodes, 6 soft tissues, 7 scalp, 8 bone marrow, 9 other

Recently at the San Antonio Breast Cancer Symposium held in December 2011, there were two posters presented related to the issues of chemotherapy-induced alopecia and scalp cooling devices. The first was from the Netherlands and included 1,696 scalp cooled breast cancer patients from 43 hospitals from 2006-2011. 1,057 of these patients were included in the analysis; 48% of them had hair preservation defined as not needing a head cover. As of November 2011 no scalp metastasis had been reported. This study also standardized the cooling times with a 30 minute pre-cooling time and a 90 minute post-cooling time (C. van den Hurk 2011). The second poster was from Canada and looked at survival in women with breast cancer who used or did not use a scalp cooling device in the neoadjuvant /adjuvant setting. This was a retrospective study of 1,370 women with breast cancer diagnosed between June 1998 and June 2002. There was no difference in survival between these 2 groups of women (J Lemieux 2011).

In the past there has been a theoretical concern for scalp metastases. The literature and studies to date clearly show that there is not an increased rate of scalp metastases or a difference in survival compared to women who did not receive scalp cooling. The known rate of scalp metastases in breast cancer patients is <2.5%. The rate of scalp metastases in review of the NSABP data by Rugo and Melin as a single site is 0.025% (Rugo 2010). The rate of scalp metastasis in women with breast cancer is very small, and as a single site of recurrence is exceedingly rare. If a patient has scalp metastases, there are usually multiple other sites of metastatic disease and there are usually other sites cutaneous metastases. Studies done to date do not show an increase in scalp metastasis in breast cancer patients receiving scalp cooling to prevent alopecia.

### C.5 Other Side Effects with Scalp Cooling

The effect of scalp cooling on patient comfort, possible side effects, and well-being has been evaluated. Based on published accounts of more than 2,000 patients, it is concluded that the majority of patients tolerate scalp cooling very well (Breed 2004). The side effects

of scalp cooling are not frequent and are not serious. Side effects are rarely a reason for stopping the cooling.

Common side effects reported with scalp cooling include headache, complaints of coldness, and/or uncomfortable sensations, heavy feeling of the head, transient lightheadedness, and neck pain (Massey 2004). Uncomfortable cold sensations and headaches were more frequently reported in studies when pre-cooled caps (which are chilled to  $-15^{\circ}\text{C}$  to  $-25^{\circ}\text{C}$ ) were used. Patients also complain about a heavy feeling of the head and transient light-headedness following cap removal. In addition, patients experienced neck pain due to heavy weight of some cooling caps. Cold injuries have never been reported. A potential disadvantage of scalp cooling is the additional pre-cooling and post-cooling time required which would have patients remain in the oncology clinic for a longer duration.

Known short-term adverse effects anticipated to occur during or following scalp cooling with the Orbis Paxman Hair Loss Prevention System (based on clinical experience with scalp cooling, including that obtained from use of the previous PSC model of scalp cooling system manufactured by Paxman Coolers) are as follows:

- complaints of coldness/cold-related discomfort (during scalp cooling)
- headache, ranging from mild to severe (during and following scalp cooling)
- forehead pain (during scalp cooling) resulting from pressure and tightness from the cooling cap
- light-headedness or dizziness (during scalp cooling and/or following removal of the cooling cap at the end of scalp cooling)
- complaints of uncomfortable sensations
- heavy feeling of the head
- transient lightheadedness
- transient neck pain
- cold injuries
- nausea

All of these adverse effects are transient in duration and of relatively low clinical significance. As such, the potential clinical benefits to the patient associated hair preservation through scalp cooling using the Orbis Paxman Hair Loss Prevention System (i.e. improved quality of life through avoidance of negative body image and depression resulting from alopecia) outweigh the risks associated with the known short-term adverse effects of scalp cooling.

The only known potential long-term adverse effect associated with scalp cooling (and which could thus occur following use of the Orbis Paxman Hair Loss Prevention System) is an increased incidence of scalp metastases. At the time this concern was initially raised during the late 1980s, there was little long-term data available to address this risk. However, since that time, a number of published studies extending out to more than 5 years (described in section C.4) have identified that:



- the rate of incidence of scalp metastases as the first site of recurrence in breast cancer patients is extremely low (2 out of 7,800 subjects, or 0.025%)
- the rate of incidence of scalp metastases in breast cancer patients is generally low (up to 2.5%) and is always greatest in patients with multiple metastatic sites
- the rate of incidence of scalp metastases in patients who have undergone scalp cooling during chemotherapy is low (1.1%) and is not significantly different from the incidence of scalp metastases in patients who did not receive scalp cooling (1.2%)
- there is not an increased rate of scalp metastases or a difference in survival compared to women who did not receive scalp cooling

Given that this study is specifically designed to investigate scalp cooling in breast cancer patients who are newly diagnosed with stage I – II breast cancer, and that patients with a history of scalp metastases, or with any other metastatic site are specifically excluded from enrollment, then it is considered that the risk relating to increased incidence of scalp metastases is low. In particular, this risk is outweighed by the potential clinical benefits to the patient associated with hair preservation through scalp cooling, given that up to 8% of women surveyed have reported that they would decline chemotherapy (and thus risk compromising their clinical outcome) because of the fear of chemotherapy-induced hair loss. The above points notwithstanding, the sponsor has additionally committed to a program of ongoing, post-study 5 year follow-up of all participating subjects to check for the incidence of scalp metastases, with annual reports to the FDA.

### **C.6 Psychosocial Effects of Scalp Cooling System for Alopecia Prevention in Patients with Cancer Undergoing Chemotherapy**

There is considerable evidence that the wide range of surgical, chemotherapeutic, and radiations therapies can leave permanent damage to organs and physiological functioning and disfigurement, across the different cancer diagnoses (Llescher LJ 1989). Consequently, body image has frequently been included in many studies of survivors in order to assess the long-term psychological impact of these injuries to the body (Sneeuw KCA 1992). The findings from several studies underscore the fundamental point that body image often reflects one's physical ability to function as well as appearance. Further, poorer body image appears to be broadly related to 'survivors' coping with chronic uncertainty and frequent reminders of their past treatment ordeal (Sugarbaker PH 1982) (Kornblith 1998).

## **D) Investigational Device Information**

### **D.1 Identification of the Device**

The investigational device which will be used in this study is the Orbis Paxman Hair Loss Prevention System. This device is manufactured by:

Paxman Coolers Limited  
International House  
Penistone Road  
Fenay Bridge

Huddersfield  
HD8 0LE  
United Kingdom

There are two models of the Orbis Paxman Hair Loss Prevention System:

- Orbis I
- Orbis 2

Only the Orbis 1 model will be used to provide the scalp cooling intervention in this study: Both models have the same performance characteristics – the only difference between them is that the Orbis I can be used with one patient at a time, whereas the Orbis 2 can be used with either one or two patients at a time.

## **D.2 Description of the Device**

The Orbis Paxman Hair Loss Prevention System is a free-standing, electrically-powered, mobile refrigeration unit which circulates a refrigerated liquid coolant, at a pre-set temperature and flow rate, through a cooling cap which is attached to, and covers, the top of the patient's head.

A detailed description of the Orbis Paxman Hair Loss Prevention System, including the cooling caps and cap covers necessary for scalp cooling, is provided in Appendix A. The Orbis I device used in this study will use software version V 1.1.3

## **D.3 Intended Use of the Device**

The Orbis Paxman Hair Loss Prevention System is intended by the manufacturer to be used for scalp cooling of patients who are receiving anthracycline- or taxane-based chemotherapy for the treatment of solid tumors, in order to reduce the risk of chemotherapy-induced alopecia.

The use of the Orbis Paxman Hair Loss Prevention System is contraindicated in the following situations:

- patients with hematological malignancies (leukemia and lymphomas)
- patients with cold urticaria
- patients with cold agglutinin disease
- patients with manifest scalp metastases
- patients who are scheduled for bone marrow ablation chemotherapy
- patients who are scheduled to undergo skull irradiation

## **D.4 Training and Experience Necessary for Use of the Device**

The Orbis Paxman Hair Loss Prevention System is a professional use device, intended for use by qualified oncology nursing staff.

Successful results from scalp cooling are dependent on the correct fitting of the cooling cap to the patient's head and on correct operation of the scalp cooling system. As such, all potential users of the Orbis Paxman Hair Loss Prevention System in this study will receive formal training in the setting up, use and post-scalp cooling procedures to be followed.

This training will take the form of Paxman Coolers' standard device familiarity training which is provided to all new users. This training will be provided by Paxman Coolers qualified training personnel. A record will be maintained in the clinical study file of staff at each participating center who has received this training.

Fitting of cooling caps, cooling cap covers and operation of the Orbis Paxman Hair Loss Prevention System for scalp cooling in this study will only be performed by staff who have received this formal training. All sites will receive the same training on use of the Orbis Paxman Hair Loss Prevention System.

### **D.5 Device Traceability**

The Orbis Paxman Hair Loss Prevention Systems used in the study shall be traceable by the unique serial number printed on the manufacturer's identification plate, which is affixed to the back of each unit.

Cooling caps and cap covers shall both be traceable by the unique serial number affixed to each cap and cover.

The Sponsor/Principal Investigator shall maintain a record of the serial numbers of every Orbis Paxman Hair Loss Prevention System, cooling cap and cap cover used in this study, stratified by participating center. Following completion of the last scalp cooling procedure in the study, every Orbis Paxman Hair Loss Prevention System, cooling cap and cap cover released for use in the study shall be recovered and returned to the device manufacturer's manufacturing facility in the UK.

## **E) Risk Benefit Analysis**

### **E.1 Anticipated Risks and Adverse Device Effects**

#### **E.1.1 Efficacy Risks and Evaluation of Risk Benefit**

The only known efficacy risk is that scalp cooling with the Orbis Paxman Hair Loss Prevention System will not result in a reduced risk of chemotherapy-induced alopecia.

Existing published clinical data for scalp cooling has demonstrated a variable success rate for hair preservation, which depends on a number of factors, including:

- the type of scalp cooling device used
- the chemotherapy regimen being used
- the scalp cooling procedure used
- patient compliance with the scalp cooling procedure

The risk of failure to reduce chemotherapy-induced alopecia has been minimized in this study through the careful selection of a patient population (i.e. stage I – II breast cancer patients), chemotherapy regimens (anthracycline or taxane based) and scalp cooling procedure, for which there is evidence of acceptable levels of clinical effectiveness from published clinical studies which used equivalent continuous-cooling systems (i.e. the Paxman Scalp Cooling system). Moreover, the published clinical data demonstrate that scalp cooling using the Orbis Paxman Hair Loss Prevention System is generally well-tolerated by patients, with only a few percent choosing to discontinue the treatment.

As such, the potential clinical benefits to the patient associated with hair preservation through scalp cooling using the Orbis Paxman Hair Loss Prevention System (i.e. improved quality of life through avoidance of negative body image and depression resulting from alopecia) outweigh the risk of failure to reduce chemotherapy-induced hair loss.

#### E.1.2 Adverse Device Effects and Evaluation of Risk Benefit

Common side effects reported with scalp cooling include headache, complaints of coldness, and/or uncomfortable sensations, heavy feeling of the head, transient lightheadedness, and neck pain (Massey 2004). Uncomfortable cold sensations and headaches were more frequently reported in studies when pre-cooled caps (which are chilled to -15 to -25°C) were used. Patients also complain about a heavy feeling of the head and transient light-headedness following cap removal. In addition, patients experienced neck pain due to heavy weight of some cooling caps. Cold injuries have never been reported. A potential disadvantage of scalp cooling is the additional pre-cooling and post-cooling time required which would have patients remain in the oncology clinic for a longer duration.

Known short-term adverse effects anticipated to occur during or following scalp cooling with the Orbis Paxman Hair Loss Prevention System (based on clinical experience with scalp cooling, including that obtained from use of the previous PSC model of scalp cooling system manufactured by Paxman Coolers) are as follows:

- complaints of coldness/cold-related discomfort (during scalp cooling)
- headache, ranging from mild to severe (during and following scalp cooling)
- forehead pain (during scalp cooling) resulting from pressure and tightness from the cooling cap
- light-headedness or dizziness (during scalp cooling and/or following removal of the cooling cap at the end of scalp cooling)
- complaints of uncomfortable sensations
- heavy feeling of the head
- transient lightheadedness
- transient neck pain
- cold injuries
- nausea

All of these adverse effects are transient in duration and of relatively low clinical significance. As such, the potential clinical benefits to the patient associated hair preservation through scalp cooling using the Orbis Paxman Hair Loss Prevention System (i.e. improved quality of life through avoidance of negative body image and depression resulting from alopecia) outweigh the risks associated with the known short-term adverse effects of scalp cooling.

The only known potential long-term adverse effect associated with scalp cooling (and which could thus occur following use of the Orbis Paxman Hair Loss Prevention System) is an increased incidence of scalp metastases. At the time this concern was initially raised

during the late 1980s, there was little long-term data available to address this risk. However, since that time, a number of published studies extending out to more than 5 years (described in section C.4) have identified that:

- the rate of incidence of scalp metastases as the first site of recurrence in breast cancer patients is extremely low (2 out of 7,800 subjects, or 0.025%);
- the rate of incidence of scalp metastases in breast cancer patients is generally low (up to 2.5%) and is always greatest in patients with multiple metastatic sites;
- the rate of incidence of scalp metastases in patients who have undergone scalp cooling during chemotherapy is low (1.1%) and is not significantly different from the incidence of scalp metastases in patients who did not receive scalp cooling (1.2%);
- there is not an increased rate of scalp metastases or a difference in survival compared to women who did not receive scalp cooling.

Given that this study is specifically designed to investigate scalp cooling in breast cancer patients who are newly diagnosed with stage I – II breast cancer, and that patients with a history of scalp metastases or with any other metastatic site are specifically excluded from enrollment, then it is considered that the risk relating to increased incidence of scalp metastases is low. In particular, this risk is outweighed by the potential clinical benefits to the patient associated with hair preservation through scalp cooling, given that up to 8% of women surveyed have reported that they would decline chemotherapy (and thus risk compromising their clinical outcome) because of the fear of chemotherapy-induced hair loss. The above points notwithstanding, the sponsor has additionally committed to a program of ongoing, post-study 5 year follow-up of all participating subjects to check for the incidence of scalp metastases, with annual reports to the FDA.

## **E.2 Additional Study Measures to Minimize Risk**

Every precaution will be taken pre-, during and post- procedure in order to minimize the risk of technical and procedural complications to patients.

Examples of control measures implemented within the study design to achieve this aim include:

- Selection of suitably qualified investigators and center personnel, who have suitable experience of the administration of the specified chemotherapy regimens to breast cancer patients
- Investigators and center personnel to be trained by the device manufacturer, prior to the commencement of the study, in the safe and effective use of the Orbis Paxman Hair Loss Prevention System for its intended purpose, and in particular in the Instructions For Use supplied with the device.

## **E.3 Risk Benefit Conclusion**

Taking into account all of the known risks related to the use of the Orbis Paxman Hair Loss Prevention System in this study for the reduction of chemotherapy-induced alopecia in breast cancer patients, together with the published clinical evidence concerning the safety

and effectiveness of scalp cooling, it is considered that the potential clinical benefits of successful hair preservation outweigh the clinical risks.

## **F) Purpose**

Demonstrate that the Orbis Paxman Hair Loss Prevention System is safe and effective in reducing chemotherapy-induced alopecia in woman with breast cancer undergoing neoadjuvant or adjuvant chemotherapy.

## **G) Hypothesis**

- a) The Orbis Paxman Hair Loss Prevention System will significantly reduce chemotherapy-induced alopecia in woman with breast cancer undergoing neoadjuvant or adjuvant chemotherapy;
- b) Women who do not have clinically significant alopecia will have a better quality of life compared to those with alopecia and that the reduction of alopecia in breast cancer patients undergoing chemotherapy is associated with a lower risk of depression;
- c) Scalp cooling using the Orbis Paxman Hair Loss Prevention System is not associated with any unanticipated, clinically significant short-term safety effects, and the scalp cooling procedure is well-tolerated by patients undergoing chemotherapy;
- d) Scalp cooling using the Orbis Paxman Hair Loss Prevention System does not present an increased risk of scalp metastases for patients newly diagnosed with stage I – II breast cancer

Data collected in this clinical investigation will be used to support a premarket approval (PMA) application to the US FDA for approval to market the Orbis Paxman Hair Loss Prevention System in U.S.A., for the intended use of reduction of chemotherapy-induced alopecia in stage I – II breast cancer patients who are receiving neoadjuvant or adjuvant chemotherapy with anthracycline or taxane based drug regimens.

## **H) Endpoints**

### **H.1 Primary Endpoints**

**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) specified in section M.3.5.

### **H.2 Secondary Endpoints**

**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-30, 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.

## I) Participant Selection

### I.1 Inclusion Criteria

- New diagnosis of breast cancer stage I-II
- Planning to undergo neoadjuvant or adjuvant chemotherapy with curative intent
- Chemotherapy must be planned for at least 4 cycles of full-dose anthracycline or taxane based chemotherapy regimen,
  - Defined as one of the following regimens:
    - Adriamycin 60 mg/m<sup>2</sup> with cyclophosphamide 600 mg/m<sup>2</sup>
    - Epirubicin 90-100 mg/m<sup>2</sup> with cyclophosphamide 600 mg/m<sup>2</sup>
    - Doxorubicin 50 mg/m<sup>2</sup> with 5-Fluorouracil 500 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup>
    - Paclitaxel 80-90 mg/m<sup>2</sup> weekly (every 3 weeks constitutes a cycle), or 175 mg/m<sup>2</sup> every 2-3 weeks as a single agent
    - Paclitaxel 80-90 mg/m<sup>2</sup> weekly with carboplatin AUC of 6 every 3 weeks
    - Paclitaxel 80-90 mg/m<sup>2</sup> weekly with carboplatin AUC of 2 weekly
    - Docetaxel 100 mg/m<sup>2</sup> as a single agent
    - Docetaxel 75-100 mg/m<sup>2</sup> with pertuzumab and trastuzumab at standard doses
    - Docetaxel 75 mg/m<sup>2</sup> with cyclophosphamide 600 mg/m<sup>2</sup>
    - Docetaxel 75 mg/m<sup>2</sup> with carboplatin AUC of 6
  - Concurrent trastuzumab and/or pertuzumab at standard doses is allowed.
  - Administration of chemotherapy on a dose dense schedule is allowed as clinically indicated.
  - Subjects who have an allergic reaction to taxane-based chemotherapy are allowed to continue on trial with paclitaxel protein-bound (Abraxane) 80 mg/m<sup>2</sup> – 100 mg/m<sup>2</sup> weekly (every 3 weeks constitutes a cycle), or 200 mg/m<sup>2</sup> – 260 mg/m<sup>2</sup> every 3 weeks as a single agent or in combination with cyclophosphamide 600 mg/m<sup>2</sup> to complete the course of chemotherapy that was originally planned.
- Subjects must have TSH collected within 1 year prior to treatment and found within acceptable limits (defined under exclusion criteria).
- If subject has a history of diabetes, hemoglobin A1c must be drawn within 3 months prior to treatment and found to be within acceptable limits (defined under exclusion criteria).
- CBC and CMP should be done within 4 weeks prior to treatment and found to be within acceptable limits (defined under exclusion criteria).

## **I.2 Exclusion Criteria**

- Stage III-IV breast cancer or any other concurrent malignancy including hematological malignancies (i.e. leukemia or lymphoma)
- Baseline alopecia (defined CTCAE v4.0 grade > 0, see Appendix B)
- Subjects with cold agglutinin disease or cold urticaria
- Subjects who are scheduled for bone marrow ablation chemotherapy
- Subjects receiving chemotherapy with concurrent anthracycline and taxane (AT or TAC)
- Male gender
- Age  $\geq$  70 years
- Personal history of migraines, cluster or tension headaches as defined as actual medical diagnosis by a physician and/ or prescribed medications. If personal history of migraines was related to a past medical problem that is now resolved, subject may go on study at the discretion of the Principal Investigator.
- Elevated liver enzymes or bilirubin defined as 3 times the upper limits of normal
- Serum Albumin < 3.0
- Subjects with anemia (defined as a hemoglobin < 10)
- Abnormal TSH, AND:
  - If high, abnormal free T4 defined as out of normal limits
  - If low, abnormal free T4 or T3 defined as out of normal limits
- Subjects who have diabetes with a Hgb A1c > 7
- Subjects who have lichen planus or lupus
- Subjects who are underweight (defined as a BMI < 17.5)
- Subjects who have had previous chemotherapy exposure

## **I.3 Inclusion of Underrepresented Populations**

Individuals of all races and ethnic groups are eligible for this trial. There is no bias towards age or race in the clinical trial outlined.

## **J) Study Design**

### **J.1 General Aspects of Study Design**

This is a prospective, randomized, controlled, multi-center, pivotal clinical investigation to be conducted in up to 10 centers within the USA which are routinely engaged in the administration of adjuvant or neoadjuvant chemotherapy to women with stage I – II breast cancer.

This is a non-blinded, parallel group (no intervention control), clinical outcome study.



The study will require 213 response evaluable subjects and ~325 consented patients (see section P.2 for sample size justification). Subjects will be randomized to either scalp cooling or non-scalp cooling (control) on a 2:1 basis.

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.

In each case the scalp cooling protocol followed will comprise:

- Minimum 30 minutes pre-infusion cooling
- Cooling for the duration of chemotherapy infusion
- Minimum 90 minutes post-infusion cooling

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.

## **J.2 Center Selection**

Participating centers will be chosen based on their experience in conducting clinical studies, their experience in administering neoadjuvant or adjuvant chemotherapy to breast cancer patients, excellent academic and medical reputation as well as their ability to recruit a robust study population.

Each participating center is required to have a study coordinator to assist the Principal Investigator. In addition, each center must have the time and resources available to participate in the study and fulfill their obligations under this protocol.

## **J.3 Lead Center**

Baylor College of Medicine will be designated the Lead Center for this multi-center study and is the place of work of the Sponsor/Principal Investigator.

The Lead Center will be responsible for the acquisition of all regulatory documentation prior to the activation of all other participating centers and will be responsible for assuring the quality and accuracy of data provided by the other participating centers.

## **J.4 Other Participating Centers**

All participating centers are responsible for providing all required documentation to the Lead Center.

## **J.5 Study Population**

Women with stage I-II breast cancer who will undergo either neoadjuvant or adjuvant chemotherapy.

## **J.6 Subject Screening & Enrollment**

Screening and enrollment of each individual subject will be performed prior to the subject receiving her first chemotherapy infusion under this protocol.

### **J.6.1 Screening Procedure**

The screening procedure is intended to determine whether or not a patient meets the eligibility criteria for inclusion in the study. All screened patients will be asked to sign the informed consent form.

### **J.6.2 Enrollment**

A subject will be considered enrolled in the study when all of the following three steps are completed:

- Signed informed consent is obtained.
- Based on the screening assessment, it is determined that the subject meets all of the specified inclusion criteria and none of the specified exclusion criteria.
- Subject is randomized.

Eligible subjects will be randomized and entered on study centrally at the Lead Center by the Study Monitor or designee. All sites will send the applicable eligibility source documents to the Study Monitor via email ([otte@bcm.edu](mailto:otte@bcm.edu)) or fax (713-798-8884) to verify eligibility.

Following randomization, subjects should begin protocol treatment within 4 weeks. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a subject does not receive protocol therapy following registration within the allowed time period, the subject will become ineligible and will be withdrawn from the study, and will be inevaluable for efficacy and safety.

## **J.7 Subject Identification**

Subjects will be identified using unique subject identification numbers. Subject identification numbers will be assigned centrally by the Study Monitor after a subject signs the informed consent form and will be assigned consecutively, starting at 1. All sites must contact the Study Monitor to receive a subject identification number for all subjects who sign consent.

## **K) Study Procedures**

### **K.1 Randomization Procedure**

To avoid bias, subjects included in the study will be randomly assigned to either the intervention (scalp cooling) group or to the control (no scalp cooling).

Randomization will be performed prior to performing any procedures and will use the permuted block method. Randomization will be stratified by major chemotherapy type and center.

## **K.2 Baseline Assessment**

All subjects who have satisfied the enrollment criteria will be subjected to baseline assessment prior to performing any study procedures. All information collected will be recorded for each subject.

The following baseline data will be collected for all subjects prior to performing any study procedures:

- Subject demographics (date of birth, weight, height, race, ethnicity)
- Clinical information (stage of breast cancer, scheduled chemotherapy regimen)
- History & Physical including menopausal status, and history of hormone replacement therapy and oral contraceptive use
- ECOG Performance Status
- Current medication(s)
- Baseline EORTC QLQ-C30, HADS, and BIS Questionnaires
- Baseline Alopecia Score assessed by the subject's oncologist/nurse practitioner and the blinded healthcare provider
- Baseline photographs to include the following views of the subject's head: front hairline, back, top, left and right

## **K.3 Procedures**

Subjects randomized to the scalp cooling group will undergo the procedures described in sections K.3.1 through K.3.3.

Subjects randomized to the control (no scalp cooling) group will not use the device and will undergo the procedures described in section K.3.4.

### **K.3.1 Preparation for Scalp Cooling**

Effective scalp cooling relies on good contact between the inner surfaces of the cooling cap and the patient's scalp. As such, prior to the first scalp cooling procedure, each subject must undergo a cooling cap fitting with a healthcare professional trained in use of the Orbis Scalp Cooler. This fitting process is necessary to ensure that the most appropriate size of cooling cap is selected. For optimum cooling, the cap must both fit snugly onto the head at the crown and also cover the entire scalp area down to the hairline. Effective scalp cooling over the entire scalp is only achieved with the combination of correct size of cooling cap and correct size of cooling cap cover; the cover – with its adjustable straps – is necessary to ensure that the cooling cap is maintained securely and comfortably in the correct position on the subject's head for the duration of the scalp cooling process. For some subjects, the cap fitting process will simply involve the selection of the most appropriate size cooling cap and corresponding cap cover. For subjects whose head size does not correspond to one of the five available cooling cap sizes, a combination of the larger size cooling cap and smaller size cover is used to obtain the required cooling cap contact with the scalp.

Selection and fitting of the optimum size of cooling cap and cooling cap cover for each subject will be performed in accordance with the instructions provided in the user manual supplied with the Orbis Paxman Hair Loss Prevention System. The user manual describes the use of both pre-cooled and warm caps. Either option can be chosen for patient tolerance.

A record will be maintained in the study file at each center of the size of cooling cap and cap cover selected for each subject at that center as well as if the cap was pre-cooled or warm, based on the above process. The Principal Investigator will retain a copy of this record from each participating center.

### K.3.2 Scalp Cooling

Scalp cooling will occur with each dose of chemotherapy. Prior to scalp cooling, the cooling cap is always attached to the subject's head with the cap disconnected from the coolant lines. Before placing the cooling cap on the subject's head, it is placed inside the appropriate size of cap cover and manually pressed into position against the inner surface of the cover, such that the entire cooling cap is within the cover. The cooling cap and cover are then placed onto the study participant's head such that the cap is on straight and covers the subject's entire scalp to the hairline. The cover chin-strap and circumferential straps are then adjusted to achieve a snug fit of the cooling cap to the scalp, which is also comfortable for the subject. The healthcare professional then checks the fit of the cooling cap to ensure good contact all over the scalp – particularly at the crown and hairline. Once this is done, the subject is ready to begin scalp cooling and the cooling cap outward and return tube quick release connectors are connected to the corresponding connectors on the distal end of the coolant lines.

Powering on the system using the power switch on the back of the main unit activates the refrigeration unit, which then reduces the temperature of the coolant in the coolant tank to between  $-4.0^{\circ}\text{C}$  and  $-5.0^{\circ}\text{C}$  through standard refrigeration technology. Once this temperature is attained, the coolant temperature in the coolant tank is maintained within this temperature range by the system software, which monitors the coolant temperature from an electronic sensor in the reservoir and electronically switches off the refrigeration compressor when the temperature reads  $-4.0^{\circ}\text{C}$  and switches on the compressor when the sensor temperature reads  $-3.0^{\circ}\text{C}$ .

Once the pre-set coolant temperature is reached, the pump is activated using a separate switch on the rear of the main unit. This causes the refrigerated coolant to be pumped from the reservoir at a pre-set constant flow rate via the outward coolant line through the cooling cap and back to the reservoir via the return coolant line. Coolant flow rate is monitored via flow turbines located in the return tube. In the event of a low coolant flow rate ( $< 0.6 \text{ L/min}$ ) being detected (which may indicate coolant loss, or kinking of one of the coolant lines), the software displays a warning message on the touch screen and sounds a buzzer to alert the user.

The touch screen controller provides feedback to the user concerning the status of the Orbis Scalp Cooler as it relates to achievement of the pre-set temperature of the coolant, operation of the recirculation pump and connection of a cooling cap to the system. The software also provides a countdown timer function which allows the user to set a post

infusion cooling time. At the end of the pre-set time, a message is displayed on the touch screen and a buzzer sounds to alert the user to the fact that the scalp cooling time is complete.

Following completion of scalp cooling, the recirculation pump is switched off and the cooling cap and cover are then removed from the subject's head. The device will be worn for a standardized pre-cooling time of at least 30 minutes, during chemotherapy, and a standardized post-cooling time of at least 90 minutes. After the post-cooling time, the cap will be loosened and left in place for at least 5 minutes to allow the cap to warm up before removal. In addition, the subject will be given at least 5 additional minutes to acclimatize before being asked to stand up.

Administration of the chemotherapy agent will be performed according to the standard procedure at each center for the intravenous infusion of the chemotherapy regimen concerned, using the recommended volume and infusion rate for the specific chemotherapy regimen.

If the subject is being treated with a regimen that includes trastuzumab and/or pertuzumab, these can be administered during the 90 minute post-cooling phase, as they are not chemotherapy drugs.

For each subject who undergoes scalp cooling, a record will be maintained at each participating center of the details of each scalp cooling procedure. This record will include the following details:

- subject ID
- date of treatment
- serial number of the Orbis Paxman Hair Loss Prevention System used for scalp cooling
- size and serial number of the cooling cap and cooling cap cover used for scalp cooling
- the name of the healthcare professional who fitted the cap and cap cover, who operated the scalp cooling device and who removed the cap and cap cover at the end of the scalp cooling process
- start and finish time of the pre-infusion scalp cooling, of the infusion scalp cooling and of the post-infusion scalp cooling for each use
- side effects reported by the subject during scalp cooling
- the time and duration of, and the reason for, any temporary, or permanent interruption to the scalp cooling process
- the time of occurrence of any alarms or warning messages from the Orbis Paxman Hair Loss Prevention System used for scalp cooling
- the time and duration of, and the reason for, any temporary, or permanent interruption to the chemotherapy infusion process
- if a subject withdraws from the study, the reason for withdrawal

### K.3.3 Visit Assessments

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 independent observer will assess the subject either before or after the subject sees the clinician. By signing the consent, the clinician and the subject agree not to tell the independent observer the subject's randomization assignment. 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 (see Appendix B).

Photographs of the heads of the first 25 subjects' enrolled from each site who complete at least 1 cycle of chemotherapy will be taken at each alopecia assessment (until the subject develops grade 2 alopecia), and these photographs will be included in the final study report. For subjects enrolled after these 25 subjects, photographs will only be taken at baseline, after 4 cycles, and after completion of chemotherapy (if receiving more than 4 cycles). If a subject develops grade 2 alopecia at a visit prior to the post-Cycle 4 or post-completion visit, photographs should be taken at the visit and do not need to be taken from that point forward.

These photographs will be taken with a digital camera or camera phone in a well-lit exam room with the subject sitting and the photographer standing. There will be 5 photographs taken which will include the following views: front hairline taken 8-12" from the subject, right side & left side taken 15-25" from the subject, back of the head taken 15-25" from the subject, and top of the head taken 8-12" from the subject.

The EORTC QLQ-C30, HADS, and BIS questionnaires will be administered at baseline, after 4 cycles of chemotherapy and after completion of chemotherapy (if subject is receiving more than 4 cycles). Immediately after each cycle, subjects will be administered a comfort scale after the scalp cooling device has been removed.

Duration of device use will depend on the type of chemotherapy the subject is receiving, if the subject is assessed as having grade 2 alopecia during the study, and will occur with each cycle of chemotherapy (maximum of 8 cycles).

Subjects who develop grade 2 alopecia (determined by the blinded independent provider, the delegated physician/nurse practitioner and the subject) will discontinue alopecia assessments at subsequent visits. Photographs will only continue if the subject elects to continue to wear the device after development of grade 2 alopecia.

### K.3.4 Control Group Procedures

Administration of the chemotherapy agent will be performed according to the standard procedure at each center for the intravenous infusion of the chemotherapy regimen concerned, using the recommended volume and infusion rate for the specific chemotherapy regimen.

At baseline and after each cycle, subjects will have an alopecia assessment by a physician or nurse practitioner and a second 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 independent observer will assess the subject either before or after the subject sees the clinician. By signing the consent, the clinician and the subject agree not to tell the independent observer the subject's randomization assignment. 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 (see Appendix B).

Photographs of the heads of the first 25 subjects' enrolled from each site who complete at least 1 cycle of chemotherapy will be taken at each alopecia assessment (until the subject develops grade 2 alopecia), and these photographs will be included in the final study report. For subjects enrolled after these 25 subjects, photographs will only be taken at baseline, after 4 cycles, and after completion of chemotherapy (if receiving more than 4 cycles). If a subject develops grade 2 alopecia at a visit prior to the post-Cycle 4 or post-completion visit, photographs should be taken at the visit and do not need to be taken from that point forward.

These photographs will be taken with a digital camera or camera phone in a well-lit exam room with the subject sitting and the photographer standing. There will be 5 photographs taken which will include the following views: front hairline taken 8-12" from the subject, right side and left side taken 15-25" from the subject, back of the head taken 15-25" from the subject, and top of the head taken 8-12" from the subject.

The EORTC QLQ-C30, HADS, and BIS questionnaires will be administered at baseline, after 4 cycles of chemotherapy and after completion of chemotherapy (if receiving more than 4 cycles).

Subjects who develop grade 2 alopecia (determined by the blinded independent provider, the delegated physician/nurse practitioner and the subject) will discontinue alopecia assessments and photographs at subsequent visits.

#### **K.4 Concomitant Treatment and Supportive Care Guidelines**

Subjects are allowed to be on other research studies that do not have additional chemotherapeutic agents that are associated with alopecia.

#### **K.5 Duration of Follow-Up**

Subjects will be followed 2-4 weeks after completion of chemotherapy when the final alopecia assessment will occur (if grade 2 alopecia has not been reached) and the questionnaires will be administered. Subjects will be followed post-study for 5 years during routine clinic follow-up for survival, recurrence and site of recurrence.

## **K.6 Criteria for Removal from Study**

The reasons for removal from the study include:

- Subject withdraws consent for follow-up
- Subject is lost to follow-up
- Study is terminated for any reason
- The subject's best interest as determined by the treating investigator with approval from the Principal Investigator

Subjects who complete at least one cycle of chemotherapy will be included in the overall evaluation of response (intent-to-treat analysis). All reasons for removal from the study should be documented clearly in the medical record.

## **K.7 Criteria and Procedures for Discontinuation of Treatment**

The reasons for discontinuation of protocol treatment include:

- Non-compliance with the study protocol, including, but not limited to: not attending the majority of scheduled visits, and not using the device for at least 80% of the prescribed time on the cooling device (defined as time device worn divided by the sum of 30 minute pre-cooling time + duration of chemotherapy + 90 minute post-cooling time) without medical reason. The Protocol Chair will determine when non-compliance should lead to removal from study.
- Unacceptable major adverse events.
- At subject's own request.
- Study is closed for any reason.
- Development of CTCAE v4.0 grade 2 alopecia, as assessed by the delegated physician/nurse practitioner, the blinded healthcare provider, **and** the subject.
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the opinion of the treating investigator.

If a subject is assessed as having grade 2 alopecia (by the physician/nurse practitioner, blinded provider and the subject), or if the subject decides she no longer wants to participate in treatment with the device, the device will be discontinued. The required alopecia assessments and photographs will be performed on the day of determining grade 2 alopecia, but should not be performed at subsequent visits. All subjects (both cooling and non-cooling), regardless of whether or not treatment was discontinued early, must complete the QOL questionnaires after Cycle 4 and after completion of chemotherapy (if receiving more than 4 cycles).

Subjects who discontinue treatment will still be included in the overall evaluation of response (intent-to-treat analysis) if they have completed at least one cycle of chemotherapy prior to withdrawal/discontinuation.



## **K.8 Delays**

If a subject's chemotherapy is delayed because of toxicities from chemotherapy (i.e. neutropenic fever or infection) she will be allowed to continue on study. Chemotherapy delays do routinely occur because of chemotherapy toxicities. When the subject requires a delay in chemotherapy due to toxicities and when chemotherapy is safe to resume will be left to the discretion of the subject's physician. Delays > 2 weeks will have to be approved by the Sponsor/Principal Investigator.

## L) Study Calendar

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

## **M) Adverse Events**

### **M.1 Reportable Adverse Events**

Any adverse events that are possibly, probably or definitely related to the Orbis Paxman Hair Loss Prevention System will be reported to the Sponsor/Principal Investigator via the Adverse Event case report form. If the related event is serious, the study will be put on hold while the toxicity is investigated and until the safety of the device is ensured.

Any adverse events or toxicities that are determined to be related to the chemotherapy should NOT be reported unless they are unusual (i.e. not listed in the chemotherapy package insert).

### **M.2 Adverse Event Reporting Requirements**

#### **M.2.1 General**

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) that is available at <http://ctep.cancer.gov/reporting/ctc.html> for the grading of safety with the exception of the comfort scale (see Appendix C).

Information on all adverse events, whether reported by the subject, directly observed, or detected by physical examination or other means, will be collected, recorded, followed and reported as described in the following sections.

Adverse events experienced by subjects will be collected and reported from initiation of study device, throughout the study, and within 30 days of the last use of study device. Subjects who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

Subjects should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The Investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a subject has discontinued or terminated study participation that may reasonably be related to the study.

### **M.3 Adverse Event Definitions**

#### **M.3.1 Adverse Event (AE)**

An adverse event is any undesirable sign, symptom, medical condition or experience that develops or worsens in severity after starting the first device treatment, even if the event is not considered to be related to the device.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

All reportable adverse events which occur during this clinical study will be graded as shown in table 2. Grades refer to the severity of the AE. The CTCAE displays grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.

Table 2: Grading of Severity of Adverse Events

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADLs)*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

\*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

\*\*Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The relationship of the adverse event to the device which is the subject of this clinical investigation will be graded as shown in Table 3.

Table 3: Expectedness & Attribution

Expectedness

Expected	Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered <u>expected</u> when it appears in the current adverse event list, the Investigator’s Brochure, the package insert or is included in the informed consent document as a potential risk.
Unexpected	An adverse event is considered <u>unexpected</u> when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator’s Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

Attribution

Attribution is the relationship between an adverse event and the study treatment. Attribution will be assigned as follows:

Definite	The AE is clearly related to the study device
Probable	The AE is likely related to the study device

Possible	The AE may be related to the study device
Unlikely	The AE is doubtfully related to the study device
Unrelated	The AE is clearly NOT related to the study device

### M.3.2 Serious Adverse Event (SAE)

A serious adverse event is an undesirable sign, symptom, or medical condition which:

- is fatal or life-threatening;
- requires or prolongs inpatient hospitalization;
- results in persistent or significant disability/incapacity;
- constitutes a congenital anomaly or birth defect; or
- jeopardizes the subject and requires medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

### M.3.3 Adverse Device Effect (ADE)

This is an adverse event which is possibly, probably, or definitely related to the study device. This includes any event which occurred due to:

- insufficiency or inadequacy in the instructions for use provided with the device;
- installation and/or use of the device;
- malfunction of the device; or,
- user error.

### M.3.4 Serious Adverse Device Effect (SADE)

This is an adverse event related to the study device which:

- has led to the death a patient, user, or other person
- has led to a serious deterioration in the health of a patient, user, or other person
- could have led to the death, or serious deterioration in the health, of a patient, user, or other person, if fortunate circumstances or the intervention of healthcare personnel had not prevented it, and might lead to this if the same event occurred again

### M.3.5 Anticipated Adverse Device Effects (AADE)

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 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

### M.3.6 Unanticipated Adverse Device Effect (UADE)

This is any adverse device effect which was not previously identified in the device manufacturer's risk management documentation for the design and use of the Orbis Paxman Hair Loss Prevention System for the management of chemotherapy-induced alopecia, and was not identified in the informed consent form for this study.

## **M.4 Adverse Event Reporting**

Information on all reportable adverse events (AEs, SAEs, ADEs, SADEs and UADEs) experienced by subjects during the course of the study, from initiation of study treatment up until final follow-up assessment at 3 weeks  $\pm$  1 week after the last cycle of chemotherapy, will be collected, recorded and reported. It is the responsibility of the Investigator at the center where the event occurred to ensure that all event information is recorded on the relevant case report form (CRF) and entered accurately into the electronic database.

Details recorded should include the following information:

- study center identifier
- description of the event
- the dates of the onset and resolution of the event
- any action taken and the outcome of this action
- the relationship of the event to the device
- whether or not the adverse event meets the criteria for designation as 'serious'
- whether the adverse events arises from insufficiencies in the IFU
- whether the adverse event arises from user error

Subjects who experience an ongoing AE, SAE, ADE, SADE or UADE related to the study device will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating Investigator.

Additionally, subjects will be instructed to report all serious post-study AEs, SAEs, ADEs, SADEs and UADEs that might reasonably be related to participation in this study, specifically to the device use.

An adverse event may be detected by a physical examination or may be volunteered by subjects, elicited from questioning by an Investigator or designee, or collected via observation by an Investigator. The Investigator will determine whether or not the event is related to the device and/or procedure, and whether or not the event meets the criteria for designation as ‘serious.’

In the event of an adverse event, the Investigator and/or other professional personnel in attendance will undertake whatever therapy is indicated by established standards of care that will protect the life and health of the subject.

All reportable serious adverse events, serious adverse device effects and unanticipated adverse device effects must be fully recorded and notified to the Sponsor/Principal Investigator within one (1) working day after the Investigator at any other participating center becomes aware of the event. The nature and causes of the problem and any treatment that is administered will be reported on the relevant form.

The Sponsor/Principal Investigator will be responsible for immediate reporting of SAEs, SADEs and UADEs to the DSMB, IRBs of the participating centers, to the US FDA and to the device manufacturer, within one (1) working day of becoming aware of the event. SAEs, SADEs and UADEs should be reported to the US FDA, either using a MedWatch form (ref. 3500) available on the FDA website at <https://www.accessdata.fda.gov/scripts/medwatch/>, or by telephone (1-800-FDA-1088), or by fax (1-800-FDA-0178) using the form available at <http://www.fda.gov/medwatch/report/hcp.htm>). The Lead Center will be responsible for correspondence with the FDA regarding adverse events for all participating centers.

It is the responsibility of the Sponsor/Principal Investigator, in conjunction with the device manufacturer’s appointed clinical and regulatory advisors, to conduct an evaluation of each reportable adverse event which occurs. If the event is determined to be an SAE, SADE or UADE, the Sponsor/Principal Investigator will notify all participating Investigators within five (5) working days of becoming aware of the event.

If it is determined through the evaluation process that an ADE presents an unreasonable risk to the subject population, study enrollment will be terminated. Termination will occur no later than five (5) working days after the determination is made, and no later than fifteen (15) working days after initial notification of the ADE. A terminated investigation will not resume at any participating center without approval from the relevant IRB and from the US FDA.

The Sponsor/Principal Investigator, will ensure that all AEs and ADEs are reported and reviewed with the clinical investigator(s) and, where appropriate, that all SAEs and all SADEs are reported to the relevant IRBs and to the US FDA, in accordance with relevant national reporting requirements.

## **N) Informed Consent**

Written informed consent will be obtained for all patients who are potential study candidates before any study-specific tests or procedures are performed. The subject will be given adequate time to consider to the risks associated with participation in any study procedures and to ask any questions the subject may have. The subject (or the subject’s legal

representative) must sign the IRB-approved informed consent form prior to participation in the study. Failure to provide informed consent renders the subject ineligible for the study.

For each subject consented to the study, the original signed informed consent form will be retained on file at the center where the subject was consented; a copy of this form will also be given to the subject. Case histories (subject charts) will also document that informed consent was obtained prior to the subject's participation in the study.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject's authorization to release medical information to the study sponsor or allow the sponsor, and/or the US FDA and/or the IRB of any of the participating centers to access study subjects' medical information that includes all hospital records relevant to the study, including study subjects' medical history.

## **O) Investigation Administration**

### **O.1 Ethical Conduct**

The study will be conducted in accordance with Good Clinical Practice, as defined in ISO 14155:2011 and in the US Code of Federal Regulations (21 CFR §50) governing the protection of human subjects and the obligations of clinical investigators, and in accordance with the requirements of the Declaration of Helsinki concerning the protection of human subjects.

The Sponsor/Principal Investigator is responsible for the ongoing safety of the device and will promptly notify all participating investigators, the DSMB, the IRBs and the US FDA of all findings that could adversely affect the safety of subjects, affect the conduct of the study, or alter the IRB's and US FDA's approval for the study.

### **O.2 Regulatory Requirements**

This study will be conducted in compliance with the Code of Federal Regulations concerning clinical investigation in USA with non-approved medical devices (ref. 21 CFR §812), as well as Good Clinical Practice (GCP) for the clinical investigation of medical devices, as defined in ISO 14155:2011.

All participating centers are required to maintain at the site the appropriate regulatory and study documentation, which documentation should be made available for inspection by the Lead Center and /or the US regulatory authorities, on request.

#### **O.2.1 Study Approvals Prior to Study Initiation**

The protocol and supporting documents for this study will be reviewed and approved by the appropriately constituted IRB of each participating center and by the US FDA, prior to study initiation.

All reviews and approvals will be in accordance with Good Clinical Practice (GCP) as contained in ISO 14155:2011, and the Declaration of Helsinki.

Prior to study initiation, the Sponsor must have received:



- a letter from the IRB documenting approval of: the investigator(s) (who must be identified by name), the study protocol, (must be identified by title and revision number), and the patient information brochure and Subject Informed Consent Form
- a letter from the US FDA, documenting approval of the study protocol and supporting documentation.

### O.2.2 Study Reporting

A progress report will be submitted by the Sponsor/Principal Investigator to the study's DSMB at intervals specified by the DSMB.

If required, a progress report will be submitted by the Sponsor/Principal Investigator to the IRB and to US FDA at intervals specified by the IRB or by the US FDA. A copy of the progress report will be sent to the device manufacturer.

After completion of the study, the Sponsor/Principal Investigator will submit a signed clinical safety summary of the study to the IRB and to the US FDA.

### **O.3 Responsibilities of the Sponsor**

The Sponsor has the overall responsibility for the management and monitoring of this study. The sponsor may delegate some aspects of conducting and monitoring the study to other qualified individuals (such as the Principal Investigator).

The Sponsor and/or the Sponsor's designee will oversee the progress of this clinical study and ensure it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, FDA requirements, GCP, on-site monitoring and regular communication with each participating center by telephone or correspondence and applicable country specific regulatory requirements.

The Sponsor's contact details are listed below:

Julie Nangia, MD  
Assistant Professor  
Lester & Sue Smith Breast Center at  
Baylor College of Medicine  
660 MB, One Baylor Plaza,  
Houston, TX 77030  
USA

Phone: 713-798-1311

Fax: 713-798-8884

Email: [nangia@bcm.edu](mailto:nangia@bcm.edu)

The Sponsor is responsible for:

- selecting suitably qualified investigators and providing them with the information they need to conduct the study properly
- ensuring proper monitoring of the investigation
- ensuring that prior IRB and US FDA approval for the study are obtained

Additionally, the Sponsor is responsible in ensuring that the IRBs and the US FDA

are promptly informed of significant new information about the investigation. The Sponsor is responsible for compliance with applicable governmental regulations in the USA concerning the conduct of the study.

## **O.4 Responsibilities of the Investigator**

### O.4.1 Definitions

According to 21 CFR 56.102 (h) the Investigator is defined as an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

According to ISO 14155:2011, 9.2 (a), the Investigator is an individual who is qualified by education, training and experience to assume responsibility for the proper conduct of the clinical investigation in accordance with the aforementioned International Standard.

### O.4.2 Investigator Responsibilities

The Investigator(s) shall be responsible for the day-to-day conduct of the clinical investigation as well as for the safety and well-being of the human subjects involved in the clinical investigation. The Investigator(s) shall thus take responsibility for the following:

- having the resources to conduct the clinical investigation properly
- ensuring that conducting the clinical investigation will not give rise to a conflict of interest
- obtaining from the sponsor the information which the clinical investigator judges essential about the device, being familiar with this information and being well acquainted with the clinical investigation plan before signing it
- supporting the monitor and auditor, if applicable, in their activities to verify compliance with the clinical investigation plan, to perform source data verification and to correct the case report form where inconsistencies or missing values are identified
- discussing with the sponsor and the monitor any question of modification of the clinical investigation plan, and obtaining the written approval of the sponsor
- making sure that the clinical investigation plan is followed by all responsible for the conduct of the clinical investigation at his institution. Any deviation shall be documented and reported to the sponsor.
- making the necessary arrangements to ensure the proper conduct and completion of the clinical investigation
- making the necessary arrangements for emergency treatment, as needed, to protect the health and welfare of the subject
- ensuring that appropriate IRB approval has been received to start the clinical investigation at his center providing the results from the IRB to the sponsor

- informing the IRB and asking for its opinion and/or approval regarding any significant change in the clinical investigation plan that has been approved by the sponsor and the reasons for the change
- informing the IRB and, if applicable, the US FDA about any serious adverse device effects
- informing the sponsor about all adverse events and adverse device effects in a timely manner
- endeavoring to ensure an adequate recruitment of subjects
- ensuring that the subject has adequate information to give informed consent
- ensuring that informed consent is obtained and documented
- ensuring that clinical records shall be clearly marked to indicate that the subject is enrolled in a particular clinical investigation

#### Sub-Investigator

A Sub-Investigator participates in the study (e.g., obtains subject informed consent, performs clinical procedures using the investigational device, conducts subject follow-up examinations) under the direction of the Principal Investigator.

#### Research Coordinator

The research coordinator assists with clinical study activities as assigned under the direct supervision of the Principal Investigator. The duties of the research coordinator may include ensuring that the required test and evaluations are done for each subject at the required intervals, completing the data entry based on the medical records, assisting with administrative activities, and scheduling subject follow-up appointments.

Each Investigator agrees to comply with all applicable governmental regulations and the requirements of this study. Investigators who do not comply with the protocol, or conditions included in approvals granted by the reviewing committee, will have their participation in the study terminated.

## **O.5 Study Monitor**

### O.5.1 General

The Lead Center will conduct investigational site monitoring of all participating centers to ensure that all investigators are in compliance with the protocol, regulatory requirements and the Investigator's agreement. The Study Monitor will ensure that the completed CRFs and data entered into the electronic database match the Sponsor records and resolve differences. The Sponsor will evaluate circumstances where an investigator deviates from the clinical protocol and will retain the right to remove either the investigator or the investigational center from the study.

The Sponsor will review significant new information, including unanticipated adverse events and ensure that such information is provided to the study investigators and all reviewing IRBs and the US FDA as required.

### O.5.2 Study Monitor Responsibilities

Monitoring functions shall be performed in compliance with Good Clinical Practices, ISO 14155-2011, and as outlined in 21CFR§821.43(d) and 21CFR§812.46.

The major function of the Study Monitor is to observe and assess the quality of the clinical study. For this study, qualified personnel appointed by the Sponsor will serve as clinical monitors and will operate under written procedures to assure a high quality study. Thus, periodic visits are intended to assess investigators' adherence to the protocol, maintenance of records and reports, and review of source documents for accuracy, completeness, and legibility. At the close of the study, the Study Monitor may be required to make a final on-site visit to assure that all study data has been properly completed and that the investigational product has been returned to the manufacturer.

Reports of on-site visits shall be made by the Study Monitor and should include, as applicable, resolution of concerns, completion of appropriate follow-up activities, completion of assigned tasks, and corrective actions.

### O.5.3 Monitoring Visits

Site monitoring visits will follow a documented monitoring plan in order to:

- ensure Investigator adherence to the study protocol;
- ensure correct maintenance of study records;
- verify the accuracy and integrity of recorded study data.

During these visits, the Study Monitor will review the collected data against the subject charts and any additional source data, to verify its accuracy and completeness. When discrepancies are identified, only the site personnel will correct the data.

The Study Monitor will discuss any findings or concerns with the Principal Investigator and/or appropriate site study staff and make suggestions for corrective action. All discussions, suggestions, and corrective actions will be documented in the visit follow-up letter. These and other observations regarding the conduct of the study at the site will be documented in a site monitoring report that is maintained on file with the Sponsor.

## **O.6 Investigator Selection Criteria**

The Sponsor/Principal Investigator is responsible for the overall conduct of the study at all participating centers. The Sponsor/Principal Investigator must be qualified by education, training, and experience in oncology and in the administration of chemotherapy to breast cancer patients.

The following criteria will be used to select the Investigators for participation in the clinical investigation:

- Ensure a Confidentiality Disclosure Agreement is in place and filed with the Sponsor.
- The Sponsor/Principal Investigator and all participating center Investigators agree to follow the study protocol and to ensure the compliance of all Investigators, Sub-investigators and other study personnel.

- The Sponsor/Principal Investigator and all participating center Investigators have appropriate experience of chemotherapy to breast cancer patients and also clinical investigation experience.
- Each investigational center has a sufficient subject population to support the implant requirements for the study.
- The Sponsor/Principal Investigator and all participating center Investigators agree to perform all procedures and report results according to the study protocol.
- Each participating center has a designated and easily accessible Research Coordinator.
- The Sponsor/Principal Investigator will obtain IRB approval for the investigation and will obtain renewal of this approval as per local requirements.
- All investigators participating in this study will provide the Sponsor/Principal Investigator with curriculum vitae (CV) to be maintained in the Sponsor/Principal Investigator's files as documentation of appropriate previous medical experience and training for the procedures covered by the study protocol.

Additional specific training, as needed, for use of the investigational device and compliance with the study protocol will be provided by the device manufacturer.

Each Investigator agrees to comply with all applicable governmental regulations and the requirements of this study. Investigators who do not comply with the protocol, or conditions included in approvals granted by the reviewing IRB, will have their participation in the study terminated.

## **O.7 Study Initiation**

Prior to study initiation, the Sponsor/Principal Investigator must confirm the following documents are on file:

- a signed contract/clinical study agreement to include the budget
- a signed protocol signature page
- a signed original FDA Form 1572
- copies of the US FDA and IRB approval letters
- a financial disclosure form for all personnel listed on the FDA Form 1572
- a copy of the US FDA / IRB-approved Informed Consent Form
- signed and dated CVs (including current professional licenses) from all site personnel listed on the FDA Form 1572

## **O.8 Records and Reports**

### **O.8.1 General**

All records and reports related to this investigation are subject to inspection. The records from this study will be retained together in an organized, retrievable manner for a minimum of two (2) years after either the date the clinical study is terminated or the date that the records are no longer required to support regulatory approval of the device as determined by the sponsor, whichever is longer.

#### O.8.2 Review of Data Collection

The Sponsor, or the Sponsor's designee, will review all data collection for errors, omission, and discrepancies

All morbid events and related documentation will be reviewed.

#### O.8.3 Investigator Records and Reports

The Investigator is responsible for the retention, and in some cases, preparation of the records and reports cited below:

- all correspondence that pertains to the investigation;
- subject records, including but not limited to:
  - screening forms of all subjects screened for the study, whether included or excluded
  - each enrolled subject's signed Informed Consent Form
  - all relevant source documents including preoperative medical history
  - information on the condition of the subject during the investigation, the results of all diagnostic tests, a record of the exposure of each subject to the device, and records of any other therapy initiated
  - observation of adverse device effects, whether anticipated or unanticipated
  - signed copy of the study protocol
- copy of all signed Investigator agreements and the CV of each investigator at the participating centers;
- IRB approval documentation and correspondence; the Sponsor/Principal Investigator will obtain IRB approval for the investigation and will obtain renewal of this approval per local requirements.

The Investigator will arrange for the retention of the subject identification log for at least three (3) years after the final report has been signed. All other documentation related to this trial (source documents, informed consent forms, approvals) will be kept at the Lead Center no less than two (2) years after the later of the date of which the study is terminated or completed, or the date that the records are no longer required to support marketing applications.

The Investigator will not relocate or dispose of any study documents before obtaining written permission from the Sponsor/Principal Investigator.

#### O.8.4 Sponsor Records and Reports

The Sponsor/Principal Investigator will maintain the following records and reports:

- All correspondence and reports pertaining to the investigation
- Records of shipment and disposition of devices, including records of devices returned to the device manufacturer
- Signed Investigator agreements and the CV of each participating Investigator
- Records concerning adverse device effects (whether anticipated or unanticipated) and complaints

- The IRB- and FDA-approved study protocol, including all amendments or modification, and reports of prior investigations
- Pre-study visit reports
- Monitoring reports
- Copies of IRB and US FDA approvals for the study and all correspondence relating to these approvals
- Final report of the study. A preliminary report will be prepared upon obtaining adequate data to evaluate the primary efficacy endpoint. A final report will be prepared after adequate data have been collected to evaluate all secondary endpoints. When adequate data have been collected, or when the clinical study is terminated for any reason, each Investigator will be notified in writing. This letter will briefly describe the status of the study and will inform the Investigator of any remaining responsibilities he/she may have to the study. A study close-out visit may also be conducted.

### **O.9 Data Monitoring and Quality Control**

Case report forms (CRFs) will be used to collect all subject data during the study and must be fully completed for each subject and signed by the site Principal Investigator. CRFs should be completed at the first earliest opportunity after the data are obtained.

An electronic database for capture of clinical data will reside on a central server via the internet. Data entry is performed by a study coordinator on a dedicated website. All data entered is subjected to data type verification and range checking. The operator is notified of errors that may occur, and depending on the data verification sub-routines, the operator might need to resolve that error before moving to the next entry field.

The database hosting facility is a multi-level protected environment. Access is severely restricted with high-end user recognition technology. Multi-point backup of critical data is standard. Firewalls and other undisclosed technologies provide strong data security. The database is available year-round, 24 hours a day.

### **O.10 Quality Assurance Auditing and Inspection**

During the course of this clinical study, the Sponsor will appoint Quality Assurance personnel to provide audit of the administration and conduct of the study, both at the participating study centers and at the Sponsor's coordination center. These procedures are in accordance with Good Clinical Practice (GCP) to ensure that:

- complete, accurate and timely data are collected
- the study protocol requirements are followed and that all complications and adverse events are reported in a timely manner

The US FDA may also conduct audits/inspections of participating study centers and of the Sponsor. The Investigator and the relevant center personnel must set aside a reasonable amount of his/her time for study-related monitors, audits and inspection by the Sponsor, IRB, US FDA, and institution compliance and quality assurance groups, and provide adequate access to all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.).

## **O.11 Patient Confidentiality**

All information and data sent to the data management center concerning subjects of their participation in this study will be considered confidential according to local data protection laws. Only authorized data management center personnel from the regulatory authorities have the right to inspect and copy all records pertinent to this study. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the patient. The Sponsor will keep all data related to subject identification in strict confidence. Subject identity will not be revealed in any of the reports or publication resulting from this study.

## **O.12 Investigator/Study Discontinuation**

### O.12.1 Investigator Discontinuation

Any investigator will be subject to removal from the study if he/she demonstrates a pattern of non-adherence to the study protocol and/or unethical behavior.

### O.12.2 Study Discontinuation

The study may be discontinued if:

- At any time, in the opinion of the hospital ethics committee and the Principle Investigator, the study represents an unreasonable medical risk to patients
- The device manufacturer decides to terminate the study due to company considerations

## **O.13 Protocol Modifications**

### O.13.1 Protocol Deviations

The instructions and procedures specified in this protocol require diligent attention to their execution. The Investigator will not deviate from the protocol without the prior written approval of the Sponsor except in medical emergencies in which proper care for the protection, safety and well-being of the study subject requires alternative treatment, or in unforeseen, isolated instances where minor changes are made that will not increase the subject's risk or affect the validity of the study. The Sponsor must be notified of all such deviations within two (2) working days of each occurrence.

Periodic monitoring of protocol compliance will be performed for each participating center. The Sponsor holds the right to halt enrollment in centers deemed to have excessive protocol compliance issues.

### O.13.2 Protocol Amendments

The approved study protocol cannot be amended by the investigators, or study personnel, without first obtaining review and documented written approval of the Sponsor. The Sponsor will hold the responsibility of notifying all Investigators of all proposed changes to the protocol. The Sponsor will be responsible for forwarding any changes to the IRBs and for notifying all involved study personnel of approved changes to the protocol.



Medically significant amendments to the protocol (i.e. those which affect the rights, safety, or welfare of the human subjects involved in the investigation, the scientific soundness of the investigational plan, the validity of data or information resulting from the completion of an approved protocol, or the relationship of likely patient risk to benefit relied upon to approve a protocol or if they are otherwise significant inclusion of new categories of patients, etc.) may not be instituted prior to regulatory approval by the IRBs and the US FDA.

#### **O.14 Supply and Disposition of Devices**

Orbis Paxman Hair Loss Prevention Systems and associated accessories (including cooling caps and cap covers) will be supplied to the investigational site, free of charge and prior to investigation initiation.

These devices are authorized for use only in subjects enrolled under this protocol and under the supervision of the investigator. Furthermore, the scalp cooling devices and accessories will be clearly marked as investigational products to prevent unauthorized use. Upon study completion all devices will be returned to the device manufacturer.

#### **O.15 Training**

The training of appropriate participating center personnel will be the responsibility of the Sponsor. To ensure proper device usage, uniform data collection and protocol compliance, the Sponsor, in conjunction with the device manufacturer, will present a formal training session to study site personnel which will review:

- The instructions for use of the Orbis Paxman Hair Loss Prevention System
- The study protocol
- Techniques for the identification of the eligible patient;
- Instructions on in-hospital data collection
- Methods for soliciting data from patients
- Regulatory requirements

#### **O.16 Meetings**

At least annually, the study's Data Safety Monitoring Board (coordinated by the Dan L. Duncan Cancer Center office) will review and monitor study progress, adverse events, safety and other data from this trial. Information that raises any questions about participant safety or protocol performance will be addressed with the Principal Investigator, statistician and study team members. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the trial. Any events that are reportable to the IRB should be simultaneously reported to the DSMB Chair.

After study completion, annually for 5 years, a report will be sent to the FDA with information on breast cancer recurrence, site of first recurrence, and survival.

### **P) Statistical Considerations**

### **P.1 Study Design**

We propose to conduct a multi-center parallel group, 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.

Data collected in this clinical investigation will be used to support a premarket approval (PMA) application to the US FDA for approval to market the Orbis Paxman Hair Loss Prevention System in USA, for the intended use of reduction of chemotherapy-induced alopecia in stage I-II breast cancer patients who are receiving neoadjuvant or adjuvant chemotherapy with anthracycline- or taxane-based drug regimens.

### **P.2 Sample Size/Accrual Rate**

The trial will require 213 response evaluable subjects and we expect to consent at most 325 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 (Table 2).

Table 2 – Power to detect differences under difference scenarios

	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

The study will require 213 response evaluable subjects and ~325 consented patients. Considering a 22% drop-out rate, we expect to accrue 273 subjects so that we will have 213 evaluable subjects at the final analysis. If we also consider a 16% screen failure, we will need to consent 325 subjects for this study.

### **P.3 Interim Analysis**

One interim analysis will take place about two-thirds of the way through the study after 95 patients are enrolled to the cooling group and 47 patients 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% patients 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.

Looks	Accumulated 'Information'	Evaluable N (cooling group)	Evaluable N (no cooling group)	Superiority Boundary (Z value) <sup>1</sup>	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.

#### **P.4 Stratification Factors**

Randomization will be stratified by two major chemotherapy types (anthracycline or taxane) and up to 10 centers with total of up to 20 strata, and employ permuted blocks with block size of 6: 4 in the experimental arm and 2 in the control arm.

#### **P.5 Analysis of Primary Endpoints**

Descriptive and summary statistics will be computed for demographic and clinical data of all subjects enrolled in each treatment group at each center. A table of baseline subjects' demographic and clinical data, grouped by major chemotherapy type and center will be reported. Since randomization will be stratified by major chemotherapy type and center, each center will contribute the same number of subjects to each treatment group. A non-significant test for interaction between the treatment effect and center will be performed to confirm the consistency of the treatment effect. Summary table will also be provided for the status of the protocol treatment such as the number of subjects who stop the scalp cooling earlier and the reason of stopping.

The primary efficacy analysis will be based on the intent to treat (ITT) population, defined as eligible and randomized subjects who undergo at least one cycle of chemotherapy. 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 who is blinded to study treatment. The rates of hair preservation in the scalp cooling group and the control group will be calculated and summarized. The hypothesis testing for the primary effectiveness endpoint is  $H_0: p_t = p_c$  [i.e., proportion of women in the treated group who have CTCAE v4.0 grade 0 or 1, equals to the proportion of women in control group who have CTCAE v4.0 grade 0 or 1], versus  $H_a: p_t \neq p_c$  testing for 2-sided alpha of 5% level of significance. 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% confidence interval will be reported.

The primary safety endpoint is anticipated adverse device effects specified in section M.4. All study subjects who begin the first cycle of chemotherapy will be evaluable for adverse events. All adverse device effects, including serious adverse device effect and unanticipated adverse device effect, will be described and summarized. The primary safety analysis will be based on incidence rates of adverse device effects and their exact 95% confidence intervals.

The primary efficacy and safety endpoints will be used to obtain marketing approval for the Orbis Paxman Hair Loss Prevention System.

### **P.6 Analysis of Secondary Endpoints**

The secondary effectiveness and safety endpoints analysis will be based on the intent to treat (ITT) population, defined as eligible and randomized subjects who undergo at least one cycle of chemotherapy.

Data of hair preservation assessed by subject self and oncologist, and the use of wig or head wrap will be analyzed using descriptive statistics with rates and their 95% confidence intervals. Comparison of secondary effectiveness endpoints between the scalp cooling group to the control group will not be performed.

Lack of compliance is also seen as a threat to evaluation of the efficacy of the device, and high rates of non-compliance will reduce clinical utility. Compliance will be assessed by proportion of prescribed time (defined as 30 minutes pre-chemotherapy + duration of chemotherapy + 90 minutes post-chemotherapy) to the time that the device is worn. In the event of high rates of noncompliance, exploratory analyses will attempt to discern potentially modifiable factors associated with noncompliance.

Improved quality of life as a result of reduced hair loss is a primary motivator for developing the Paxman Scalp Cooling device. Quality of life 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 C-30, HADS and BIS. Subjects will be evaluated at multiple time points and data will be analyzed using descriptive methods with median and inter quartile range to assess the effect of treatment group and alopecia status on functioning, quality of life and depression.

Subject-reported comfort is categorized into 5 levels from very comfortable to very uncomfortable. The comfort data will be summarized using median and range.

A post-market approval follow-up for safety data will be done yearly for 5 years looking at time to first recurrence, overall survival, site of first recurrence, and incidence of isolated scalp metastasis. This will be collected during routine clinical observation. A report of this will be sent to the FDA annually for 5 years. Time to first recurrence and overall survival will be estimate using the Kaplan-Meier survival curve median and 95% confidence interval. Site of first progression will be tabulated. Incidence rate of isolated scalp metastasis and its 95% confidence interval will be estimated and will be compared to the scalp metastasis rate reported in NSABP (see Background B.4).

## **P.7 Reporting and Exclusions**

**Evaluable for response.** All eligible study subjects who receive at least one cycle of chemotherapy will be evaluable for hair-preservation response. Participants 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. Any missing questionnaire assessment will be handled as last observation carried forward.

**Evaluable for adverse events.** All study subjects who begin the first cycle of chemotherapy will be evaluable for adverse events.

## **Q) Publication**

Publication or public presentation of the overall clinical study results from this study requires the prior written approval of the device manufacturer.

It is understood that any manuscript or releases resulting from the collaborative research will be circulated to all participating sites prior to submission for publication or presentation.

## REFERENCES

- Aaronson, N. K., S. Ahmedzai, et al. (1993). "The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology." Journal of the National Cancer Institute 85(5): 365-376.
- American Cancer Society, e. a. (2011). "What are the key statistics about breast cancer?" Retrieved 9/22/11 from <http://www.cancer.org/Cancer/BreastCancer/DetailedGuide/breast-cancer-key-statistics>.
- Benjamin, B., Ziginskis, D., Harman, J. & Meakin, T. (2002). "Pulsed electrostatic field (ETG) to reduce hair loss in women undergoing chemotherapy for breast cancer: A pilot study." Psycho-Oncology 11: 244-248.
- Breed, W. (2004). "What is wrong with the 30-year-old practice of scalp cooling for the prevention of chemotherapy-induced hair loss? ." Support Care Cancer 12: 3-5.
- Breed, W., van der Hurk, CJ, Peerbooms, M (2011). "Presentation, impact and prevention of chemotherapy-induced hair loss, scalp cooling potentials and limitations." Expert Rev Dermatol 6(1): 109-125.
- C. van den Hurk, e. a. (2011). Multicenter results of scalp cooling to prevent chemotherapy-induced alopecia in 1500 breast cancer patients. . San Antonio Breast Cancer Conference. San Antonio, TX, AACR. Poster P5-20-08.
- Christodoulou, C. T., G, Galani, E, Skarlos, DV (2006). "Scalp metastases and scalp cooling for chemotherapy-induced alopecia prevention." Ann Oncol 17(2): 350.
- Fayers, P., N. Aaronson, et al. (2001). The EORTC QLQ-C30 Scoring Manual (3rd Edition). Brussels, European Organisation for Research and Treatment of Cancer.
- Grevelman, E. B., WP (2005). "Prevention of chemotherapy –induced hair loss by scalp cooling." Ann.Oncol 17(2): 352-358.
- J Lemieux, e. a. (2011). Survival in women with breast cancer who used or did not use scalp cooling in the neoadjuvant/adjuvant setting. San Antonio Breast Cancer Symposium San Antonio, TX, AACR. Poster P5-20-06.
- Kaderman, C., Kaderman, R., & Toonkei, R (1999). "The psycho-social aspects of breast cancer." Nurse Practitioner Forum 10(3): 165-174.
- Kornblith, A. (1998). "Psychosocial adaptation of cancer survivors. ." Holland JC ed. Psycho-Oncology. Holland JC ed. : 223-241.
- Kroenke, K., R. L. Spitzer, et al. (2001). "The PHQ-9: validity of a brief depression severity measure." Journal of general internal medicine 16(9): 606-613.
- Lemieux, J., Amireault, C, Provencher, L, Maunsell, E (2009). "Incidence of scalp metastases in breast cancer: A retrospective cohort study in women who were offered scalp cooling." Breast Cancer Res Treat 118: 547-552.
- Lemieux, J., Maunsell, E., & Provencher, L (2008). "Chemotherapy-induced alopecia and effects on quality of life among woman with breast cancer: A literature review." Psycho-Oncology 17: 317-328.
- Llescher LJ, W.-M. D., Laigh SA, et al (1989). "Surviving adult cancers. Part 1: Physiologic effects." Ann Intern Med 111(411-432).
- Massey, C. (2004). "A multicentre study to determine the efficacy and patient acceptability of the Paxman Scalp Cooler to prevent hair loss in patients receiving chemotherapy." European Journal of Onc Nursing 8: 121-130.

- Mols, F., van den Hurk, CJ, Vingerhoets, AJJM, & Breed, W (2009). "Scalp cooling to prevent chemotherapy-induced hair loss: Practical and clinical considerations." Support Care Cancer 17(181-189).
- Rugo, H. M., SA (2010). Expert statement on scalp cooling with adjuvant/neoadjuvant chemotherapy for breast cancer and the risk of scalp metastases.
- Sneeuw KCA, A. N., Yarnold JR, et al (1992). "Cosmetic and functional outcomes of breast conserving treatment for early stage breast cancer. 2: Relationship with psychosocial functioning." Radiother Oncol 25: 160-166.
- Spaeth, D., Luporsi, E, Weber, S, et al (2008). "Efficacy and safety of cooling helmets for the prevention of chemotherapy-induced alopecia: A prospective study of 911 patients." J Clin Oncol 26 (May Suppl)(abstract 9564).
- Sugarbaker PH, B. I., Rosenberg SA, Gianola FJ (1982). "Quality of life assessment of patients in extremity sarcoma clinical trials." Surgery 91: 17-23.
- Trueb, R. (2009). "Chemotherapy-induced alopecia." Semin Cutan Med Surg 28(1): 11-14.
- Van den Hurk, C., Mols, F, Vingerhoes, AJ, Breed, WP (2010). "Impact of alopecia and scalp cooling on the well-being of breast cancer patients." Psycho-Oncology 19: 701-709.
- Wang, J., Ku, Z, Au, JL (2006). "Protection against chemotherapy-induced alopecia." Pharm Res 23(11): 2505-2514.

## **APPENDICES**

- A) Orbis Paxman Hair Loss Prevention System**
- B) CTCAE v4.0 Grading Scale and Alopecia Pictorial Tool**
- C) Comfort Scale**
- D) QOL Questionnaires**



## **Appendix A: Orbis Paxman Hair Loss Prevention System**

### **DEVICE DESCRIPTION**

The Orbis Scalp Cooler (newer generation of Paxman Scalp Cooling System) is a free-standing, electrically-powered, mobile refrigeration unit which circulates a refrigerated liquid coolant, at a pre-set temperature and flow rate, through a cooling cap which is attached to, and covers, the top of the patient's head.

Two models of the Paxman Cooling System also known as the Orbis Scalp Cooler are available:

- 1) Orbis 1 - designed for scalp cooling of one patient at a time; and,
- 2) Orbis 2 - designed for scalp cooling of up to 2 patients at a time.

Photographs of the front and rear aspects of the Orbis 2 model are provided in figures 1 and 2 (on pages 4 and 5). The Orbis 1 model differs from the Orbis 2 model only in that the former features one pair of coolant lines for attaching and treating one patient at a time, instead of two pairs of coolant lines. Only the Orbis 1 device will be used in this study.

### **Technological Characteristics**

#### **Hardware Configuration**

The Orbis Scalp Cooler is composed of the following components:

- Main unit
- Touch screen controller
- Software
- Coolant lines
- Cooling caps and covers
- Coolant

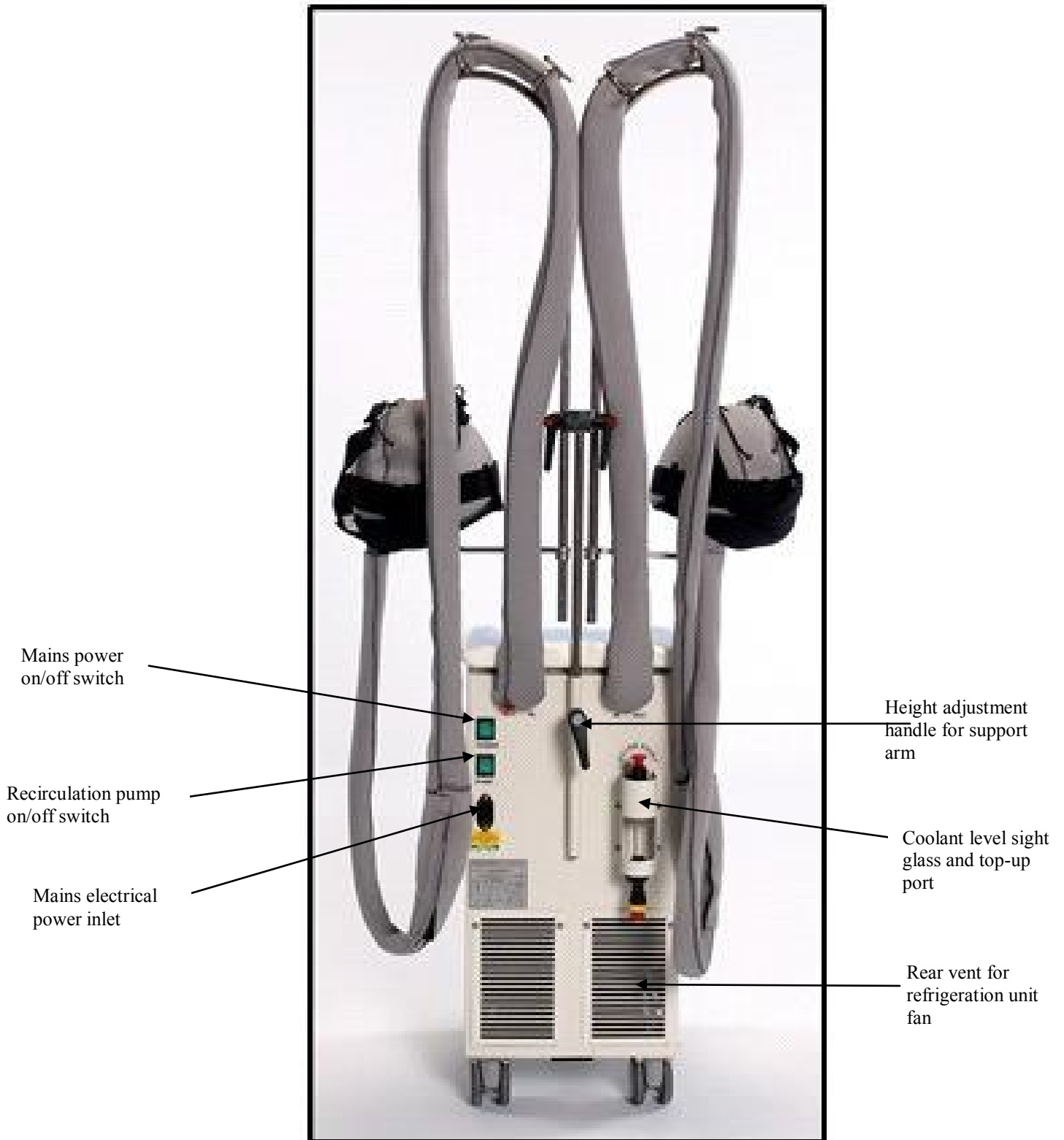
#### **Main Unit**

This comprises a plastic-fronted, coated steel cabinet which contains the refrigeration unit, coolant tank, recirculation pump, mains power and fuse block, microprocessor control unit; a touch-screen user interface is built in to the plastic front cover of the unit. The back of the unit features the mains power inlet, mains power and recirculation on/off switches, a sight glass for visualizing the level of liquid coolant in the coolant tank and a capped top-up port for addition of liquid coolant. The unit is fitted with 4 swivel castors – one on each corner of its base – to provide for unit mobility; it also has a lifting handle on each side to enable the unit to be lifted over obstacles (should this be required). The two castors at the front of the unit feature a foot-operated brake mechanism to allow the unit to be secured in position prior to its use. The unit also features a height-adjustable, stainless steel support arm for the coolant lines.

Figure 1: Photograph of front aspect of Orbis Scalp Cooler model Orbis 2



Figure 2: Photograph of rear aspect of Orbis Scalp Cooler model Orbis 2



Physical characteristics:

Height: 25.2 inches

Extended height (i.e. with support arm fully extended): 64.7 inches

Width: 12.6 inches

Depth: 16.5 inches

Weight: 64.9 lbs.

Electrical characteristics:

Power requirements: 110 - 120v 60Hz single phase

Input rating: 432W

Current: 8.0A (start) / 3.6A (running)

Classification (under IEC 60601-1 ed.3.0 b: 2005): Class I

Description of components

Refrigeration unit

This is composed of standard refrigeration components – i.e. a compressor, condenser, evaporator and cooling. The refrigerant used is R-134a (1,1,1,2-tetrafluoroethane) – a chlorofluorocarbon-free, inert gas, which has been used for domestic refrigeration and automobile air-conditioners since the 1990s.

Coolant tank

This is a sealed tank of 2.5 liter capacity, manufactured from AISI grade 304 stainless steel, in a fully welded construction. Tank inlets and outlets are located in the top of the reservoir. The coolant tank is not pressurized and is insulated.

Recirculation pump

A centrifugal mechanically coupled pump is mounted in the top plate of the coolant tank. The pump helps achieve an even temperature throughout and also pumps the coolant, via the coolant lines, to the cooling cap and back to the coolant tank.

The Orbis 1 is fitted with a 30W pump (Totton Pumps, model SPC-51); the Orbis 2 is fitted with a 60W pump (Totton Pumps, model SPC-42). Both are semi-submersible column pumps with the column and pump body constructed in glass-filled acrylonitrile butadiene styrene (ABS), with an IPX4 motor housing, polypropylene impellers, and a stainless steel shaft and nylon agitator. Both pumps operate at a flow rate of 1.5 liters/minute.

Touch screen controller unit

This comprises 3 printed circuit boards mounted beneath, and connected to, a touch screen. The primary function of the control unit is to monitor and control the temperature of the coolant, monitor the coolant flow rate and provide for user initiation and time monitoring of the scalp cooling process.

### Touch screen

This is a 5.7-inch, transmissive, color, TFT-LCD, with a display resolution of 320 x 240 pixels (4:3 aspect ratio). The touch screen is a resistance type with an antiglare surface.

### Microprocessor unit

The printed circuit boards are a bespoke design, manufactured specifically for Paxman Coolers. The main board incorporates a Microchip Technology Inc. Peripheral Interface Controller (PIC) and is programmed in C general purpose computer programming language.

### Coolant lines

Refrigerated coolant is circulated through the cooling cap and back to the coolant tank in the main unit via a pair of 2-metre long coolant lines – one line to transport the coolant from the unit to the cap and one line to return coolant from the cap to the main unit. Each coolant line is composed of silicone tubing (the silicone used is medical grade, USP Class VI, Shore A 60) with an outer diameter of 0.315 inches and an inner diameter of 0.197 inches. The tube is encased in closed cell, elastomeric, nitrile rubber insulation material (Armaflex<sup>®</sup>). Each end of the coolant line terminates in a push-fit quick release coupling composed of polypropylene (John Guest Speedfit<sup>®</sup>). A male connector is used on one line and a female connector on the other. The couplings are fitted with rapid action non-return valves, which are designed to prevent leakage of residual coolant from the tubes following disconnection from the unit.

Each pair of coolant lines is covered with a neoprene shroud, the purpose of which is to absorb any condensation which forms on the outer surfaces of the coolant lines.

### Cooling cap

The cooling cap is manufactured from extruded, clear silicone tubing (the silicone used is medical grade, USP Class VI, Shore A 40) with an outer diameter of 0.315 inches and an inner diameter of 0.236 inches. The tubing is formed into a cap shape by gluing the spiral-wound tubing together using a one-part, solvent-free, USP Class VI silicone adhesive (MED-1000, Nusil Technology LLC).

Caps are available in 5 different sizes (extra small, small, medium, large and extra-large) to account for variation in patient head size. Each cap has a color-coded apex for ease of size identification:

- extra small = yellow
- small = red
- medium = purple
- large = blue
- extra-large = green

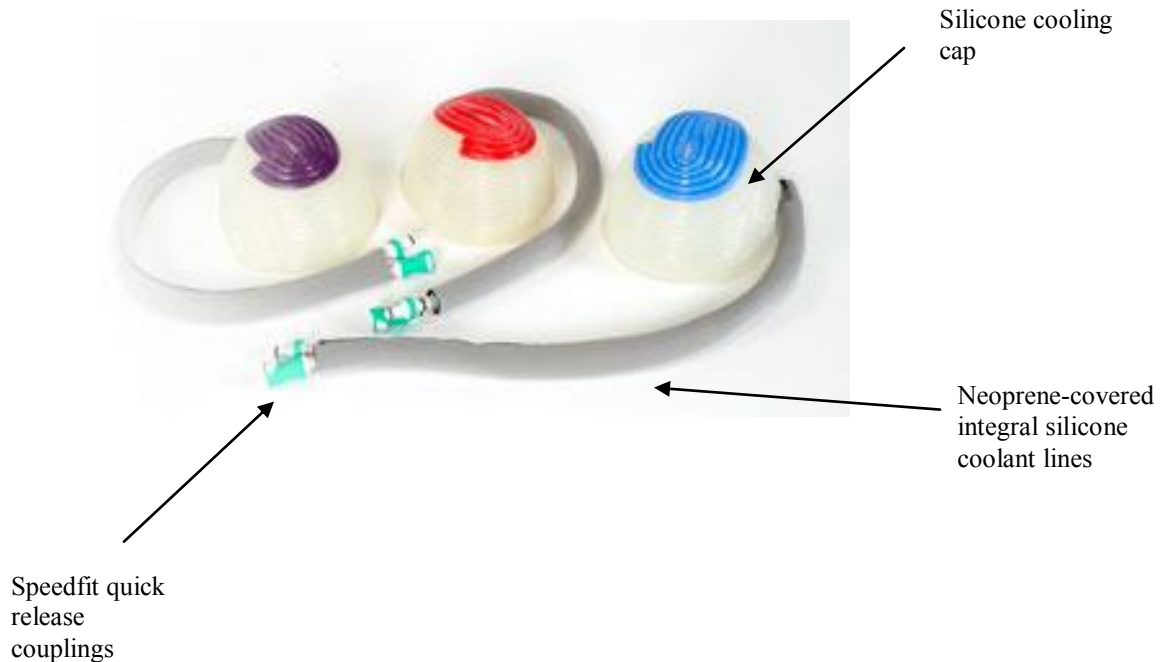
A photograph of the cooling caps is shown in Figure 3.

The cooling caps are supplied with integral outward and return cooling lines composed of the same silicone material as the caps. These two cooling lines terminate in one

male and one female quick release coupling, for connection to the corresponding connectors on the outward and return coolant lines.

The silicone cap is supplied non-sterile and is reusable.

Figure 3: Photograph of Orbis Scalp Cooler Cooling Caps



#### Cap cover

Each silicone cooling cap comes supplied with a neoprene cap cover which is designed to be worn over the cap and is required to secure the cap in the correct position on top of the patient's head. The cap cover incorporates an adjustable chin strap and adjustable circumferential strap to enable the cover to be securely fastened onto the patient's head so that the cooling cap maintains optimum coverage of, and contact with the scalp, for the duration of the scalp cooling procedure. The neoprene cap cover also absorbs any condensation which may form on the exterior surface of the cap.

Cap covers are available in 5 sizes, corresponding to the available cap sizes. The cap cover is supplied non-sterile and is reusable.

#### Coolant

The coolant used in the Orbis Scalp Cooler is a specially designed solution designated OrbisC – it is an aqueous solution of potassium formate and corrosion inhibitors (30% – 70% w/v), colored with a purple food-grade, vegetable dye for ease of visualization. The coolant has a density of 1.17 – 1.34 g/cm<sup>3</sup>, a pH between 10.6 and 11.4 and freezes solid at - 15°C.

The coolant is designed to remain within the circulation system and does not come into direct contact with the patient or user during normal operation.

### Software Configuration

The software within the touch screen controller unit is written in C Programming language and serves three functions:

- a) the touch screen displays a menu-driven, graphical user interface (GUI) which provides information to the user concerning the operational status of the scalp cooling unit; it also prompts the user to initiate certain actions relating to the scalp cooling procedure and provides a timer count-down function (for scalp cooling sessions). The software GUI does not, however, directly control the scalp cooling process. An example of the GUI home screen (system powered on and at operating temperature but recirculation pump not yet switched on) is shown in figure 4.

Figure 4: Photograph of Orbis Scalp Cooler Touch Screen Displaying GUI



- b) the software monitors the temperature of the coolant in the coolant reservoir, interpreting an incoming resistance signal from the temperature probe in the coolant tank using a standard mathematical algorithm which accounts for non-linearity of the probe over a known temperature range. The software also electronically switches the compressor on or off in response to the measured temperature, when pre-set upper and lower temperature limits ( $-5^{\circ}\text{C}$  and  $-4^{\circ}\text{C}$ ) are recorded. The software also monitors the flow rate of the liquid coolant returning to the coolant tank via signals received from turbines placed in the coolant return tube;
- c) in the event of pre-set limits for coolant temperature and flow rate being exceeded, the software displays an appropriate visual cue on the GUI and sounds an audible buzzer to alert the user to the situation, and - under certain conditions - the software will shut down the unit.

### Principle of Operation

The Orbis Scalp Cooler is designed to reduce the epicutaneous temperature of a patient's scalp to between 16°C and 19°C. This is achieved by circulation of a refrigerated coolant through a silicone cap attached to the patient's head, covering and in contact with the entire scalp area. The reduction in temperature is designed to effect both vasoconstriction of the blood vessels in the scalp which supply the hair follicles and also a reduction in the metabolic rate of the hair follicle cells, both of which mechanisms are intended to reduce the damage caused to the scalp hair follicle cells by cytostatic chemotherapy agents in the blood.

Scalp cooling is initiated at least 30 minutes prior to chemotherapy administration and is maintained continuously thereafter during administration of the chemotherapy agent and also for a period of time after the agent has been administered. The duration of post-infusion scalp cooling varies from 45 minutes to 2 hours and is based on the known pharmacokinetics of the chemotherapy treatment administered. Recommended post-infusion cooling times for a variety of commonly used chemotherapy treatments, but for the purposes of this study have been standardized at 90 minutes. These regimens are designed to ensure that adequate cooling of the scalp occurs during the time when the concentration in the blood of the cytostatic agent is at its peak.

As indicated above, effective scalp cooling relies on good contact between the inner surfaces of the cooling cap and the patient's scalp. As such, prior to the first scalp cooling procedure, each patient undergoes a cooling cap fitting with a healthcare professional trained in use of the Orbis Scalp Cooler – this fitting process is necessary to ensure that the most appropriate size of cooling cap is selected. For optimum cooling, the cap must both fit snugly onto the head at the crown and also cover the entire scalp area down to the hairline. Effective scalp cooling over the entire scalp is only achieved with the combination of correct size of cooling cap and correct size of cooling cap cover; the cover – with its adjustable straps – is necessary to ensure that the cooling cap is maintained securely and comfortably in the correct position on the patient's head for the duration of the scalp cooling process. For some patients, the cap fitting process will simply involve the selection of the most appropriate size cooling cap and corresponding cap cover. For patients whose head size does not correspond to one of the five available cooling cap sizes, a combination of the larger size cooling cap and smaller size cover is used to obtain the required cooling cap contact with the scalp.

Prior to scalp cooling, the cooling cap is always attached to the patient's head with the cap disconnected from the coolant lines. Before placing the cooling cap on the patient's head, it is placed inside the appropriate size of cap cover and manually pressed into position against the inner surface of the cover, such that the entire cooling cap is within the cover. The cooling cap and cover are then placed onto the patient's head such that the cap is on straight and covers the patient's entire scalp to the hairline. The cover chin-strap and circumferential straps are then adjusted to achieve a snug fit of the cooling cap to the scalp, which is also comfortable for the patient. The healthcare professional then checks the fit of the cooling cap to ensure good contact all over the scalp – particularly at the crown and hairline. Once this is done, the patient is ready to begin scalp cooling and the cooling cap outward and return tube quick release connectors are connected to the corresponding connectors on the distal end of the coolant lines.



Powering on the system using the power switch on the back of the main unit activates the refrigeration unit, which then reduces the temperature of the coolant in the coolant tank to between  $-5^{\circ}\text{C}$  and  $-4.0^{\circ}\text{C}$  through standard refrigeration technology. Once this temperature is attained, the coolant temperature in the coolant tank is maintained within this temperature range by the system software, which monitors the coolant temperature from an electronic sensor in the reservoir and electronically switches off the refrigeration compressor when the temperature reads  $-4.0^{\circ}\text{C}$  and switches on the compressor when the sensor temperature reads  $-3.0^{\circ}\text{C}$ .

Once the pre-set coolant temperature is reached, the pump is activated using a separate switch on the rear of the main unit. This causes the refrigerated coolant to be pumped from the reservoir at a pre-set constant flow rate via the outward coolant line through the cooling cap and back to the reservoir via the return coolant line. Coolant flow rate is monitored via flow turbines located in the return tube. In the event of a low coolant flow rate ( $< 0.6 \text{ L/min}$ ) being detected (which may indicate coolant loss, or kinking of one of the coolant lines), the software displays a warning message on the touch screen and sounds a buzzer to alert the user.

The touch screen controller provides feedback to the user concerning the status of the Orbis Scalp Cooler as it relates to achievement of the pre-set temperature of the coolant, operation of the recirculation pump and connection of a cooling cap to the system. The software also prompts the user to initiate scalp cooling for at least 30 minutes prior to administration of the chemotherapy agent and allows the user to select a pre-set post-administration scalp cooling time, which should be appropriate to the type of chemotherapy agent used. The software also provides a timer count-down function for the initiated pre- and post-infusion cooling procedure. At the end of the pre-set time, a message is displayed on the touch screen and a buzzer sounds to alert the user to the fact that the scalp cooling time is complete.

Following completion of scalp cooling, the recirculation pump is switched off and the cooling cap and cover are then removed from the patient's head.

## **2.1 Development and Marketing History**

The Orbis Scalp Cooler range (incorporating models Orbis 1 and models Orbis 2) was launched commercially in Europe in 2010; it represents the latest design iteration of liquid coolant-based, continuous scalp cooling devices manufactured by Paxman Coolers, which are indicated for use to reduce of chemotherapy-induced alopecia in patients who are undergoing chemotherapy for the treatment of solid tumors, such as breast cancer. To date, 150 units of the Orbis Scalp Cooler have been sold.

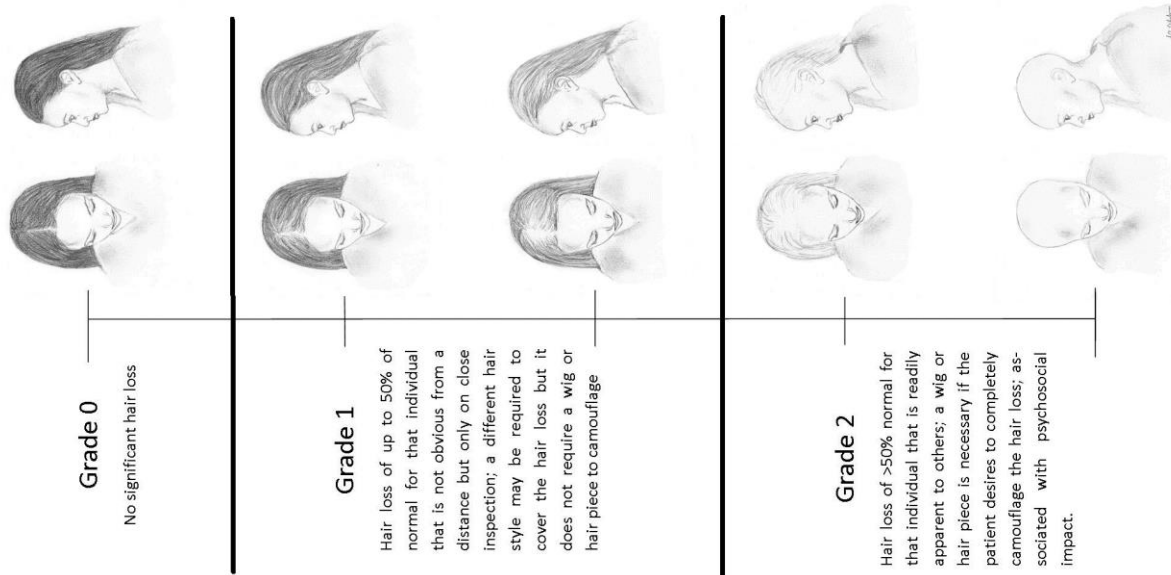
The design of the Orbis Scalp Cooler is based heavily on the previous PSC range (comprising models PSC1 and PSC2) of Paxman Cooler scalp cooling devices, which have been marketed commercially since 1997, with a total of 928 units sold to date.

The Orbis Scalp Cooler models use the same principle of operation as the PSC devices, and – in many cases – the same components as are used in the PSC devices. As such, the Orbis Scalp Cooler is essentially a design modification of the PSC device, featuring cosmetic and functional design changes which are intended to further improve both the user's and the patient's experience of scalp cooling.



## Appendix B

### Alopecia (Hair Loss) Pictorial Tool



Artist is Ashley Whittington  
 Grading from the CTCAE v4.0.  
 © 2002-2013, Baylor College of Medicine. All rights reserved.

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.

## Appendix C

Comfort Scale used in the Massey study (Massey 2004). Patients will also be asked if they find the procedure to be acceptable or unacceptable as was done in the Massey study.

<b>How comfortable were you in general throughout the scalp-cooling period?</b>
Very Comfortable
Reasonably Comfortable
Comfortable
Uncomfortable
Very uncomfortable

## **Appendix D: QOL Questionnaires**

1. EORTC QLQ-30
2. HADS
3. BIS

### EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

--	--	--	--	--

Your birthdate (Day, Month, Year):

--	--	--	--	--	--	--	--	--	--

Today's date (Day, Month, Year):

31

--	--	--	--	--	--	--	--	--	--

	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 <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> 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

Please go on to the next page

**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 in 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 <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> 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 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



### Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.  
 Don't take too long over you replies: your immediate is best.

D	A		D	A	
		<b>I feel tense or 'wound up':</b>			<b>I feel as if I am slowed down:</b>
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		<b>I still enjoy the things I used to enjoy:</b>			<b>I get a sort of frightened feeling like 'butterflies' in the stomach:</b>
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		<b>I get a sort of frightened feeling as if something awful is about to happen:</b>			<b>I have lost interest in my appearance:</b>
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		<b>I can laugh and see the funny side of things:</b>			<b>I feel restless as I have to be on the move:</b>
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		<b>Worrying thoughts go through my mind:</b>			<b>I look forward with enjoyment to things:</b>
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		<b>I feel cheerful:</b>			<b>I get sudden feelings of panic:</b>
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		<b>I can sit at ease and feel relaxed:</b>			<b>I can enjoy a good book or radio or TV program:</b>
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

**Scoring:**

Total score: Depression (D) \_\_\_\_\_ Anxiety (A) \_\_\_\_\_

0-7 = Normal

8-10 = Borderline abnormal (borderline case)

11-21 = Abnormal (case)



## Body Image Scale (BIS)

		Not at all	A little	Quite a bit	Very Much
1	Have you been feeling self-conscious about your appearance?				
2	Have you felt <u>less</u> physically attractive as a result of your disease or treatment?				
3	Have you been <u>dissatisfied</u> with your appearance when dressed?				
4	Have you been feeling <u>less</u> feminine/masculine as a result of your disease or treatment?				
5	Did you find it difficult to look at yourself naked?				
6	Have you been feeling <u>less</u> sexually attractive as a result of your disease or treatment?				
7	Did you avoid people because of the way you felt about your appearance?				
8	Have you been feeling the treatment has left your body less whole?				
9	Have you felt <u>dissatisfied</u> with your body?				
10	Have you been <u>dissatisfied</u> with the appearance of your scar(s)?				