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Clinical Performance, Efficacy and Safety of the DigniCap™ System, a Scalp Hypothermia System, in Preventing Chemotherapy Induced Alopecia in Patients with Early Stage Breast Cancer

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SYNOPSIS

TITLE	Clinical Performance, Efficacy and Safety of the DigniCap™ System, a Scalp Hypothermia System, in Preventing Chemotherapy Induced Alopecia in Patients with Early Stage Breast Cancer
PHASE	IDE PMA Study
BACKGROUND	<p>Alopecia is a non-life threatening complication of the majority of effective adjuvant chemotherapy regimens for early stage breast cancer. It has a significant impact on quality of life and affects decisions regarding the risks and benefits of treatment.</p> <p>Scalp cooling prevents hair loss through vasoconstriction, and thus a lower concentration of chemotherapy is delivered to the scalp. Scalp cooling also decreases cellular uptake of drugs and decreases the intra-follicular metabolic rate.</p> <p>We propose to study the safety and efficacy of the DigniCap™ System in women undergoing standard adjuvant chemotherapy for early stage breast cancer at 5 centers in the United States. The study design is a two arm study with a non-randomized active arm and a concurrent non-randomized control group. We believe that scalp cooling, now commonly used around the world outside of the U.S., is an important tool that should be studied in American women.</p>
OBJECTIVES	<p>The overall objective is to assess the clinical performance, efficacy and safety of a Scalp Hypothermia System in breast cancer patients receiving specific chemotherapy treatments that, unless counteracted by simultaneous hypothermia treatment, result in hair loss.</p> <p>Primary Objective: To assess the ability of the DigniCap™ System to prevent hair loss in women receiving specific chemotherapy regimens for early stage breast cancer. Efficacy will be measured by assessment of hair loss up to 4 weeks (3-6 week window) after the completion of the last chemotherapy cycle by patient self-assessment of standardized photographs using the Dean scale by patients in the treatment and control groups</p> <p>Secondary Objectives: To assess safety of the DigniCap™ System in women receiving specific chemotherapy regimens for early stage breast cancer.</p> <p>To assess the incidence of scalp metastases in women who used the DigniCap™ System annually for a total of five years after</p>

	<p>completion of chemotherapy</p> <p>To assess tolerability of the Digni-Cap™.</p> <p>To evaluate hair loss and recovery as assessed by the patient during and following chemotherapy using the alopecia self-report.</p> <p>To evaluate hair re-growth at 3 and 6 months after completion of chemotherapy as assessed by the patient using the Hair Re-growth Follow Up Survey.</p> <p>To assess patient quality of life and satisfaction with hair during and after treatment with the DigniCap™ System.</p> <p>To assess the impact of hair loss on treatment decisions.</p>
STUDY ENDPOINTS	<p>Primary endpoint: Success of the DigniCap™ System to prevent hair loss, defined as a maximum Dean score of ≤ 2 using standardized photographs graded by the patient up to 4 weeks after the last chemotherapy treatment, in at least 50% of patients enrolled in the treatment group with a lower bound of the 95% CI greater than 40%, and statistical superiority over a concurrent control group.</p> <p>Secondary endpoints: Safety as determined by spontaneous reporting of adverse events and as negative scalp changes determined by physical examination.</p> <p>Safety defined as the number of scalp metastases over a 5-year period, compared to the incidence in an untreated control group.</p> <p>Tolerability is defined as the percentage of patients who complete all planned cycles of chemotherapy do so using the DigniCap™ System.</p> <p>Patient assessment of hair loss by the alopecia self-report at each chemotherapy.</p> <p>Hair re-growth assessed by the patient using the Hair Re-growth Follow Up Survey.</p> <p>Quality of life as measured by the EORTC-QLQ-BR23 quality of life questionnaire and a Body Image Scale.</p>

	Assessment of the impact of hair loss on breast cancer treatment decisions at 6 months after completion of chemotherapy.
PATIENT POPULATION AND SAMPLE SIZE	<p>110 women with stage I or II breast cancer scheduled to receive at least 4 cycles of specific anthracycline or taxane based chemotherapy regimens in the adjuvant or neoadjuvant setting will be enrolled to ensure a sample size of at least 100 patients that complete the study.</p> <p>At each site an age- and treatment regimen-matched control group of up to 30 total patients will be enrolled; hair loss will be assessed during treatment using the same procedures as the treatment group.</p>
INVESTIGATIONAL PRODUCTS:	The DigniCap™ System
PATIENT SELECTION CRITERIA Treatment Group	<p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. Female patients ≥ 18 years of age 2. Documented diagnosis of stage I or II breast cancer. 3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens: <ul style="list-style-type: none"> • Doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 2 - 3 weeks • Docetaxel 75 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 3 weeks • Paclitaxel 80 mg/m² weekly IV x at least 12 weeks with or without IV trastuzumab • Paclitaxel 175 mg/m² IV every 2 weeks x 4 – 6 cycles (without an anthracycline) • Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks • Docetaxel 75 mg/m² and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks • Pertuzumab, trastuzumab, and docetaxel every 3 weeks (in the neoadjuvant setting) for 3-6 cycles • Targeted agents such as trastuzumab or pertuzumab are allowed 4. Plan to complete chemotherapy within 6 months 5. At least two years out from the last chemotherapy causing hair loss with complete recovery of hair 6. Karnofsky performance status $\geq 80\%$ 7. Willing and able to sign informed consent for protocol

	<p>treatment</p> <ol style="list-style-type: none"> 8. Willing to participate in study procedures including having photographs of the head before each cycle of chemotherapy and 1 month after the last chemotherapy 9. Willing to enroll in an extension protocol for follow up for 5 years following the end of chemotherapy treatment
	<p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. Patients with female pattern baldness resembling picture I-3 or higher on the Savin scale (Appendix IB) 2. Autoimmune disease affecting hair; e.g. alopecia areata, systemic lupus with associated hair loss 3. A history of whole brain radiation 4. Plans to use a chemotherapy regimen other than those specified in the inclusion criteria. Specifically, patients receiving a regimen including both an anthracycline and a taxane are not eligible for this trial (AC/T, EC/T, TAC, etc.) 5. Concurrent hormone therapy with chemotherapy. Hormone therapy should be used as indicated following completion of chemotherapy 6. Underlying clinically significant liver disease including active viral hepatitis with abnormal liver function tests >1.5 times the upper limit of normal, including alkaline phosphatase, AST, and total bilirubin. Patients with Gilbert's disease (elevated indirect bilirubin only) will be eligible for participation. 7. Clinically significant renal dysfunction defined as serum creatinine > the upper limit of normal. 8. A serious concurrent infection or medical illness that would jeopardize the ability of the patient to complete the planned therapy and follow-up 9. A history of persistent grade 2 (or higher) alopecia induced by prior chemotherapeutic regimens 10. Participation in any other clinical investigation or exposure to other investigational agents, drugs, device or procedure that may cause hair loss 11. Intercurrent life-threatening malignancy 12. A history of cold agglutinin disease or cryoglobulinemia 13. Evidence of untreated or poorly controlled hyper- or hypothyroidism 14. A history of silicon allergy 15. American Society of Anesthesiologist Class ≥ 3 (Appendix IV.A)
PATIENT SELECTION CRITERIA	<p>Inclusion Criteria:</p> <ol style="list-style-type: none"> 1. Female patients ≥ 18 years of age 2. Documented diagnosis of stage I or II breast cancer.

Control Group	<p>3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens:</p> <ul style="list-style-type: none"> • Doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 2 - 3 weeks • Docetaxel 75 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 3 weeks • Paclitaxel 80 mg/m² weekly IV x at least 12 weeks with or without IV trastuzumab • Paclitaxel 175 mg/m² IV every 2 weeks x 4 – 6 cycles (without an anthracycline) • Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks • Docetaxel 75 mg/m² and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks • Pertuzumab, trastuzumab, and docetaxel every 3 weeks (in the neoadjuvant setting) for 3-6 cycles • Targeted agents such as trastuzumab or pertuzumab are allowed <p>4. At least two years out from the last chemotherapy causing hair loss with complete recovery of hair</p> <p>5. Karnofsky performance status \geq 80%</p> <p>6. Willing and able to sign informed consent for protocol treatment</p> <p>7. Willing to participate in study procedures including having photographs of the head before each cycle of chemotherapy and 1 month after the last chemotherapy</p> <p>8. Chooses not to use scalp cooling during chemotherapy</p> <p>9. Willing to enroll in an extension protocol for follow up for 5 years following the end of chemotherapy treatment</p>
	<p>Exclusion Criteria:</p> <ol style="list-style-type: none"> 1. Patients with female pattern baldness resembling picture I-3 or higher on the Savin scale (Appendix IB) 2. Autoimmune disease affecting hair; e.g. alopecia areata, systemic lupus with associated hair loss 3. A history of whole brain radiation 4. Plans to use a chemotherapy regimen other than those specified in the inclusion criteria. Specifically, patients receiving a regimen including both an anthracycline and a taxane are not eligible for this trial (AC/T, EC/T, TAC, etc.) 5. Concurrent hormone therapy with chemotherapy. Hormone therapy should be used as indicated following completion of chemotherapy 6. Underlying clinically significant liver disease including

	<p>active viral hepatitis with abnormal liver function tests >1.5 times the upper limit of normal, including alkaline phosphatase, AST, and total bilirubin. Patients with Gilbert’s disease (elevated indirect bilirubin only) will be eligible for participation.</p> <ol style="list-style-type: none"> 7. Clinically significant renal dysfunction defined as serum creatinine > the upper limit of normal. 8. A serious concurrent infection or medical illness that would jeopardize the ability of the patient to complete the planned therapy and follow-up 9. A history of persistent grade 2 (or higher) alopecia induced by prior chemotherapeutic regimens 10. Participation in any other clinical investigation or exposure to other investigational agents, drugs, device or procedure that may cause hair loss 11. Intercurrent life-threatening malignancy 12. Evidence of untreated or poorly controlled hyper- or hypothyroidism 13. American Society of Anesthesiologist Class ≥ 3 (Appendix IV.A)
<p>STUDY DESIGN</p>	<p>This is a prospective, non-randomized, concurrent age- and treatment-matched control, clinical trial. The control group will establish whether a similar group of women based on disease, age, and treatment regimen will experience an expected high percentage of hair loss. An interim analysis will be conducted and if at least 12 out of the first 15 control group women have a Dean score of 4 (lose greater than 75% of their hair) at any chemotherapy visit, enrollment of the control group will be discontinued. The primary efficacy outcome will be based on graded photographs 4 weeks after the last chemotherapy. The incidence of scalp metastases will be based on a 5-year follow up.</p>

1. BACKGROUND AND RATIONALE

1.1 Chemotherapy Induced Hair Loss

Chemotherapy acts on cells with a high proliferation rate, targeting not only tumor cells but also benign proliferating cells, including those comprising the hair follicles. One previously unavoidable and emotionally distressing side effect from chemotherapy is chemotherapy-induced hair loss, or alopecia.

Chemotherapy is commonly utilized as adjuvant therapy for potentially curable malignancies such as breast cancer; the majority of patients with early stage disease will receive some sort of adjuvant chemotherapy. Different chemotherapy agents as well as variations in dose and schedule of administration result in varied effects on hair follicles. However, the most effective and most commonly administered adjuvant chemotherapy regimens for breast cancers include those that cause complete alopecia, anthracyclines and/or taxanes [1]. In contrast, some agents used primarily in the metastatic setting are not associated with significant hair loss, such as capecitabine and vinorelbine. Despite improvements in supportive care, and new chemotherapy regimens with less systemic toxicity, hair loss remains universal in the early stage setting.

Although genomic assays that predict chemotherapeutic benefit are an exciting approach that already are helping to determine which patients are most likely to benefit from adjuvant chemotherapy, hair loss remains a major issue in decision making for many patients. Patients with cancer rate chemotherapy induced alopecia as one of the most distressing side effects of treatment [2]. Complete alopecia is a constant reminder for the patient and others of their disease. This side effect is mostly, but not always, reversible [3]. It takes months to a year after completion of chemotherapy for the hair to recover, and it may be different in quality, color, and thickness, and baldness is a public declaration of illness. Cranial prostheses, or wigs, are helpful but uncomfortable, and often readily identifiable.

1.2 Methods Of Preventing Chemotherapy Induced Hair Loss

Chemotherapy induced hair loss potentially can be prevented by various methods, including minoxidil, CDK2 (cell division protein kinase) inhibitors, and scalp cooling. However, the efficacy of minoxidil and CDK2 inhibitors to prevent chemotherapy induced hair loss has not been very successful [4]. The most widely used and successful method today is scalp cooling.

1.2.1 Scalp Cooling Rationale

Scalp cooling prevents hair loss through vasoconstriction, and thus a lower concentration of chemotherapy is delivered to the scalp. Scalp cooling also decreases cellular uptake of drugs and decreases the intra-follicular metabolic rate. Cooling is normally initiated 30 minutes prior to the chemotherapy infusion, then continues during the infusion and for a period of time after the infusion is completed. The post infusion cooling time depends on the chemotherapy regimen and dose that is administered, but cooling normally continues for 60-90 minutes after termination of the infusion.

1.2.2 Scalp Cooling Development

Scalp cooling was first performed using ice packs that were placed on the patient's head, but with unsatisfactory results. The ice packs were subsequently replaced with ice caps. The most

common system of this type is called the Penguin Cold Cap [5]. The caps are frozen when placed on the patient's head and then thaw over time. The caps therefore have to be replaced frequently (approximately every 20 minutes). Numerous caps are required for a chemotherapy session. Every time a cap has been used it needs a certain time (12-24h) in the freezer before it can be used again. In order for a center to support the use of these ice caps, a large freezer as well as refrigerated storage are required, and each patient needs multiple caps for a single chemotherapy session. The frequent changing of caps is labor-intensive and requires a caregiver or health care worker. In addition, the fluctuation of temperature could potentially affect efficacy. This led to the development of cooling systems that could provide continuous cooling of the scalp.

1.2.3 Continuous Scalp Cooling

The DigniCap™ System has been available since 1999. The scalp is cooled by a liquid coolant that is flowing from a refrigeration unit through tubes into the channels of the DigniCap™ and then back to the cooling system. The DigniCap™ is a silicone cap that fits uniformly to the scalp, with internal automatic temperature regulation. The cap is available in four different sizes and is specifically designed not to cover the patient's ears for comfort. Each cap contains two cooling compartments and the temperature in both compartments is monitored and automatically adjusted by a security sensor to prevent side effects from excessive cooling. Two patients can be treated at the same time using one refrigeration unit. Default time and temperature settings can easily be altered for patient comfort. In September 2009, the new generation of the DigniCap™ System was introduced: the Digni C3/DigniCap™ System. This new generation device offers a number of improvements in design, potentially improving both tolerance and efficacy.

The competing scalp cooling system on the European market is the Paxman hair loss prevention system [6]. In analogy with the DigniCap™ System, the Paxman system offers continuous scalp cooling and consists of a refrigeration unit, cooling caps and a liquid coolant. On the contrary, Paxman does not measure the temperature on the head and has only one cooling circuit.

1.3 The Efficacy Of Scalp Cooling To Prevent Chemotherapy Induced Hair Loss

1.3.1 Efficacy Determinants

The efficacy of scalp cooling depends on several factors [7-9]: chemotherapy regimen and dose, dose interval, performance status of the patient, scalp cooling temperature, post cooling time, and the scalp cooling system. The optimal scalp cooling system can maintain a constant low temperature of the scalp and comes with a snug fitted cap. 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.

1.3.2 Efficacy Measures

Hair preservation is generally evaluated by assessing hair loss. Assessments are performed either by the patient herself and/or by the clinician. Clinicians assess hair loss either directly, when meeting with the patient, or afterwards when looking at photographs. Different scales for assessing hair loss are used: the modified WHO scale, the Dean scale and the visual analogue scale (VAS) [39]. The modified WHO scale and the Dean scale are both 5-grade scales but with different cut-points for the grades. The VAS is a continuous scale used for patient assessment of, in this case, hair loss.

Another way to measure efficacy of scalp cooling is wig use. This is a subjective method that may or may not reflect efficacy but rather patient satisfaction with their hair. Another method is the Cohen's Cross Section Trichometer, a device for measuring hair quantity. This is a new promising method that has not yet been evaluated in scalp cooled patients [10]. Clearly a number of methods to measure hair loss exist, without clear superiority to one method. However, the Dean scale is a validated measure of hair quantity that can be graded based on photographs taken at 5 angles, and may be the most reproducible measure for use in multicenter studies.

1.3.3 Literature Review

In the extensive review by Breed in 2011 [9], the efficacy of scalp cooling was evaluated. 57 studies and 3 personal communications involved over 6000 patients were treated with scalp cooling were included. The author states that scalp cooling is effective, but not for all patients. In the review by Poder et al. [11] it is concluded that, "scalp cooling seems to get good performance in its aim to prevent hair loss in patients receiving chemotherapy."

The efficacy and safety of the DigniCap™ System has been evaluated in a number of studies [12-17]. These studies are described in detail in the Dignitana Clinical Evaluation Report [18]. Overall the data demonstrates the ability of the system to prevent chemotherapy induced hair loss in a number of settings. There is an ongoing evaluation of the DigniCap™ System in Japan [16]. The latest report was presented in St. Gallen in 2011, in 359 women diagnosed with early stage breast cancer. Photographs were taken and hair loss was evaluated using VAS. 70% of the patients were treated with weekly dose paclitaxel 60 mg/m² plus cyclophosphamide 400 mg/m², 8% were treated with paclitaxel plus trastuzumab, 15% were treated with epirubicin 40 mg/m² and cyclophosphamide 400 mg/m² biweekly, and 7% were treated with combinations including fluorouracil, irinotecan, vinorelbine or capecitabine. 48% of the patients did not lose any hair, 33% experienced a little hair loss, and 16% experienced mild hair loss. Only 4% experienced moderate hair loss and reported using a wig.

The clinical experience regarding efficacy and safety was reviewed in the Dignitana Post Market Surveillance Report [19]. Data was collected through phone calls and clinic visits. From 2001 until August 2011, more than 6000 patients have used the DigniCap™ System in Sweden, Norway, Denmark, Finland, England, Germany, Greece, Turkey, Russia, Japan, Singapore, Chile and Venezuela. The majority of patients in the report are breast and ovarian cancer patients. The overall success rate in terms of patient satisfaction is approximately 83%. Since most of the clinics do not log the number of patients or the results of scalp cooling, the numbers presented are conservative estimations by the treating nurse. Taken together, the DigniCap™ System has been evaluated in a variety of chemotherapy regimens, both in the adjuvant and in the palliative setting.

1.4 Safety Of Scalp Cooling

1.4.1 Short Term Side Effects

Based on published accounts of more than 2000 patients, it is concluded that scalp cooling is generally very well tolerated [20] with infrequent and mild side effects that rarely result in stopping cooling. 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 [8]. Uncomfortable cold sensations and headaches were especially pronounced in

studies where pre-cooled caps, which are usually chilled to -15°C to -25° , were used. Patients also complain about a heavy feeling of the head, and transient light-headedness following cap removal [1]. In addition, patients experienced neck pain due to heavy weight of some cooling caps [1]. Frostbite or freezing of skin has never been reported. There are only a few small, older studies in which more than 10% of the patients reported that side effects were a reason for stopping scalp cooling [8].

Side effects reported specifically from the use of the DigniCap™ System are limited. In a pilot study of 26 patients, it was reported that the side effects and the extra time required for scalp cooling was acceptable [13]. When evaluating discomfort during scalp cooling using a 10 point graded visual analogue scale (VAS) (0=none, 10=as bad as it could be), the discomfort was modest among the entire group (median value 1.5; range 0.5–8). In a larger study, only two out of 74 patients discontinued the treatment, one because of discomfort and one due to hair loss and discomfort [14]. Interestingly, side effects from chemotherapy such as uncomfortable scalp itching and distinctive scalp pain, and dermatitis (including hyperemia and skin flaking), appeared to be less frequent in the patients treated with the DigniCap™ System as compared to non-cooled patients [15].

1.4.2 Long Term Side Effects

Scalp cooling prevents hair loss through vasoconstriction, decreases cellular uptake of drugs, and decreases the intra-follicular metabolic rate. A theoretical increased risk of scalp metastases among breast cancer patients has been of concern since breast tumors may metastasize to the scalp. However, scalp metastases are rare in breast cancer, occurring in approximately 1% of all patients and almost always occurring in the presence of additional sites of disease[21]. Only a fraction of patients (0.025%), experience scalp metastasis as the first site of recurrence [22].

In the Dignitana Post Market Surveillance [19] including 6000 patients scalp cooled with the DigniCap™ system, only two patients have been reported with scalp metastases. Both patients had multiple sites of metastatic disease at the time of diagnosis with scalp involvement.

Breed et al. concluded, regarding scalp metastases, that “for breast cancer patients the theoretical risk of scalp cooling during adjuvant chemotherapy seems to be minimal” [9]. A recent extensive literature review has been conducted and the conclusion is that scalp cooling has not been shown to increase the incidence of scalp metastases in patients with both early and late stage breast cancer [23]. The author’s opinion is that scalp cooling can and should be offered to breast cancer patients who will be treated with adjuvant chemotherapy, and also to those who are offered palliative chemotherapy associated with a significant risk of alopecia. The risks involved in scalp cooling 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 [23].

1.5 Scalp Cooling In Relation To Well Being

Well-being has been evaluated in breast cancer patients treated with and without scalp cooling [24]. Patients completed questionnaires (including the EORTC QLQ-C30 and EORTC-QLQ-BR23, and BIS) before, during, and after completion of the last cycle of chemotherapy. At all three times of measurement, alopecia was considered among the most distressing problems. The

study showed a positive trend towards higher well-being in successfully scalp-cooled patients as indicated by a general better health-related quality of life and better body image.

1.6 Scalp Cooling: Available To Cancer Patients World Wide

Scalp cooling has been used for decades in Europe, and is now also under evaluation in the United States, Japan, the Middle East, Canada and South America.

Previously, scalp cooling was not available in the U.S. In 1991 the FDA stopped the approval of scalp cooling because of lack of documentation about efficacy and safety [25]. There has been increasing interest in scalp cooling in the United States, with increasing numbers of websites, TV shows and articles that discuss scalp cooling [26-37], and development of an advocacy group.

At this time, outside of a clinical trial, only Penguin Cold Caps are available to patients in the U.S. and are marketed by a group in Southern California and shipped from the U.K. directly to patients. Outside of the setting of a clinical investigation, patients generally investigate the caps through online research and chat rooms, then coordinate and pay themselves for the cap rental. Sharing of caps orchestrated by the company is quite common, allowing patients to obtain the caps with short notice. As of late 2010, BreastCancer.org had more than 1500 posts related to cold cap therapy, and seven medical centers in the U.S. currently or will soon have freezers dedicated to cooling Penguin Cold Caps on site (37).

A study on scalp cooling using the Penguin Cold Caps was presented at the San Antonio Breast Cancer Symposium, but has not yet been published [38]. The objective of the study was to determine the effectiveness of scalp hypothermia in patients with stage I-IIIc breast cancer receiving either anthracycline (n=22) or non-anthracycline based adjuvant chemotherapy (n=12). For patients who used scalp hypothermia through chemotherapy, the median incidence of alopecia was 10% for those treated with the combination of docetaxel-cyclophosphamide and docetaxel-carboplatin-trastuzumab. In patients treated with doxorubicin-cyclophosphamide, doxorubicin-cyclophosphamide followed by paclitaxel, and docetaxel-doxorubicin-cyclophosphamide combined, the median incidence of alopecia was 50%. Hair loss was thus reduced in those receiving anthracyclines and almost completely prevented in the group receiving non-anthracycline based chemotherapy. These data document existing use of scalp cooling in the U.S., and use is clearly increasing (personal communication, Frank Fronza).

1.7 Feasibility Study Of Scalp Cooling With The Dignicap™ System In The US

A pilot study was conducted in the United States at the University of California San Francisco, and Wake Forest University, evaluating the feasibility of use of the DigniCap™ System in patients with breast cancer receiving adjuvant chemotherapy known to cause significant alopecia. Eligible patients included women diagnosed with stage I breast cancer planning to receive chemotherapy in the adjuvant or neo-adjuvant setting. 20 patients were enrolled. The majority (80%) received docetaxel and cyclophosphamide (TC) every three weeks for four to six doses. Other chemotherapy regimens included 12 cycles of weekly paclitaxel with trastuzumab (10%), and docetaxel and carboplatin with trastuzumab every three weeks for six cycles (10%).

The primary endpoint of the pilot study was to determine the feasibility of use of the DigniCap™ System in this setting. Feasibility was defined as less than 50% of patients discontinuing use of

the cap due to cap-associated toxicity. Nineteen of 20 patients (95%) completed all chemotherapy using the DigniCap™ System, indicating that this system is feasible for use by women with breast cancer receiving adjuvant chemotherapy.

Secondary endpoints included prevention of hair loss, assessed by an independent panel as well as by patients. The Dean scale was used to grade extent of hair loss, with up to grade 2 ($\leq 50\%$ hair loss) considered successful prevention of hair loss. Using these criteria, the independent panel assessed that 75% of patients had no more than grade 2 alopecia at any time during their treatment and follow-up. The patient-reported hair loss using the Dean scale was also considered a success, as 55% of patients experienced grade 2 or less alopecia throughout their entire treatment and follow-up.

Overall, scalp cooling was well tolerated, with 68% and 32% of patients experiencing grade 1 and 2 toxicity respectively. With a median follow-up under two years, no scalp metastases have been observed.

The most common side effects experienced by patients using the DigniCap™ System were head pain, scalp pain, and feeling chilled. The majority of patients took over-the-counter pain medications as prophylaxis before starting the cooling process to counteract the initial headache. Head pain was experienced by 65% of patients during only one treatment (31%) or at most during three treatments (31%). More patients (50%) reported head pain during their second treatment than during any other treatment. The average level of head pain ranged from 39 (Cycle 2) to 46 (Cycle4) as assessed on a scale from 0-100.

Scalp pain was experienced by 95% of patients during at least one treatment. More patients (80%) reported scalp pain during their third treatment than during any other treatment. Most patients (65%) experienced scalp pain during 2 or 3 treatments, and this symptom was most prevalent during the third treatment, as 80% of patients reported scalp pain at this time. The average level of scalp pain ranged from 38 (Cycle 2) to 46 (Cycle1) as assessed on a scale from 0-100.

Chill was experienced by 80% of patients. Of these patients, 40% felt chilled during every treatment. The third treatment caused the most number of patients to feel chilled (80%). the average level of chill during treatment ranged from 42 (Cycle 1) to 54 (Cycle 3), as assessed on a scale from 0-100.

Overall, average patient satisfaction with hair was 85% at baseline, and 82% three months after the completion of chemotherapy. This pilot study demonstrated both feasibility and success of the DigniCap™ System in terms of preventing significant hair loss in the majority of women receiving non-anthracycline based adjuvant chemotherapy. These data support the planned pivotal trial to better evaluate the use of scalp cooling in women with early stage breast cancer receiving adjuvant chemotherapy.

1.8 The Need For A Prospective Study Of Scalp Cooling

Alopecia is a non-life threatening complication of the majority of effective adjuvant chemotherapy regimens for early stage breast cancer, but has a significant impact on quality of life and affects decisions regarding the risks and benefits of treatment. A safe and well tolerated system to prevent the majority of hair loss would be a powerful addition to our expanding

armamentarium of tools for supportive care, and would improve quality of life for women undergoing adjuvant therapy for these common malignancies.

2. OBJECTIVES

The overall objective is to assess the clinical performance, efficacy and safety of a Scalp Hypothermia System in breast cancer patients receiving specific chemotherapy treatments that, unless counteracted by simultaneous hypothermia treatment, result in hair loss.

2.1 Primary Objective

To assess the ability of the DigniCap™ System to prevent hair loss in women receiving specific chemotherapy regimens for early stage breast cancer. Efficacy will be measured by assessment of hair loss up to 4 weeks (3-6 week window) after the completion of the last chemotherapy cycle by patient self-assessment of standardized photographs using the Dean scale by patients in the treatment and control groups.

2.2 Secondary Objective

- To assess safety of the DigniCap™ System in women receiving specific chemotherapy regimens for early stage breast cancer.
- To assess the incidence of scalp metastases in women who used the DigniCap™ System annually for a total of five years after chemotherapy
- To assess tolerability of the DigniCap™ System
- To evaluate hair loss and recovery as assessed by the patient during and following chemotherapy using the alopecia self-report.
- To evaluate hair re-growth at 3 and 6 months after completion of chemotherapy as assessed using the Hair Re-growth Follow Up Survey.
- To assess patient quality of life and satisfaction with hair during and after treatment with the DigniCap™ System.
- To assess the impact of hair loss on treatment decisions.

3. TREATMENT ENDPOINTS

3.1 Primary Endpoint

Success of the DigniCap™ System to prevent hair loss, defined as a maximum Dean score of ≤ 2 using standardized photographs graded by the patient up to 4 weeks after the last chemotherapy treatment, in at least 50% of patients enrolled in the treatment group with a lower bound of the 95% CI greater than 40%, and statistical superiority over a concurrent control group.

3.2 Secondary Endpoints

Safety as determined by spontaneous reporting of adverse events and as negative scalp changes determined by physical examination.

Safety defined as the number of scalp metastases over a 5-year period, compared to the incidence in an untreated control group.

Tolerability is defined as the percentage of patients who complete all planned cycles of chemotherapy do so using the DigniCap™ System.

Patient assessment of hair loss by the alopecia self-report at each chemotherapy.

Hair re-growth assessed by the patient using the Hair Re-growth Follow Up Survey.

Quality of life as measured by the EORTC-QLQ-BR23 quality of life questionnaire and a Body Image Scale.

Assessment of the impact of hair loss on breast cancer treatment decisions at 6 months after completion of chemotherapy.

4. TREATMENT PLAN**4.1 Schedule Of Investigational Events for Treatment and Control Group**

Assessments	Baseline ¹	Each Chemo-therapy cycle	1 month (3-6 weeks) after last chemo-therapy infusion	Follow-up Visit (3 months ± 2 weeks)	Follow-up Visit (6 months± 2 weeks)	Annual Follow-up Visits at 1, 2, 3, 4 and 5 years (± 2 weeks)
Chemotherapy treatment		X				
Scalp cooling ²		X				
Signed Informed Consent, Appendix III	X					
Eligibility checklist, Appendix I	X					
Baseline Case Report Form, Appendix IV	X					
Case Report Form for all chemotherapy cycles, Appendix V		X				
Treatment follow-up form at 3 months after chemotherapy completion, Appendix VI				X		
Treatment follow-up form at 6 months after chemotherapy completion, Appendix VII				X	X	
Photographs of hair/scalp (Section 8.1; Appendix XXI)	X	X ³	X			
Alopecia self-report, Appendix VIII	X	X	X	X	X	
Patient symptoms survey ^{2,3} , Appendix IX		X				
EORTC-QLQ-BR233, Appendix X	X	X ⁴	X	X	X	
Body Image Scale (BIS), Appendix XI	X	X ⁴	X	X	X	
Impact of hair loss on treatment decision, Appendix XII					X	
Hair Re-growth Follow Up Survey, Appendix XIII				X	X	
Case Report Form for safety follow up visits,				X	X	X

Appendix XV						
Medwatch, Appendix XIV		X	X	X	X	X
Case Report Form for Device Use ⁵ , Appendix XXIII		X				
Screening Log- Non Enrolled Patients, (If applicable), Appendix II	X					

¹All baseline measurements must be done prior to treatment administration unless otherwise specified.

²This survey should be administered at the end of each chemotherapy session.

³Patients receiving weekly paclitaxel treatment will have photographs taken at weeks 1, 2, 4, 6, 8, 10, and 12

⁴QOL (EORTCQLQ-BR233 and BIS) to be completed at Cycle 4 only during Chemotherapy and at the last Chemotherapy Visit if the patient is discontinued early because of hair loss

⁵Not applicable for the control group

5. PATIENT SELECTION CRITERIA

5.1 Treatment Group

5.1.1 Inclusion Criteria

In order to be eligible for the study, patients should fulfil all of the following inclusion criteria:

1. Female patients ≥ 18 years of age
2. Documented diagnosis of stage I or II breast cancer.
3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens:
 - Doxorubicin 60 mg/m^2 and cyclophosphamide $600 \text{ mg/m}^2 \times 4 - 6$ cycles IV every 2 - 3 weeks
 - Docetaxel 75 mg/m^2 and cyclophosphamide $600 \text{ mg/m}^2 \times 4 - 6$ cycles IV every 3 weeks
 - Paclitaxel 80 mg/m^2 weekly IV x at least 12 weeks with or without IV trastuzumab
 - Paclitaxel 175 mg/m^2 IV every 2 weeks x 4 – 6 cycles (without an anthracycline)
 - Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles and trastuzumab IV weekly or every 3 weeks
 - Docetaxel 75 mg/m^2 and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles and trastuzumab IV weekly or every 3 weeks
 - Pertuzumab, trastuzumab, and docetaxel every 3 weeks (in the neoadjuvant setting) for 3-6 cycles
 - Targeted agents such as trastuzumab or pertuzumab are allowed
4. Plan to complete chemotherapy within 6 months
5. At least two years out from the last chemotherapy causing hair loss with complete recovery of hair
6. Karnofsky performance status $\geq 80\%$
7. Willing and able to sign informed consent for protocol treatment
8. Willing to participate in study procedures including having photographs of the head before each cycle of chemotherapy and 1 month after the last chemotherapy
9. Willing to enroll in an extension protocol for follow up for 5 years following the end of chemotherapy treatment

5.1.2 Exclusion Criteria

1. Patients with female pattern baldness resembling picture I-3 or higher on the Savin scale ([Appendix IB](#))
2. Autoimmune disease affecting hair; e.g. alopecia areata, systemic lupus with associated hair loss
3. A history of whole brain radiation
4. Plans to use a chemotherapy regimen other than those specified in the inclusion criteria. Specifically, patients receiving a regimen including both an anthracycline and a taxane are not eligible for this trial (AC/T, EC/T, TAC, etc.)
5. Concurrent hormone therapy with chemotherapy. Hormone therapy should be used as indicated following completion of chemotherapy
6. Underlying clinically significant liver disease including active viral hepatitis with abnormal liver function tests >1.5 times the upper limit of normal, including alkaline

phosphatase, AST, and total bilirubin. Patients with Gilbert's disease (elevated indirect bilirubin only) will be eligible for participation.

7. Clinically significant renal dysfunction defined as serum creatinine > upper limit of normal.
8. A serious concurrent infection or medical illness which would jeopardize the ability of the patient to complete the planned therapy and follow-up
9. A history of persistent grade 2 (or higher) alopecia induced by prior chemotherapeutic regimens
10. Participation in any other clinical investigation or exposure to other investigational agents, drugs, device or procedure that may cause hair loss
11. Intercurrent life-threatening malignancy
12. A history of cold agglutinin disease or cryoglobulinemia.
13. Evidence of untreated or poorly controlled hyper or hypothyroidism
14. A history of silicon allergy
15. American Society of Anesthesiologist Class ≥ 3 ([Appendix IV.A](#))

5.2 Control Group

5.2.1 Inclusion Criteria

In order to be eligible for the study, patients should fulfil all of the following inclusion criteria:

1. Female patients ≥ 18 years of age
2. Documented diagnosis of stage I or II breast cancer.
3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens:
 - Doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 2 - 3 weeks
 - Docetaxel 75 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 3 weeks
 - Paclitaxel 80 mg/m² weekly IV x at least 12 weeks with or without IV trastuzumab
 - Paclitaxel 175 mg/m² IV every 2 weeks x 4 – 6 cycles (without an anthracycline)
 - Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles and trastuzumab IV weekly or every 3 weeks
 - Docetaxel 75 mg/m² and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles and trastuzumab IV weekly or every 3 weeks
 - Pertuzumab, trastuzumab, and docetaxel every 3 weeks (in the neoadjuvant setting) for 3-6 cycles
 - Targeted agents such as trastuzumab or pertuzumab are allowed
4. At least two years out from the last chemotherapy causing hair loss with complete recovery of hair
5. Karnofsky performance status $\geq 80\%$
6. Willing and able to sign informed consent for protocol treatment
7. Willing to participate in study procedures including having photographs of the head before each cycle of chemotherapy and 1 month after the last chemotherapy
8. Chooses not to use scalp cooling during chemotherapy
9. Willing to enroll in an extension protocol for follow up for 5 years following the end of chemotherapy treatment

5.2.2 Exclusion Criteria

1. Patients with female pattern baldness resembling picture I-3 or higher on the Savin scale ([Appendix IB](#))
2. Autoimmune disease affecting hair; e.g. alopecia areata, systemic lupus with associated hair loss
3. A history of whole brain radiation
4. Plans to use a chemotherapy regimen other than those specified in the inclusion criteria. Specifically, patients receiving a regimen including both an anthracycline and a taxane are not eligible for this trial (AC/T, EC/T, TAC, etc.)
5. Concurrent hormone therapy with chemotherapy. Hormone therapy should be used as indicated following completion of chemotherapy
6. Underlying clinically significant liver disease including active viral hepatitis with abnormal liver function tests >1.5 times the upper limit of normal, including alkaline phosphatase, AST, and total bilirubin. Patients with Gilbert's disease (elevated indirect bilirubin only) will be eligible for participation.
7. Clinically significant renal dysfunction defined as serum creatinine > upper limit of normal.
8. A serious concurrent infection or medical illness which would jeopardize the ability of the patient to complete the planned therapy and follow-up
9. A history of persistent grade 2 (or higher) alopecia induced by prior chemotherapeutic regimens
10. Participation in any other clinical investigation or exposure to other investigational agents, drugs, device or procedure that may cause hair loss
11. Intercurrent life-threatening malignancy
12. Evidence of untreated or poorly controlled hyper or hypothyroidism
13. American Society of Anesthesiologist Class ≥ 3 ([Appendix IV.A](#))

6. INVESTIGATIONAL DEVICE

6.1 The Dignicap™ System

The DigniCap™ System consists of the digitized system for controlled scalp cooling (Digni C3) in conjunction with the soft, tight-fitting silicon cap (DigniCap™), the neoprene outer cap (DigniTherm™), and the liquid coolant (DigniCool™). DIGNISTICK™ is prepared to log data from a treatment when inserted in the slot. DIGNICARD™ is a key card which has to be inserted in order to start a treatment.

The liquid coolant circulates from the cooling unit to and through the channels of the cap and back to the cooling unit again. The scalp temperature is monitored by three separate thermometers. Deviations from the pre-set temperature are immediately and automatically adjusted by the system (scalp temperature can be controlled with an accuracy of $\pm 2.0^{\circ}\text{C}$).

6.2 Dignicap™

6.2.1 Composition

The silicon cap has two separate cooling circuits, one for the front of the head and one for the back of the head (as the front of the head is warmer than the back of the head). Two sensors for controlling the cooling circuits, plus one for the safety system are attached.

6.2.2 Product Safety

Minimal risk associated with rare incidence of silicon allergy.

6.2.3 Storage Requirements

Product should be protected from non-operator handling and cleaned with alcohol swabs after each use.

6.2.4 Biocompatibility

Silicon is tested < 24h contact with intact skin without any remarks (cytotoxicity, sensitization, intracutaneous reactivity).

6.3 Dignitherm™

An outer neoprene cap that insulates and keeps the inner cap in place.

6.4 Digni C3

6.4.1 Specifications

Voltage 115 VAC 50-60 Hz.

Maximum Volt ampere 1500 VA.

Digni C3 weighs approximately 76 kg.

6.4.2 Temperature Control

The temperature in the DigniCap™ is kept at $\pm 2.0^{\circ}\text{C}$ from the set value. The safety system controls that the temperature never goes below 0°C . The unit is fully hermetically sealed and is using CFC-free R404A refrigerant.

6.5 Dignicool™

6.5.1 Product Name

Monopropylene Glycol diluted with water. DigniCool™ Hazards Information and Material Safety Data, [Appendix XXV](#).

6.6 Labeling

Guide to Device Labeling, please see [Appendix XXIV](#).

6.7 Investigational Device Accountability

When a device shipment is received at the site, a designee of the investigational team at each site should verify the contents, sign the packing invoice provided with the shipment, and maintain the original copy for review by the study monitor.

Each shipment of investigational supplies will contain an accountability log to allow maintaining current and accurate inventory records covering receipt, dispensing, and disposition of the investigational device. During the study, the following information must be noted in the accountability log: the identification number(s), initials of patient(s) to whom device is dispensed, the date(s) that the investigational device is dispensed, and the initials of the designee who dispensed it.

The study monitor will examine the inventory during the study. Additionally, the inventory records must be readily available and may be subject to regulatory authorities, the local regulatory agency, or an independent auditor's inspection at any time. At the completion of the study, to satisfy regulatory requirements regarding device accountability, all remaining investigational device items, used as well as unused, should be found in the inventory, reconciled and retained or destroyed according to applicable state and federal regulations.

Device Accountability Log, [Appendix XXII](#).

6.8 Training And Experience For The Use Of The Device

Dignitana AB is responsible for installation of the DigniCap™ System and instruction and training of dedicated medical personnel.

Appropriate training on the hardware, software and fitting of the caps and communication with patients are ensured through a 3 day training program. Supplementary training can be performed in case of need. Education in handling and maintenance for dedicated medical personnel is performed at sufficient level to ensure correct experience and knowledge to carry out recommended use and maintenance.

Training of personnel will be performed according to Training Protocol, [Appendix XIX](#), and is to be documented in the Checklist Training of Personal, [Appendix XX](#).

7. STUDY DESIGN

This trial will be conducted in compliance with the GCP, Declaration of Helsinki and applicable regulatory requirements.

Only patients receiving chemotherapy treatment that may result in hair loss by the completion of chemotherapy will be included in the study.

Patients who choose not to undergo scalp cooling during chemotherapy are eligible to enrol in the study as part of the concurrent control group. The control group is being enrolled to determine whether the expected frequency of almost total hair loss will occur using the criteria of this study. The control patients will be matched to a patient at the same investigative site by disease (breast cancer), age (± 5 years) and chemotherapy treatment regimen. If at least 12 out of the first 15 control patients have a Dean score of 4, or lose greater than 75% of their hair, enrolment of the control group will be discontinued. Otherwise, a total of 30 control patients will be recruited.

Patients will be followed annually for 5 years in order to obtain long term follow up information on the risk of scalp metastases.

7.1 Study Treatment

No study specific assessments or treatments will commence prior to obtaining written signed informed consent from the patient.

Patients will receive scalp hypothermia as delivered by the DigniCap™ System. Scalp cooling will begin 30 minutes prior to administration of chemotherapy. Scalp temperature will be maintained at $+3^{\circ}\text{C}$ (37°F) throughout drug administration and for 90-120 minutes after discontinuing the infusion, depending on the chemotherapy regimen as outlined in Section 7.2.

7.2 Point Of Enrollment

Patients must be recruited and sign informed consent before initiation of treatment in order to be checked for eligibility and enrolled in the study. The Eligibility Checklist ([Appendix I](#)) should be completed prior to enrolment. If the patient meets all eligibility criteria and treatment must be started over a weekend or during a holiday, a maximum of 72 hours may elapse between the initiation of treatment and enrolment of the patient.

Eligible patients must be scheduled to receive either anthracyclines or taxanes as outlined in Section 5.1.

Patients found to be ineligible following study enrolment will be replaced in order to guarantee a 110-patient study population enrolment. Ineligible patients who have received treatment using the DigniCap™ System will be monitored for potential device-associated toxicity for 30 days following treatment. Upon determination of ineligibility, these patients will not have any more photographs taken nor will they be asked to complete any more protocol-mandated surveys.

Any patients who elect to discontinue study treatment prior to chemotherapy completion will also be monitored for potential device-associated toxicity for 30 days following treatment and will be followed for recurrence and survival. Upon study withdrawal, these patients will not have

any more photographs taken nor will they be asked to complete any more protocol mandated surveys.

7.3 Chemotherapy Regimens and Cooling Times

Chemotherapy Regimen	Dose	Post Infusion Cooling Time (minutes)
AC x 4 or 6 cycles, every 2-3 weeks	Doxorubicin: 60 mg/m ² , Cyclophosphamide 600 mg/m ²	120
TC x 4 or 6 cycles, every 3 weeks	Docetaxel 75 mg/m ² , Cyclophosphamide 600 mg/m ²	120
Paclitaxel x at least 12 cycles every week	Paclitaxel 80 mg/m ²	90
Paclitaxel and Carboplatin x 6 cycles, 3 on/ 1 off	Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks	120
Paclitaxel x 4 – 6 cycles every 2 weeks	Paclitaxel 175 mg/m ² IV every 2 weeks (without an anthracycline)	120
TCH x 6 cycles every 3 weeks (pertuzumab is allowed in the neoadjuvant setting)	Docetaxel 75mg/m ² , Carboplatin AUC 6, Trastuzumab weekly or every 3 weeks	120
Pertuzumab, trastuzumab, and docetaxel every 3 weeks (in the neoadjuvant setting) for 3-6 cycles	Pertuzumab initial dose of 840 mg, followed by 420 mg 603 every 3 weeks, Trastuzumab initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks, Docetaxel 75 mg/m ²	120

Targeted therapeutics not associated with hair loss are allowed (including trastuzumab, pertuzumab, etc.).

Dose reductions if required for patient safety or toxicity are allowed but full dose therapy should be planned at treatment start.

Patients should receive standard supportive care including myeloid growth factors as indicated.

Concomitant use of hormone therapy is not allowed. Hormone therapy should be started following completion of chemotherapy.

8. ASSESSMENTS

8.1 Photographic Documentation

Photographic documentation for all treatment and control patients will be performed before initiation of the first cycle of chemotherapy, each subsequent cycle of chemotherapy, and at a visit 4 weeks (3-6 week window) after the last cycle of chemotherapy. Patients receiving weekly paclitaxel treatment will have photographs taken at weeks 1, 2, 4, 6, 8, 10, and 12. At each time point, 5 photographs should be taken: from the front (bangs should be held back), behind, both sides and the top with the hair divided in the midline with both hands (See Guidelines for Study Photographs, [Appendix XXI](#)). Hair loss will be assessed by comparing the photographs against standardized photographs to estimate the percentage of hair lost according to the Dean scale.

8.2 Assessments At Baseline

Eligible patients who consent to this study will have the following baseline assessments: Medical history, physical examination, vital signs, and Karnofsky Performance status. Each patient will be examined for cutaneous metastases of the scalp. The use of concomitant medication will also be assessed at baseline. Hair will be photographed before initiation of the first cycle of chemotherapy by the physician or study personnel as detailed above. Patients will be asked to assess their current hair status by comparing the photographs against standardized photographs using of the quantitative Dean scale. Quality of Life questionnaires including the EORTC-QLQ-BR23 scale and BIS will be filled out by the patient.

8.3 Assessments At Each Cycle Of Chemotherapy

Before infusion:

The medical history of the patients and the use of concomitant medication will be reassessed and a physical examination will be performed. Hair will be photographed by the physician or study personnel. Patients receiving weekly paclitaxel treatment will have photographs taken at weeks 1, 2, 4, 6, 8, 10, and 12. Patients (treatment and control) will be asked to assess their current hair loss by examination of the photographs using the quantitative Dean scale compared to standardized photographs. Any patient with a Dean score of 4 at any visit will be considered to have met the study definition of “treatment failure” and will not have additional photographs. Treatment and control patients with a Dean score of 3 or lower will continue to be followed with photographic documentation until 4 weeks after the last chemotherapy visit. Use of any head cover such as wig, scarves or cap will be documented as “never”, “sometimes”, or “always”. Patients will fill out the quality of life questionnaires including the EORTC-QLQ-BR23 scale and BIS before cycle 4 of chemotherapy, or at the visit that they are considered to have failed because of hair loss.

At the end of the infusion:

Discomforts such as headache, being chilled, and scalp pain will be assessed using a visual analogue scale. Any adverse events will also be reported.

Device use parameters will be reported in the Device Use Log.

8.4 Assessment 4 Weeks (3-6 Week Window) Following The Last Cycle Of Chemotherapy

Evaluation of the last chemotherapy cycle will take place 4 weeks (3-6 weeks) after the last cycle of chemotherapy. The medical history of the patient and the use of concomitant medication will be reassessed, and a physical examination will be performed. Hair will be photographed by the physician or study personnel. Patients (treatment and control) will be asked to assess their current hair loss by examination of the photograph set using the quantitative Dean scale. Use of any head cover such as wig, scarves or cap will be documented as “never”, “sometimes”, or “always”. Patients will also fill out the quality of life questionnaires including the EORTC-QLQ-BR23 scale and BIS.

8.5 Assessments At The Follow-Up Visit 3 Months (± 2 Weeks) After The Completion Of Study Treatment

Vital signs, medical history, physical examination, examination for cutaneous metastases of the scalp will be carried out in the treatment group patients. The patient will assess hair re-growth using the Hair Re-growth Follow Up Survey. Quality of life questionnaires including EORTC-QLQ-BR23 scale and BIS will be assessed.

8.6 Assessments At The Follow-Up Visit 6 Months (± 2 Weeks) After The Completion Of Study Treatment

The patient will assess hair re-growth using the Hair Re-growth Follow Up Survey. Quality of life questionnaires including EORTC-QLQ-BR23 scale and BIS will be assessed. The impact of hair loss on treatment decision will be evaluated.

The presence of any cutaneous metastases of the scalp will be documented.

8.7 Assessments at the Follow-Up Visits 1, 2, 3, 4 and 5 Years (± 2 Weeks) After Completion of Study Treatment

The incidence of scalp metastases will be determined by contacting the patient annually (12 months ± 2 weeks) following the 6 month follow up visit of Protocol DIG-001. The investigator will determine whether scalp metastases have occurred through best efforts using the following information sources:

- Examination of the patient
- Patient provided history
- Patient medical records
- Patient personal physician or other health professional

Supporting information will be additional history of recurrence of breast cancer, metastases in other body systems, other cancers and other medical conditions.

9. Adverse Events (AE)

An *Adverse Event* is any untoward medical occurrence in a patient treated with an investigational product but which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not associated to the investigational treatment.

9.1 Adverse Device Events (ADE)

An *Adverse Device Event* is any untoward and unintended response to a medical device, including any event resulting from insufficiencies or inadequacies in the instructions for use of the device, and/or any event that is a result of a user error.

All conditions that are pre-existing to treatment with the study device should be recorded on the Medical History section within the patient's Baseline Case Report Form (CRF), [Appendix IV](#).

9.2 Recording Of Adverse Events Any Adverse Device Events

Solicited adverse events/adverse device events will be asked for and will be recorded in the CRF.

Adverse events/adverse device events already documented in the CRF, e.g. at a previous visit, and were classified as "ongoing", should be reviewed at subsequent visits. If resolved or changed severity, this should be documented in the CRF accordingly.

9.3 Assessment Of Severity

The severity of an adverse event/adverse device event will be recorded according to the following guidelines;

0	None	
1	Mild	An event, which is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
2	Moderate	An event, which is sufficiently discomforting to interfere with everyday activities.
3	Severe	An event, which prevents normal everyday activities and requires medical treatment.

9.4 Assessment Of Causality

Causal relationship, if any, to treatment with the investigational product/device should be assessed according to the following categories:

NR	Not related	The event is definitely not causally related to treatment with the investigational product/device.
UL	Unlikely	There are other, more likely causes and treatment with the investigational product/device is not suspected as a cause.
SU	Suspected (<i>reasonable possibility</i>):	A direct cause and effect relationship between the treatment with the investigational product/device and the event has not been demonstrated but there is a reasonable possibility that the event was caused by treatment with the investigational product/device.
PB	Probable	There probably is a direct cause and effect relationship between the

		event and treatment with the investigational product/device.
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9.5 Follow-Up Of Adverse Events And Assessment Of Outcome

The investigator should follow patients with non-serious adverse events, until symptoms resolve or has stabilized and advise the monitor of the final outcome.

The duration in days, or in hours, (if applicable) of the adverse event should be assessed.

The outcome of the adverse event will be assessed as:

- 1 = Resolved
- 2 = Improved
- 3 = Unchanged
- 4 = Worse
- 5 = Fatal
- 6 = Not available

The action taken as a result of the adverse event will be assessed as:

- 1 = None
- 2 = Therapy required
- 3 = Procedure discontinued due to AE
- 4 = Hospitalization required or prolonged

9.6 Unexpected Adverse Event

An “*unexpected*” adverse event is one not identified in nature, severity, or frequency in the Investigator’s Brochure or the product package insert for the investigational product/device.

9.7 Serious Adverse Event

A “*serious*” adverse event is one that results in any of the following:

- fatal (leading to death)
- life threatening, i.e. placing the patient at immediate risk of death in the judgment of the investigator
- permanently disabling or impairing a body structure or a body function
- requiring inpatient hospitalization or prolongation of existing hospitalization
- requiring medical or surgical intervention to prevent permanent impairing a body structure or a body function
- leads to a congenital anomaly or birth defect, fetal distress or fetal death.

9.8 Relationship To Study Intervention

9.8.1 Probably Related

The event occurs within a reasonable time period following the intervention and cannot be reasonably explained by known patient characteristics (including use of concomitant medications) at the associated chemotherapy.

9.8.2 Unknown Relationship

The etiology of the event is not known and the event does not occur within a reasonable time period following the intervention and does not follow a known response pattern for chemotherapy.

9.8.3 Definitely Not Related

The event is known not to be related to the study intervention.

9.9 Foreseeable Investigational Treatment Related Adverse Events

9.9.1 Hypersensitivity Reactions

Allergic reactions or urticaria from contact with silicon are extremely rare, but have been reported in some patients receiving silicone gel breast augmentation. If severe hypersensitivity reactions thought to be due to silicon occur, remove the patient from protocol therapy.

9.9.2 Pain Or Discomfort Reactions

Transient cephalgia, scalp pain, has been reported in patients treated with the DigniCap™ System for systemic cytotoxic chemotherapy. Patients who report pain or discomfort will have all complaints documented and treated symptomatically if thought to not be severe. Treatment interruption will not be indicated unless the patient requires it due to patient reported severe symptoms.

9.9.3 Toxicity Reporting

Toxicity Criteria: Skin toxicity will be determined using the revised NCI Common Toxicity Criteria (CTC) version 4.0 for Toxicity and Adverse Event Reporting.

All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded with details regarding duration, severity of each episode and outcome. The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to investigational product or their clinical significance. The description of the AE will include the onset date, duration, date of resolution, severity, seriousness, etiology, and the likelihood of relationship of the AE to study treatment.

Information regarding AEs will be collected from the time the patient signs the informed consent form up to 30 days after the patient's last scalp cooling.

9.10 Reporting Adverse Events

9.10.1 Immediate Reporting By Investigator To Sponsor

Any AE considered serious by the Principal Investigator or Sub-investigator or which meets the previous criteria must be entered as an SAE on the adverse event form and communicated to Dignitana AB within one business day (24 hours) from the time that the site personnel first becomes aware of the serious adverse event.

The written SAE report must consist of the Serious Adverse Event Report Form (MEDWATCH) ([Appendix XIV](#)) and data not entered in the CRF (e.g. lab reports, ECG reports, etc.). If the patient is hospitalized because of or during the course of an SAE, then a copy of the hospital

discharge summary should be faxed to Dignitana AB as soon as it becomes available. Withdrawal from the study and all therapeutic measures will be at the discretion of the Principal Investigator or Sub-investigator. All reported SAEs (related or not to the investigational product) will be followed until satisfactory resolution or until the Principal Investigator or Sub-investigator deems the event to be chronic or the patient to be stable.

This will be documented on a MEDWATCH form ([Appendix XIV](#)). The form must be completed and supplied to Dignitana AB within 24 hours/one business day at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational intervention.

9.10.2 Non Expedited Reporting

In the event of any other types of events not requiring expedited reporting, the investigator will notify Dignitana AB within 7 business days. If at any time that the events noted in this category changes (i.e. is upgraded), the investigator should notify Dignitana AB accordingly as noted in the section above.

9.10.3 Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA and GCP safety reporting requirements. All adverse experience reports must include the patient number, age, sex, severity of reaction (mild, moderate, severe), relationship to study intervention (probably related, unknown relationship, definitely not related), date and time of administration of intervention and all concomitant medications, and medical treatment provided. The investigator will record this information on the MEDWATCH form ([Appendix XIV](#)) and will provide reports of adverse experiences on a regular basis during the study. The investigator is responsible for evaluating all adverse events to determine whether criteria for “serious” and “unexpected” as defined above are present. The investigator is responsible for reporting adverse events to Dignitana AB as described under “Immediate reporting by investigator to sponsor” and “Non Expedited Reporting” above.

Dignitana AB’s business fax number is: 46(0)46 16 30 99 and business telephone number is 46(0)46 16 30 90.

The Address of Dignitana is:

DIGNITANA AB

Ruben Rausings Gata 9, SE-223 55 Lund

PO Box 240 22, SE-224 21 Lund Sweden

9.10.4 Sponsor Reporting Responsibilities

Dignitana AB will report to FDA without any delay.

9.10.5 Deviations From The CIP And/Or Amendments

Any deviation from the CIP and/or amendments must be reported to Dignitana and will be reviewed by Dignitana AB and principle investigators.

9.11 Data Safety Monitoring Board

The Data Safety Monitoring Board will be constituted by charter to review safety and to assess the interim analysis of the concurrent control group.

10. PATIENT EVALUATION CRITERIA

10.1 Criteria For Response Assessment

Criteria for grading of alopecia will be assessed using the Dean scale [22].

- Grade 0: no hair loss
- Grade 1: greater than 0 up to 25% hair loss
- Grade 2: greater than 25 up to 50% hair loss
- Grade 3: greater than 50 up to 75% hair loss
- Grade 4: greater than 75% hair loss

Quantitative Grade 0-2 will be considered adequate protection from alopecia. Grade 3 and 4 will be considered study treatment failure.

10.2 Endpoint Variables

10.2.1 Alopecia Report Assessment by the Patient

Hair loss will be assessed by the patient review of digital photographs taken of their hair/scalps at baseline, at each chemotherapy visit, and 4 weeks (3-6 weeks window) after the last chemotherapy treatment. Patients receiving weekly paclitaxel treatment will have photographs taken at weeks 1, 2, 4, 6, 8, 10, and 12. The photographs will include 5 views and will be graded by the quantitative Dean scale as above ([Appendix VIII](#)). A Dean score of 4 at any evaluation will be considered essentially complete hair loss and the patient will not have additional photographs.

The patient will also complete the Alopecia Self Report, [Appendix VIII](#).

10.2.2 Adverse Events Related to Use of the Dignicap™ System

Adverse events related to use of the DigniCap™ System are to be reported by the patient using the Symptoms Survey, [Appendix IX](#).

The scalp of the patient will be thoroughly examined by the physician prior to each chemotherapy session, at one month after completion of chemotherapy, and at the follow-up visits at 3 and 6 months after completion of treatment using the corresponding CRFs.

10.2.3 Incidence of Scalp Metastases

The incidence of scalp metastases will be determined by contacting the patient annually. The investigator will determine whether scalp metastases have occurred through best efforts using the following information sources:

- Examination of the patient
- Patient provided history
- Patient medical records
- Patient personal physician or other health professional

Supporting information will be additional history of recurrence of breast cancer, metastases in other body systems, other cancers and other medical conditions.

10.2.4 Quality Of Life in Women Using the Dignicap™ System

Quality of Life measured by the EORTC-QLQ-BR23 scale and BIS at Baseline, Cycle 4 of chemotherapy, 4 weeks after the last cycle of chemotherapy and at 4 weeks and 3 and 6 months after the completion of chemotherapy.

10.2.5 Hair Re-Growth

Hair re-growth will be evaluated at the Month 3 and 6 visits. Information regarding quality of treatment response defined as patient reported grading of quality of hair in terms of texture, manageability, and color variation from baseline will be collected.

10.2.6 Impact of Hair Loss on Treatment Decisions

Information regarding the perceived impact of hair loss on treatment decisions will be collected at Month 6 after completion of chemotherapy.

10.3 Criteria and Procedures for Withdrawal from Protocol Treatment

Patients may withdraw from this study under the following conditions:

- The patient withdraws consent to participate in the study.
- The investigator feels that it is in the best interest of the patient.
- During study treatment patient experiences severe hypersensitivity reaction due to silicon.
- During study treatment patient reports severe symptoms of cephalgia or of severe pain/discomfort.
- The patient has a serious or life-threatening adverse event.
- Disease Progression: In the event of documented disease progression, significant clinical decline resulting in discontinuation or prolonged treatment which effect alopecia the patient will be withdrawn.
- The patient develops scalp metastases during the chemotherapy treatment.

Any patients who elect to discontinue use of the cap prior to completing their prescribed chemotherapy regimen will be considered to have entered study follow-up at the time of stopping cap use. They will have hair/scalp photographs taken and will complete surveys according to the protocol-mandated follow-up schedule. If study consent is withdrawn, patients will be monitored for potential device-associated Serious Adverse Events (SAEs) for 30 days following treatment.

10.3.1 Hypersensitivity Reactions

Allergic reactions or urticaria from contact with silicon are extremely rare, but have been reported in some patients receiving silicone gel breast augmentation. If severe hypersensitivity reactions thought to be due to silicon occur, remove the patient from protocol therapy.

10.3.2 Pain or Discomfort Reactions

Transient cephalalgia, scalp pain, has been reported in patients treated with the DigniCap™ system for systemic cytotoxic chemotherapy. Patients who report pain or discomfort will have all complaints documented and treated symptomatically if thought to not be severe. Treatment interruption will not be indicated unless the patient requires it due to patient reported severe symptoms.

10.4 Early Termination or Suspension of the Investigation

See section 12.4.

11. DEVICE RISK ANALYSIS AND RISK ASSESSMENT

List of hazards (see [Appendix XXVI](#)).

12. DATA quality

12.1 Original Data

Original data, also known as source data/records, are those data elements that represent the first recording of study data. Original data contain all the information that is necessary for the reconstruction and evaluation of the study. Examples of original data are 1) subject's information used in a clinical trial whether collected on paper or electronically at the time of the subject's visit, 2) certified copies of original records, 3) observations, and 4) laboratory data from clinical laboratories. Clinical investigators maintain control over source data from inception and until the end of the regulatory retention period. The Investigator must permit access to these data during sponsor monitoring visits, audits, IRB reviews and regulatory inspections.

In addition to original records maintained by the clinical site as part of their standard practices of patient care, this study will use direct data entry of clinical trial data into the Target e*CRF[®] (EDC) system, using the Target e*CTR[™] (Target e*Clinical Trial Record) process. This process enables clinical study site personnel to perform data entry of original data directly into Target e*CRF[®] at the time of the subject's office visit. This process stores the original data, along with transcribed data, in PDF format in the Target e*CTR data repository, access to which is controlled by the clinical Investigator. Authorized users can review these PDF documents using the Target e*CTR Viewer. In this data flow, the system stores all of the entered data first in the Target e*CTR repository (as PDF documents) before transmitting them to the Target e*CRF[®] database. At any point during the study or after completion of the study, each site can generate, or the system host will provide them with, an electronic file containing all of the records and audit trail, in PDF format, for all subjects at their site.

12.2 Target e*CRF[®] (Electronic Data Capture)

Personnel at the investigative site will enter all required clinical trial data into Target e*CRF[®], a validated 21 CFR Part 11 compliant Internet-based EDC system. Site personnel similarly manage all changes to the clinical trial data, through the EDC system's change management functionality that is subject to a full audit trail.

Target Health personnel will train investigator and site staff on the use of Target e*CRF[®] prior to enrollment of the first subject. Target Health maintains a list of authorized users and grants role-based access to the EDC system only after ensuring that site personnel have received system training. Target Health restricts access to the e*CRF database only to authorized personnel.

At the end of the study, the clinical investigator or authorized sub-investigator electronically signs the completed online eCRF. A certification must be obtained from all authorized persons in order to sign electronically, indicating that their electronic signature is equivalent to their hand-written signature. In order to sign electronically, the signer must log in with his or her username and password and then reenter this password on the page(s) requiring a signature(s). At the end of the trial, Target Health will provide each site with an electronic file containing all of the eCRF records for all subjects at their site.

12.3 Target e*CTR[®] Viewer (Target e*Clinical Trial Record Viewer)

Target e*CTR Viewer is a validated 21 CFR Part 11 compliant Internet-based software system. The PDF documents, representing both original and transcribed subject data, reside in a read-only environment. Authorized personnel at the investigative site control users' access to the Target e*CTR[®] Viewer. The Investigator can download a bookmarked PDF copy of records of individual subjects or all subjects at his/her site, including an audit trail of changes and electronic signatures. At the end of the study, the system host will provide each investigator with an electronic file containing all of the records and audit trail for all subjects at his/her site. Target Health personnel will train investigator and site staff on the use of Target e*CTR prior to enrollment of the first subject.

12.4 Certified Copies of Original Data

In the event that site personnel find that they are unable to perform direct data entry at the time of the study visit, they will record original data using paper records or equivalent media. Certified copies of these original data can be created, for example, by creating an exact copy of a paper record by scanning the paper or taking a photograph and storing it electronically. In order to do this, each site must have an SOP supporting this process. These scanned documents must be available to Target Health personnel during monitoring visits and during regulatory review.

12.5 Quality by Design (QbD)

12.5.1 Data Management

Target Health Data Management personnel create the data management plan (DMP) to specify data management activities for the study. The following summarizes the DMP:

Target Health hosts and manages the clinical database (i.e., Target e*CRF EDC system) during the lifetime of the study. At the conclusion of the study, Target Health provides a database extract to the sponsor for analysis and reporting to regulatory authorities. Target e*CRF will be used for online edit checks, batch edit checks and query management. Sponsor or authorized representatives capture the EDC specifications in an Application Setup Instructions (ASI) document. The ASI document contains the specific instructions for both the EDC development and data management (DM) staff.

The Data Validation Plan (DVP) provides specifications for the edit-checks. Within the DVP, there are three types of automated validation checks:

- Online edit-checks – Performed by the EDC system during data entry. Target Health personnel are responsible for programming and resolving any hits based on these checks.
- Batch edit-checks – Target Health personnel are responsible for programming and resolving any hits based on these checks.
- Manual checks – Performed by the monitor and data manager (DM). The DM is responsible for providing the listings if used by the monitors for manual checks.

Monitors manage queries within the Target e*CRF[®] application. Authorized site personnel (e.g., study coordinator) respond to and resolve queries. All changes to the database require a “Reason for Change” and are subject to an audit trail. The audit trail identifies the changed data,

reason(s) for change, who changed the data and the time and date of the change (based on the Target e*CRF[®] server's time).

EDC management reports are also available to view the data for consistency. Standard reports include:

- Overall Data Entry Status (By Site/Subject)
- Investigator Signature Status (By Site/Subject)
- Query Age Report (by Site)
- Query Report (by Site/Subject)
- Query Frequency by Site
- Query Frequency by Edit Check
- Query Frequency by Form
- Subject Visit Status Report (by Site / Subject)
- AE Report (By Site/Subject)
- Concomitant Medication Report (By Site/Subject)
- Serious AE Report (by Site/Subject)
- Subject Status Report (by Site)
- Protocol Violation Report (by Site / Subject)
- Treated (by Site / Subject)
- Subject Tracking Report (Individual)

Monitors and reviewers can request and specify changes to existing reports as well as additional management reports during the course of the study. Management of these requests fall under Change Control SOPs.

12.5.2 Centralized Monitoring

Study monitors carry out centralized (i.e., remote) monitoring of entered data daily or at an agreed-upon frequency, as defined in the Clinical Data Monitoring Plan (CDMoP). The following are samples of reports that assist in the centralized monitoring process. Study specific reports are found in Target e*CRF.

1. Time from subject visit to data entry
2. Online edit checks
3. Batch edit checks
4. Data listings

At the QbD meetings, monitoring findings are discussed. Clinical research and DM personnel meet to review and discuss data quality and data management issues, and capture relevant observations and decisions in meeting minutes. When necessary, the DMP and CDMoP are revised and corrective actions are implemented.

12.6 Record Retention

All study records will be retained for a period of time defined by the regulatory authority for the country in which the investigation is conducted. In general, this period is at least 2 years following the date on which the drug receives regulatory approval. In other situations (e.g., where the investigation is not in support of or as part of an application for a research or marketing permit), the retention period is 2 years following the date on which the entire clinical program is completed, terminated or discontinued, or the investigational application under which the investigation is being conducted is terminated or withdrawn by the regulatory authorities.

In the event the Investigator retires, relocates or for any other reason withdraws from the responsibility for maintaining records for the time period required, custody of the records may be transferred to any other person who will accept responsibility for the records. Notice of such a transfer must be given in writing to the sponsor. The Investigator must contact the sponsor prior to disposal of any records related to this study.

12.7 Confidentiality of Subject Data

The Investigator will preserve the confidentiality of the subjects' data. CRFs and other documents submitted to the sponsor will reference subjects only by an anonymized subject ID, which uniquely identifies the subject in the context of the study. The Investigator will maintain documents not meant for submission to the sponsor, e.g., the confidential subject identification code and the signed informed consent forms, in strict confidence. All data are subject to monitoring, audits and inspection.

12.8 Clinical Data Monitoring Plan (CDMoP)

The CDMoP identifies the monitoring schedule and the rationale for the frequency and type of monitoring visits. Since this study is using Direct Data Entry (DDE), in addition to agreed-upon source data verification (SDV), on-site monitoring visits will be limited to: assuring that the sites understand and are following the protocol, are adequately monitoring subject safety, and are managing the drug supply. The CDMoP also provides details with regard to the use of risk-based monitoring and source document verification. If the monitor is not allowed access to any e-source records during source document verification, certified printouts provided by sites can be used. In addition to on-site monitoring, monitors will perform central (i.e., remote) monitoring, electronically reviewing data in near real-time.

Communication	Timeframe
Site initiation visit (SIV)	All sites will have a SIV. The investigator meeting may serve as the SIV.
First on-site monitoring visit	See CDMoP.
Interim monitoring visits (IMV)	As specified in the CDMoP
Closeout visit (COV)	All sites must have a COV. Non-enrolling sites may have a COV over the telephone as permitted by the sponsor.

Communication	Timeframe
Site Update and Monitoring Calls	Monitors will contact sites as needed via email or telephone, based on review of site activity and the quality of data entry.
Teleconferences between the sites and CRO	Monitors will schedule teleconferences as appropriate to discuss the overall study status and to discuss study-wide related issues.
Initiation, Monitoring and Closeout Visit Reports	<p>Interim monitoring visits can be performed on-site or online. On-site visits are preceded by a confirmation letter sent to the site. The confirmation letter must outline the date, time and purpose of the monitoring visit</p> <p>Monitors will route all online Qualification, Monitoring and Closeout Visit Reports for signature to their supervisor(s). The supervisor will review the report and enter comments if needed.</p> <p>Following the completion of an on-site monitoring visit report, the monitor provides feedback to the site, identifying any outstanding issues from the visit.</p>
Study updates, Protocol Amendments, etc.	Will be forwarded to sites during study.
Adverse Events (AE) and Serious Adverse Events (SAE)	The primary method for reporting the event consists of entering data into the AE and Pharmacovigilance forms in Target e*CRF [®] .

12.9 Site Qualification Visit

Sites will undergo a qualification visit prior to the site initiation visit. The qualification of the site must include:

- The experience of the site personnel
- Availability of the population under investigation
- The suitability of the site facilities and equipment
- The suitability of the site for IMP storage
- Assurance that site personnel are not on the FDA debarment list

Sponsor or Target Health may waive the qualification visit if the study site has been previously qualified within a 12-month period of the site initiation visit for the same or similar indication. The Project Manager will document any such waivers in the project file (eTMF). Acceptable forms of documentation of previous qualification include previous approved site qualification reports from THI or similar documentation from the sponsor or their representatives.

12.10 Site Initiation Visit

The purpose of the study initiation visit is to train Investigators and site personnel on the specific requirements and procedures needed to satisfy the study protocol. This training may occur at the

Investigator site, during a joint Investigator Meeting, or via Internet-based training or teleconference.

The site initiation visit will include the following elements:

- Review of the protocol
- Review of the IMP handling procedures
- Training of appropriate staff on GCP regulations (including SAE reporting requirements)
- Training of the Investigator on the Investigator responsibilities listed on the FDA Form 1572
- Training of appropriate staff on maintenance of the Trial Master File in Target Document
- Training of appropriate staff on eCRF completion and expectations
- Training on eSource and access to the Target e*CTR Viewer

Task	Protocol-Specific Requirements
Prior to the site initiation visit, the following documents should be collected and uploaded into the Target Document electronic Trial Master File (TMF)	<ol style="list-style-type: none"> 1. Signed Confidentiality Agreement (CDA) 2. Mutually signed Clinical Trial Agreement (CTA) 3. Signed Statement of Investigator (Form 1572) 4. CV's of the Investigator and sub-Investigators (including current medical licenses). 5. Disclosure of Financial Interests and Financial Arrangements of staff listed on the 1572 (Form 3455). 6. IRB approval letter of protocol and Informed Consent Form
At the time of the site initiation visit, the following items will be available for the site personnel	<ol style="list-style-type: none"> 1. Personnel Signature Logs 2. Documentation of sponsor personnel participating in on-site visits 3. Training Records (GCP, protocol training)

12.11 First On-Site Monitoring Visit

During the first on-site monitoring visit, monitors will check:

- Adherence to the study protocol, with special focus on subject eligibility, IMP management and titration-related activities
- Informed consent process
- Medical histories and protocol eligibility, and verify transcription into Target e*CRF
- Drug accountability and storage
- SDV of paper source of questionnaires (if applicable) and verify transcription into Target e*CRF®
- Outstanding questions or issues with Investigator and study coordinator

12.12 Interim Monitoring

Monitoring of the clinical trial will occur both by on-site visits as well as by central (i.e., remote or in-house) review of eCRF forms, data management reports and the electronic Trial Master

File (eTMF). Monitors document the results of their monitoring assessments, both on-site and central, via online monitoring report functionality integrated into the EDC (eCRF) system.

The purpose of interim monitoring is to ensure protection of the rights and well-being of each subject, that the site understands and is following the protocol, that trial data are accurate, complete and verifiable, that the site is following ICH GCP guidelines, and that the trial site and staff remain qualified.

Interim monitoring activities typically include:

- Review of study and enrollment status (on-site or central)
- Review of consent forms, source documents and the eCRFs (on-site only)
- Review of study conduct and protocol adherence (on-site or central)
- Review of adverse events and that all Serious Adverse Events have been accurately been reported to the sponsor and IRB (on-site or central)
- Review of IRB approval and essential documents (on-site or central)
- IMP documentation and reconciliation (on-site only)
- Review of facility, personnel and delegation (on-site only)
- Personnel Signature Logs and delegation of authority (on-site only)
- Training Records (on-site only)
- Follow-up of outstanding issues (on-site or central)
- Documentation of sponsor personnel participating in on-site visits (on-site only)

When findings indicate that retraining is required, this must occur within 3 working days and if necessary the site will be informed not to enroll additional subjects until successful completion of the training.

It is the responsibility of the monitor to inform his/her supervisor of any issues that suggest the need for increased scrutiny across sites. The project manager will coordinate cross-site review and remediation, where warranted, to avoid or minimize repetition of the behaviors that led to the findings. Online management reports will support these cross-site reviews. These reports and all entered eCRF forms must be reviewed daily at the beginning of the study, defined as the first visit of the first subject, and corrective action reports generated as appropriate. It is critical that monitors document and share all findings that have an impact on the sites and study performance with the project manager and other study monitors.

Initially, the project manager will schedule Quality by Design meetings weekly, to review monitoring procedures and study progress. Based on findings from these meetings, the project manager will adjust the frequency of the meetings as appropriate. As well, the findings will drive remediation efforts as warranted. The project manager will document the results of each meeting and the decisions and the rationale for changing any of the procedures in the Quality by Design report.

The Monitor must immediately inform the Clinical Project Manager if he/she suspects fraud/misconduct at the site. The Clinical Project Manager will notify the sponsor of suspected fraud/misconduct and will propose an investigational action plan for approval by the sponsor.

12.13 Site Closeout

The purpose of the closeout visit is to bring to official completion all trial-related activities at the site.

During the visit, the monitor performs the following:

- Final resolution of outstanding data queries and verification of completeness of eCRFs.
- Final review for completeness of the eTMF.
- Reconciliation and disposition of the IMP.
- Review with the PI notification to the IRB that the study is closed. The correspondence should include the number of subjects enrolled, discontinued, and completed.
- Review with the site personnel the document retention requirements.

12.14 Audits

The Investigator will make all trial-related source data and records available at any time to a quality assurance auditor mandated by the sponsor or to domestic/foreign regulatory inspectors or representatives from IECs, who will audit/inspect the trial..

13. STATISTICAL CONSIDERATIONS

13.1 Objectives

This study is designed to assess the ability of scalp hypothermia using the DigniCap™ System to prevent chemotherapy induced alopecia. ‘Activity’ will be quantified using alopecia grading scales as described above, which will be used to define the proportion of responders among all evaluable patients. The primary goal of this study is to assess the efficacy of this system. To assess efficacy, the primary endpoint will be grade of alopecia 1 month after the last chemotherapy treatment as assessed by the patient with photographic documentation (digital photos), comparing current hair loss versus baseline. The primary endpoint analysis for the purpose of seeking approval for marketing will be conducted when all enrolled subjects have completed the primary outcome visit at 4 weeks after the last chemotherapy or withdrawn from the study. Patients will continue follow-up at 3 and 6 months and then annually for 5 years after the last chemotherapy. After the last patient has completed the 5 year follow up, a final safety analysis will be performed.

Comparisons of the primary endpoint will be made with a concurrent non-randomized control group and also with a pre-defined level of clinical efficacy.

A secondary objective is to examine the safety of the system, in terms of adverse symptoms and adverse device effects reported by patients during use of the DigniCap™ System and during the follow-up period 3 and 6 months after completion of treatment will be examined.

The incidence of scalp metastases at annual examinations during a 5-year follow-up is a secondary objective.

The secondary endpoints also include tolerability of the DigniCap™ System, hair loss at each chemotherapy, quality/quantity of hair re-growth at follow-up visits at 3 and 6 months, quality of life measures assessed using the EORTC-QLQ-BR23 scale and BIS during chemotherapy and follow-up visits, and the impact of hair loss on treatment decisions. These secondary outcomes will be evaluated in all patients, whether or not they are evaluable for response.

13.2 Statistical Hypothesis and Model

The primary goal of this study is determine the success rate for the DigniCap™ System in preventing hair loss among patients. A success has been determined to be when the patient grades her hair status as Grade 0-2 (Dean Scale) 4 weeks after the last chemotherapy visit. Any Dean score of 4 during the chemotherapy visits or a score of 3 or 4 at the visit 4 weeks after the last chemotherapy will be considered a failure. To assess efficacy, the primary endpoint will be the grade of alopecia 4 weeks after the last chemotherapy treatment as assessed by the patient with photographic documentation (digital photos) compared to standardized photographs.

The product will be considered a useful device if the success rate is shown to be greater than the control group rate and also is greater than 50% 4 weeks after the last chemotherapy visit whereas if the success rate for the device is shown to not be greater than the control group rate or is shown to be less than or equal to 50% then the device will be considered ineffective. As described above, a success is defined by the patient grading her hair status as Grade 0-2 4 weeks after the last chemotherapy visit. The proportion of success in preventing hair loss among all treated patients who complete their chemotherapy treatment is the primary endpoint for

evaluation of the device. We now describe our two hypotheses for primary efficacy. The first is defined as:

Null hypothesis (H₀): $P_{\text{control}}=P_{\text{treatment}}$

Alternative Hypothesis (H₁) $P_{\text{control}}\neq P_{\text{treatment}}$

A Fisher's Exact test will be used to test whether the two groups have equal proportions or not.

Since there is a high expectation that the patients in the control arm will experience a high level of failure (i.e. high amount of hair loss) there will be an early interim analysis performed to determine whether the full sample of patients in the control arm need to be included. This interim analysis will occur after 15 patients are enrolled. If 12 or more out of the first 15 control patients have a Dean score of 4 (greater than 75% hair loss at any chemotherapy treatment then the control arm will stop recruitment. However, if less than 12 out of the first 15 patients show hair loss then the remaining 15 patients (for a total of 30) will be enrolled.

Our second hypothesis for the primary efficacy is defined using only the patients in the treatment arm. It is important to distinguish between the language of the statistical hypothesis which will be used to establish a statistical test to determine efficacy and the clinical hypothesis which is linked to the threshold for efficacy that exists for the clinical realm. With this in mind the "clinical" hypothesis is that the observed success rate of the device must exceed 50% in order to be clinically effective. The "statistical" hypothesis is that in addition to the observed success rate being over 50% the lower bound of a 95% confidence interval for the observed success rate must exceed 40%. Thus, we can state this statistical hypothesis using 40% as the Null Hypothesis value since that is the success rate that we must rule out. Thus the hypotheses can be written as:

Null hypothesis (H₀): $P \leq p_0$ (40%); The success rate that we wish to statistically rule out, and

Alternative Hypothesis (H₁): $P > p_1$ (40%); A success rate of greater than 40% which we consider to be evidence that the device is clinically useful if the observed success rate also exceeds 50%..

A chi-square will be used to test the significance of the study results. In addition to performing this hypothesis test, a two-sided 95% confidence interval for the success rate will be calculated.

13.3 Sample Size and Power Estimation

This is a two-arm open label PMA study. For the comparison with the non-randomized control group there will be either 15 (if stopped at interim analysis) or 30 control patients and 110 treated patients. After accounting for a 10% drop out rate, we expect a total of 100 evaluable patients in the treatment arm.

Using a Fisher's exact test to compare the control arm to the treated arm, with a type 1 error rate of 5% (2-sided test) we will have 90% power to detect the difference between the control group proportion of 20% (or less) and the treated group proportion of 66% (or greater) when the sample sizes are 15 and 100, respectively. If we do not stop the control arm after the first 15 patients then there is 93% power to detect the difference between the control group proportion of 20% (or

less) and the treated group proportion of 56% (or greater) when the sample sizes are 30 and 100, respectively.

For the comparison within the treated group only, using a one group chi-square test for proportions, with type I error of 5% (2-sided), for a sample size of 110 patients, there is 92% power to detect the difference between the null hypothesis proportion of less than 40% versus an alternative proportion of 56% (or greater). For the evaluable population (n=100), there is 90% power to detect the difference between the null hypothesis proportion of less than 40% versus an alternative proportion of 56%. In other words, there is ample power to reject the null hypothesis that the success rate is 40% with a sample size of 110 patients (100 evaluable) if we assume that the expected proportion of patients that will be successes under the alternative hypothesis is 56% (or more). The rejection of the null hypothesis will be sufficient to rule out the possibility that the true success rate is 40% or less.

13.4 Interim Analysis and Stopping Rules

The study device has shown very promising results from large number of patients in previous trials overseas. Although we don't expect any serious adverse safety concerns in this study, a DSMB will meet every 6 months to review all safety data. If issues arise, then the DSMB can recommend changing consent/protocol or even suspending/stopping the trial. In addition, the DSMB will examine the control participant data after the first 15 patients are enrolled and if they find that 12 or more of the first 15 patients lose more than 75% of their hair then this arm will discontinue enrolment.

13.5 Handling of Missing Values/Discontinuations

Since this study is not a randomized trial, imputing "failures" into all women who drop out of the study regardless of the reason would be too conservative and likely give a biased estimate of the true failure rate of the device. Therefore, we propose the following plan for the primary analysis. All patients who drop out due to not completing the full prescribed chemotherapy cycles due to any reason such as toxicity of the chemotherapy will be excluded from the primary efficacy analysis. However, patients with missing endpoint assessment or who drop for any other reason such as toxicity or intolerability of the cap or hair loss will be considered as evaluable patients and "failures" for the primary efficacy analysis. We will recruit patients until the number of evaluable patients reaches the target (n=100) determined in the power/sample size calculation.

In addition to this primary efficacy analysis based on evaluable patients, we will perform a sensitivity analysis where we examine two different methods. The first will be an analysis where all patients that drop-out of the study (for any reason) will be considered as "failures" in the efficacy analysis. The second will be an analysis where only patients who complete the full series of measurements and adhere to the protocol are included in the efficacy analysis.

13.6 Analysis

Descriptive statistics (means, standard deviations, frequencies, etc.) will be presented for pretreatment patient characteristics and the outcome measures mentioned by treatment group.. Tables, graphs, and charts will be used to illustrate the data when appropriate. Each of the outcomes mentioned above will be analyzed and reported separately. The primary outcome analysis will be performed using a Fisher's exact test to compare the treated and control groups

based on the above definitions of success and failure. Next, a one-sample Chi-square test will be performed to test the treated group alone to rule out a lower bound of success of 40%. In addition, a 95% confidence interval will be constructed for the success rate in the treated group and the lower bound of this interval should exceed 40% while the observed success rate also exceeds 50%. Toxicity reports listing the incidence of all reported toxicities will be generated. All patients registered will be used for toxicity reports whether or not they are evaluable for efficacy response. Any Grade 4 or 5 toxicities will be reported to the Institutional Review Boards/Ethics Committee responsible for oversight of the study at the investigator's institution.

The secondary endpoints will be reported with descriptive statistics (means, medians, and measures of variability, including 95% confidence intervals for continuous measures and counts and percents, with corresponding 95% confidence intervals for categorical variables):

1. Safety assessed by a summary of the incidence and severity of adverse events and summary of scalp changes identified during physical examination.
2. Safety assessed by a summary of the incidence of scalp metastases during a 5-year follow up.
3. Tolerability defined as the percentage of patients who complete all planned cycles of chemotherapy using the DigniCap™ System.
4. Assessment of hair loss by the patient using alopecia self-report at each chemotherapy.
5. Assessment of hair re-growth by the patient using the Hair Re-growth Follow Up Survey.
6. Assessment of Quality of life during and after treatment with the DigniCap™ System by the patients using the EORTC-QLQ-BR23 scale and BIS.
7. Assessment of the impact of hair loss on cancer treatment decisions at 6 months after completion of chemotherapy.
8. All toxicities experienced will be documented.

14. PUBLICATION POLICY

The investigators are free to decide about publication of the study results in oral presentations at meetings, posters or full journal articles but are expected to give Dignitana AB a minimum of two weeks to comment on drafts.

15. SPONSOR

Dignitana AB is the sponsor of the study.

16. CONFIDENTIALITY

All study data is identified via codes and patient information is confidential and not traceable without the code key.

17. REFERENCES

General References

ICH/GCP

Declaration of Helsinki, latest version.

EN ISO 14155-1:2003, Clinical investigation of medical devices for human subjects – Part 1: General requirements.

EN ISO 14155-2:2003, Clinical investigation of medical devices for human subjects – Part 2: Clinical investigation plans.

FDA 21cfr PART 812.25.

Works Cited

1. Batchelor D. Hair and cancer chemotherapy: consequences and nursing care-a literature study. *Eur J Cancer Care* 2001; 10:147-63.
2. Mulders M, Vigerhoets A, Breed W. The impact of cancer and chemotherapy: Perceptual similarities and differences between cancer patients, nurses and physicians. *Eur J Oncol Nursing* 2008; 12:97-102.
3. Prevezas, C, Matard, B, Pinguier L, Reygagne, P. Irreversible and severe alopecia following docetaxel or paclitaxel cytotoxic therapy for breast cancer. *Br J Dermatol* 2009; 160:883-885.
4. Trüeb RM. Chemotherapy-Induced Alopecia. *Semin Cutan Med Surg* 2009 March; 28 (1): 11-14 *Hair and Nail Disorders*.
5. Medical Specialties of California (MSC) website. Penguin cold cap therapy, stopping chemotherapy induced alopecia. Retrieved February 14, 2012, from <http://www.msc-worldwide.com/indexusa.html>.
6. Paxman Coolers [Database on the Internet] www.paxman-coolers.co.uk.
7. Komen M.M.C, Smorenburg, C.H., van den Hurk C.J.G., en Nortier, J.W.R. (Hans). Hoofdhuidkoeling tegen alopecia door chemotherapie. *Ned Tidschr Geneeskd.* 2011; 155: 2053-7 (article in Dutch).
8. Grevelman and Breed. Prevention of chemotherapy-induced hair loss by scalp cooling. *Ann Oncol.* 2005 Mar;16(3):352-8.
9. Breed WPM, van den Hurk Corina JG, Peerbooms M. Presentation, impact and prevention of chemotherapy-induced hair loss: scalp cooling potentials and limitations. *Expert Rev Dermatol.* 2011; 6(1):109-25.
10. Hendriks M.A.E. et al. Evaluation of Cohens Cross-Section Trichometer for Measuring Hair Quantity. *Dermatol. Surg.* 2012; 1-4.

11. Poder T., Hez J., Lemieux R. Efficacité du casque réfrigéren Chimiothérapie. Bull Cancer. 2011; 98: 1119-28.
12. Lundgren-Eriksson L, Edbom G, Olofsson Y et al. Total prevention of taxoid-induced alopecia by a new model of cold cap (Dignitana). Eur J Cancer 1999; 35 (Suppl 4): 376.
13. Henriksen T, Jensen BK. Advanced computerized cold cap for preventing chemotherapy – induced alopecia. Herlev hospital, University of Copenhagen, Abstract and scientific poster ECCO 12. Sept 21-25 2003.
14. Ridderheim M, Bjurberg M, Gustavsson A. Scalp hypothermia to prevent chemotherapy induced alopecia is effective and safe: a pilot study of new digitized scalp-cooling system used in 74 patients Support Care Cancer 2003; 11:371-7.
15. Byahov M, Shevelev O. Alopecia prevention in chemotherapy patients. Method of controlled scalp cooling. Presentation at All-Russian Convention of Oncologists 2006. Published in Meditsinskaya Cartoteka, 2006.
16. Kato M , Sakuyama A., Imai R., Kobayashi TK. Evaluation of DigniCap System for the prevention of chemotherapy-induced hair loss in breast cancer patients. 12th St. Gallen International Breast Cancer Conference, 2011 (Poster Nb P330).
17. Abramov M., Semenova I. Cooling of the Scalp to prevent anticancer chemotherapy-induced alopecia. Eur J Cancer. 2011; 47 (suppl 1): S321 (abstract 4245).
18. Clinical Evaluation Report (Dignitana document) May 2012.
19. Dignitana AB Post Market Surveillance Report 2001-Aug. 2011. November 2011.
20. Breed WP. What is wrong with the 30-year-old practice of scalp cooling for the prevention of chemotherapy-induced hair loss? Support Care Cancer 2004; 12:3–5.
21. Lemieux J et al., [Incidence of scalp metastases in breast cancer: A retrospective cohort study in women who were offered scalp cooling](#). Breast Cancer Res Treat. 2009 Dec: 118(3): 547-52. Epub 2009 Feb 25.
22. Dean JC, Griffith KS, Cetas TC et al. Scalp hypothermia: a comparison of ice packs and the Kold Kap in the prevention of doxorubicin-induced alopecia. J Clin Oncol 1983; 1:33-7.
23. Rugo HS and Melin SA. Expert Statement on: Scalp Cooling with Adjuvant/ Neoadjuvant Chemotherapy for Breast Cancer and the Risk for Scalp Metastases. Feb 2012.
24. Van den Hurk C, Mols F, Vingerhoets J et al., Impact of alopecia and scalp cooling on the well-being of breast cancer patients. Psycho oncology. 2010 Jul:19(7):701-9
25. Camp-Sorrell D (1991) Scalp hypothermia devices: current status. ONS News 6:1–5
26. Bloomberg. Lisbon on Gel Cap That Prevents Hair Loss. Retrieved May 29, 2012, from <http://www.bloomberg.com/video/66131544/>.

27. Braff, D (2012, January 4). Cold caps show promise in keeping hair through chemo. Retrieved May 29, 2012, from <http://www.chicagotribune.com/health/sc-health-0104-chemo-cap-20120104,0,5128904.story>.
28. Ivanhoe Newswire (2011, December 26). Chemo Cold Cap: Cancer Patients Keep Their Hair. Retrieved May 29, 2012, from <http://www.newschannel5.com/story/16393701/chemo-cold-cap-cancer-patients-keep-their-hair>.
29. Aleccia, J (2010, December 20). Cold caps may help cancer patients keep their hair. Retrieved May 29, 2012, from <http://on.msnbc.com/hv3CdI>.
30. University of California – San Francisco (2010, December 14). UCSF physicians evaluate devices that could reduce hair loss in breast cancer patients undergoing chemotherapy. Retrieved May 29, 2012, from <http://bit.ly/fxvGvK>.
31. Dance, A (2010, December 27). Cooling caps tested to help cancer patients keep hair. Retrieved May 29, 2012, from <http://lat.ms/gESCzc>.
32. Johnson, C (2010, December 6). Cooling cap offers hope for chemo patients. Retrieved May 29, 2012, from <http://bit.ly/hJR8Ph>.
33. Zalkin, M (2010, October 28) Cold Cap Therapy May Help Women Undergoing Chemotherapy Keep Hair. Retrieved May 29, 2012, from <http://abcn.ws/cLg5Oi>.
34. Gregory, KL (2011, November 24). Cold Caps Aim to Preserve Hair for Cancer Patients. Retrieved February 21, 2012, from <http://m.vcstar.com/news/2011/nov/24/cold-caps-aim-to-preserve-hair-for-cancer/>.
35. Rapunzel Project website. The Rapunzel project. Retrieved February 14, 2012, from <http://www.rapunzelproject.org/>.
36. Weiss, S (2011, January 11). Breast cancer patient uses super-chilled headgear to try to retain her hair. Washington Post. Retrieved February 14, 2012, from http://www.washingtonpost.com/wp-dyn/content/article/2011/01/10/AR2011011006036.html?tid=wp_ipad.
37. Zalkin, M (2010, October 28). Cold Cap Therapy May Help Women Undergoing Chemotherapy Keep Hair. Retrieved February 21, 2012, from <http://abcnews.go.com/Health/OnCallPlus/cold-cap-therapy-women-chemotherapy-hair/story?id=11985624>.
38. Wills S, Ravipati A, Nguyen M, Dana Z, Jaiyesimi I, Margolis J, Decker D. Scalp Hypothermia Minimizes Alopecia in Breast Cancer Patients Receiving Non-Anthracycline Adjuvant Chemotherapy San Antonio Breast Symposium 2009; abstr 5040.
39. JC Dean, SE Salmon, and KS Griffith. Prevention of doxorubicin-induced hair loss with scalp hypothermia. N Engl J Med 1979; 301 (26):1421-1427.

18 APPENDICES

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APPENDIX I**ELIGIBILITY CHECKLIST – TREATMENT GROUP****PATIENT STUDY NUMBER** _____**SITE** _____**DATE** _____

Patients must have the following criteria to be eligible for the study:

- Female patient \geq 18 years of age
- Documented diagnosis of stage I or II breast cancer
- A planned course of chemotherapy in the adjuvant or neoadjuvant setting including one of the following regimens;
 - Doxorubicin 60 mg/m^2 and Cyclophosphamide 600 mg/m^2 x 4 - 6 cycles IV every 2 - 3 weeks
 - Docetaxel 75 mg/m^2 and Cyclophosphamide 600 mg/m^2 x 4 - 6 cycles IV every 3 weeks
 - Paclitaxel 80 mg/m^2 weekly IV x at least 12 weeks with or without IV trastuzumab
 - Paclitaxel 175 mg/m^2 IV every 2 weeks x 4 – 6 cycles (without an anthracycline)
 - Paclitaxel weekly and Carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles and trastuzumab IV weekly or every 3 weeks.
 - Docetaxel 75 mg/m^2 and Carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles and trastuzumab IV weekly or every 3 weeks.
 - Pertuzumab initial dose of 840mg, followed by 420 mg 603 every 3 weeks, Trastuzumab initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks, Docetaxel 75 mg/m^2
 - Targeted agents such as trastuzumab are allowed.
- Plan to complete chemotherapy within 6 months
- At least two years out from the last chemotherapy causing hair loss with complete recovery of hair
- Karnofsky performance status \geq 80%
- Willing and able to sign informed consent for protocol treatment
- Willing to participate in study procedures including having photographs of the head before each cycle of chemotherapy and 1 month after the last chemotherapy

- Willing to enroll in an extension protocol for follow up for 5 years following the end of chemotherapy treatment

Patients must NOT have any of the following criteria to be eligible for the study:

- Patients with female pattern baldness resembling picture I-3 or higher on the Savin scale, see Appendix IIB
- Autoimmune disease affecting hair; e.g. alopecia areata, systemic lupus with associated hair loss
- A history of whole brain radiation
- Plans to use a chemotherapy regimen other than those specified in the inclusion criteria. Specifically, patients receiving a regimen including both an anthracycline and a taxane are not eligible for this trial (AC/T, EC/T, TAC, etc)
- Concurrent hormone therapy with chemotherapy. Hormone therapy should be given as indicated following completion of chemotherapy
- Underlying clinically significant liver disease including active viral hepatitis with abnormal liver function tests >1.5 times the upper limit of normal, including alkaline phosphatase, AST, and total bilirubin. Patients with Gilbert's disease (elevated indirect bilirubin only) will be eligible for participation.
- Clinically significant renal dysfunction defined as serum creatinine > upper limit of normal.
- A serious concurrent infection or medical illness which would jeopardize the ability of the patient to complete the planned chemotherapy and follow-up
- A history of persistent grade 2 alopecia induced by prior chemotherapeutic regimens
- Participation in another clinical investigation or exposure to other investigational agents, drugs, device or procedure that may cause hair loss
- Intercurrent life-threatening malignancy
- A history of cold agglutinin disease or cryoglobulinemia
- Evidence of untreated or poorly controlled hyper- or hypothyroidism
- A history of silicon allergy
- American Society of Anesthesiologist Class ≥ 3 , see Appendix V.A.

Enrolling Investigator: _____ Date: _____

Study Coordinator: _____ Date: _____

ELIGIBILITY CHECKLIST – CONTROL GROUP**PATIENT STUDY NUMBER** _____**SITE** _____**DATE** _____

Patients must have the following criteria to be eligible for the study:

- Female patient \geq 18 years of age
- Documented diagnosis of stage I or II breast cancer
- A planned course of chemotherapy in the adjuvant or neoadjuvant setting including one of the following regimens;
 - Doxorubicin 60 mg/m² and Cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 2 - 3 weeks
 - Docetaxel 75 mg/m² and Cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 3 weeks
 - Paclitaxel 80 mg/m² weekly IV x at least 12 weeks with or without IV trastuzumab
 - Paclitaxel 175 mg/m² IV every 2 weeks x 4 – 6 cycles (without an anthracycline)
 - Paclitaxel weekly and Carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles and trastuzumab IV weekly or every 3 weeks.
 - Docetaxel 75 mg/m² and Carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles and trastuzumab IV weekly or every 3 weeks.
 - Pertuzumab initial dose of 840mg, followed by 420 mg 603 every 3 weeks, Trastuzumab initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks, Docetaxel 75 mg/m²
 - Targeted agents such as trastuzumab are allowed.
- At least two years out from the last chemotherapy causing hair loss with complete recovery of hair
- Karnofsky performance status \geq 80%
- Willing and able to sign informed consent for protocol treatment

- Willing to participate in study procedures including having photographs of the head before each cycle of chemotherapy and 1 month after the last chemotherapy
- Choose not to use scalp cooling during chemotherapy

Patients must NOT have any of the following criteria to be eligible for the study:

- Patients with female pattern baldness resembling picture I-3 or higher on the Savin scale, see Appendix IIB
- Autoimmune disease affecting hair; e.g. alopecia areata, systemic lupus with associated hair loss
- A history of whole brain radiation
- Plans to use a chemotherapy regimen other than those specified in the inclusion criteria. Specifically, patients receiving a regimen including both an anthracycline and a taxane are not eligible for this trial (AC/T, EC/T, TAC, etc)
- Concurrent hormone therapy with chemotherapy. Hormone therapy should be given as indicated following completion of chemotherapy
- Underlying clinically significant liver disease including active viral hepatitis with abnormal liver function tests >1.5 times the upper limit of normal, including alkaline phosphatase, AST, and total bilirubin. Patients with Gilbert's disease (elevated indirect bilirubin only) will be eligible for participation.
- Clinically significant renal dysfunction defined as serum creatinine > upper limit of normal.
- A serious concurrent infection or medical illness which would jeopardize the ability of the patient to complete the planned chemotherapy and follow-up
- A history of persistent grade 2 alopecia induced by prior chemotherapeutic regimens
- Participation in another clinical investigation or exposure to other investigational agents, drugs, device or procedure that may cause hair loss
- Intercurrent life-threatening malignancy
- Evidence of untreated or poorly controlled hyper- or hypothyroidism
- American Society of Anesthesiologist Class ≥ 3 , see Appendix V.A.

Enrolling Investigator: _____ Date: _____

Study Coordinator: _____ Date: _____

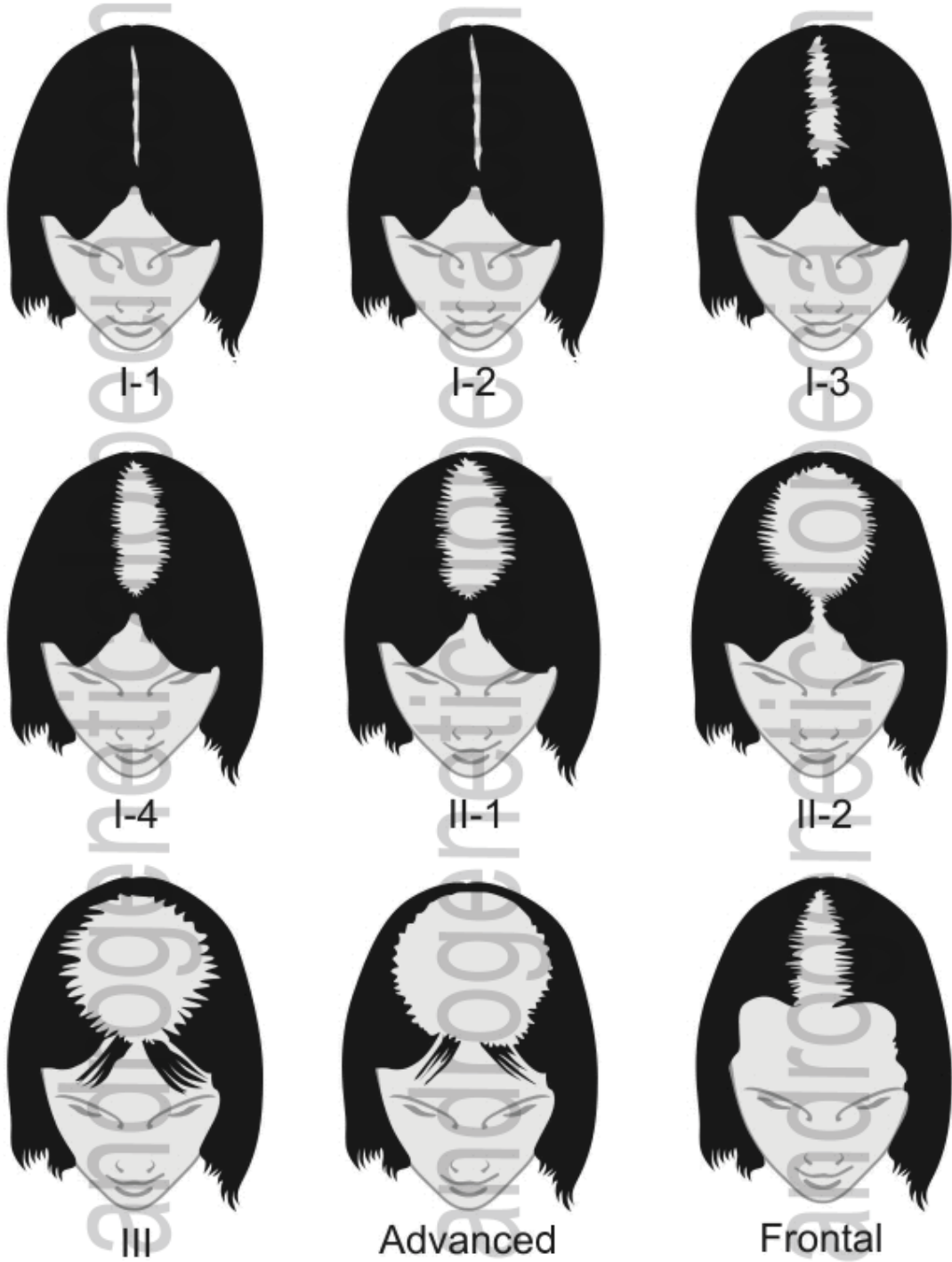
APPENDIX IA

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

APPENDIX IB

SAVIN SCALE



APPENDIX III

INFORMED CONSENT

Please see attachment.

PATIENT INFORMATION

Add Dignitana Patient information

APPENDIX IV

BASELINE CRF

DATE OF STUDY REGISTRATION (DD/MM/YYYY) _____

DEMOGRAPHICS:

PATIENT STUDY NUMBER _____

SITE _____

ETHNICITY(Chose **one**): __HISPANIC __NON-HISPANIC

RACE: (Chose **all** that apply): __WHITE __BLACK

 __ASIAN __PACIFIC ISLANDER __NATIVE AMERICAN

MEDICAL HISTORY

PRIOR RADIATION? __YES __NO

IF YES, SPECIFY SITE _____

DATE (DD/MM/YYYY)_____

DURATION_____

HISTORY OF PRIOR TREATMENT FOR BREAST CANCER? __YES __NO

IF YES, SPECIFY CHEMOTHERAPY BELOW

AGENT	DOSE	NUMBER OF CYCLES

DATE OF START (DD/MM/YYYY)_____

DATE OF COMPLETION (DD/MM/YYYY)_____

HORMONE THERAPY YES __ NO _____

TYPE OF TREATMENT _____

INCLUSIVE DATES (DD/MM/YYYY, list start and stop)_

PRIOR CHEMOTHERAPY FOR ANY REASON? __YES __NO

IF YES, SPECIFY

AGENT	DOSE	NUMBER OF CYCLES

DATE OF START (DD/MM/YYYY)_____

DATE OF COMPLETION (DD/MM/YYYY) _____

HISTORY OF SCALP SURGERY? ___ YES ___ NO
IF YES, SPECIFY DATE (DD/MM/YYYY) _____
PURPOSE _____

HISTORY OF HYPER OR HYPOTHYROIDISM? ___ YES ___ NO
IF YES, SPECIFY
APPROXIMATE DATE OF DIAGNOSIS _____
TREATMENT _____

HISTORY OF ANY OTHER SERIOUS MEDICAL ILLNESSES? ___ YES ___ NO
IF YES, SPECIFY _____

HISTORY OF HEADACHES OR MIGRAINE? ___ YES ___ NO
IF YES, SPECIFY
FREQUENCY _____
SEVERITY
0 10
USUAL TREATMENT _____
ANY HOSPITALIZATION OR ER VISITS? PLEASE SPECIFY

BREAST CANCER HISTORY
DATE OF FIRST DIAGNOSIS OF THIS BREAST CANCER _____

SURGERY DATE (DD/MM/YYYY) IF APPLICABLE _____

PLEASE ATTACH ALL PATHOLOGY REPORTS

ER STATUS
 +
 -

PR STATUS
 +
 -

HER2NEU OVEREXPRESSION/AMPLIFICATION
 POSITIVE
 NEGATIVE

METHOD OF DETERMINATION
IHC RESULT _____
FISH RESULT _____

PLANNED CHEMOTHERAPY
 ADJUVANT
 NEO ADJUVANT

PLANNED REGIMEN

PLANNED START DATE (DD/MM/YYYY) _____

PLEASE SPECIFY

DRUG	DOSE	NUMBER OF CYCLES

CURRENT MEDICATIONS ___YES ___NO

IF YES, SPECIFY

DRUG NAME	DOSE	DOSING FREQUENCY	DATE OF TREATMENT START (DD/MM/YYYY)

PHYSICAL EXAMINATION

DATE OF EXAMINATION _____

HEIGHT: _____.____ inches WEIGHT: _____.____ lbs. (actual)

SCALP

- NORMAL
- ABNORMAL, SPECIFY _____

SCALP DERMATITIS ___ YES ___ NO

OTHER _____

SKIN

- NORMAL
- ABNORMAL, SPECIFY (e.g. psoriasis, eczema, etc) _____

Skin toxicity will be determined using the revised NCI Common Toxicity Criteria (CTC) version **4.0** for Toxicity and Adverse Event Reporting.

LABS

TOTAL BILIRUBIN _____

ALKALINE PHOSPHATASE _____

AST _____

CREATININE _____

OTHER COMMENTS

APPENDICES TO BE FILLED OUT AT BASELINE

- Eligibility checklist, Appendix I
- Signed Informed Consent, Appendix III
- Alopecia self-report, Appendix VIII
- Symptoms survey, Appendix IX
- EORTC-QLQ-BR23, Appendix X
- Body Image Scale (BIS), Appendix XI
- Impact of hair loss on treatment decision, Appendix XII

Investigator

Signature: _____ Date _____

APPENDIX IV.A

AMERICAN SOCIETY OF ANESTHESIOLOGISTS CLASSIFICATION

P1	A normal healthy patient
P2	A patient with mild systemic disease
P3	A patient with severe systemic disease
P4	A patient with severe systemic disease that is a constant threat to life
P5	A moribund patient who is not expected to survive without the operation
P6	A declared brain-dead patient whose organs are being removed for donor purposes

APPENDIX V

CASE REPORT FORM FOR ALL CHEMOTHERAPY CYCLES

PATIENT STUDY NUMBER _____
SITE _____
DATE _____
CYCLE NUMBER _____

Any new medications since baseline or last cycle? ___ YES ___ NO
 IF YES, SPECIFY

DRUG NAME	DOSE	DOSING FREQUENCY	DATE OF TREATMENT START (DD/MM/YYYY)

PHYSICAL EXAMINATION

SCALP

- NORMAL
- ABNORMAL, SPECIFY _____

SCALP DERMATITIS ___ YES ___ NO

OTHER _____

SKIN

- NORMAL
- ABNORMAL, SPECIFY (e.g. psoriasis, exzema, etc) _____

Skin toxicity will be determined using the revised NCI Common Toxicity Criteria (CTC) version **4.0** for Toxicity and Adverse Event Reporting.

DATE OF EXAMINATION _____

APPENDICES TO BE FILLED OUT AT EACH CHEMOTHERAPY VISIT

- Alopecia self report (current hair loss vs baseline, wig use, hair quality, satisfaction with hair), Appendix VIII
- Patient symptoms survey, Appendix IX
- If applicable, MEDWATCH, Appendix XIV
- Case Report Form for Device Use, Appendix XXIII

Additional appendices to fill out at the chemotherapy cycle half-way through (visit 4)

- EORTC-QLQ-BR23, Appendix X
- Body Image Scale (BIS), Appendix XI

Investigator Signature: _____ Date _____

APPENDIX VI

CASE REPORT FORM FOR THE FOLLOW-UP AT 3 MONTHS AFTER COMPLETION OF CHEMOTHERAPY

PATIENT STUDY NUMBER _____

SITE _____

DATE _____

MEDICAL HISTORY

RADIATION _____ YES _____ NO

CHEMOTHERAPY _____ YES _____ NO

SURGERY _____ YES _____ NO

PRIOR INVESTIGATIONAL DRUG _____ YES _____ NO Specify: _____

VITAL SIGNS

WEIGHT: _____ kg (actual)

PHYSICAL EXAMINATION

SCALP DERMATITIS _____ YES _____ NO

DANDRUFF _____ YES _____ NO

Has the patient developed metastatic disease? _____ YES _____ NO

If yes,

Site of Metastatic Disease Date of Diagnosis Confirmation by Pathology or Imaging?

_____	_____	_____
_____	_____	_____
_____	_____	_____

Any new medications since last study visit? _____ YES _____ NO

IF YES, SPECIFY

DRUG NAME	DOSE	DOSING FREQUENCY	DATE OF TREATMENT START (DD/MM/YYYY)

Investigator Signature: _____ Date _____

**APPENDICES TO BE FILLED OUT AT THE FOLLOW-UP VISITS AT 3 MONTHS
AFTER COMPLETION OF CHEMOTHERAPY**

- Alopecia self report (current hair loss vs baseline, use of head cover, hair quality, satisfaction with hair), Appendix VIII
- EORTC-QLQ-BR23, Appendix X
- Body Image Scale (BIS), Appendix XI
- Impact of hair loss on treatment decision, Appendix XII
- Hair re-growth follow up survey, Appendix XIII
- If applicable, MEDWATCH, Appendix XIV

APPENDIX VII

CASE REPORT FORM FOR THE FOLLOW-UP AT 6 MONTHS AFTER COMPLETION OF CHEMOTHERAPY

PATIENT STUDY NUMBER _____
SITE _____
DATE _____

VITAL SIGNS

WEIGHT: ___ ___ ___ . ___ kg (actual)

PHYSICAL EXAMINATION

SCALP DERMATITIS _____ YES _____ NO

DANDRUFF _____ YES _____ NO

Has the patient developed metastatic disease? _____ YES _____ NO

If yes,

Site of Metastatic Disease **Date of Diagnosis** **Confirmation by Pathology or Imaging?**

_____	_____	_____
_____	_____	_____
_____	_____	_____

Any new medications since last study visit? _____ YES _____ NO

IF YES, SPECIFY

DRUG NAME	DOSE	DOSING FREQUENCY	DATE OF TREATMENT START (DD/MM/YYYY)

Investigator Signature: _____ **Date** _____

**APPENDICES TO BE FILLED OUT AT THE FOLLOW-UP VISITS AT 6 MONTHS
AFTER COMPLETION OF CHEMOTHERAPY**

- Alopecia self report (current hair loss vs baseline, use of head cover, hair quality, satisfaction with hair), Appendix VIII
- EORTC-QLQ-BR23, Appendix X
- Body Image Scale (BIS), Appendix XI
- Hair re-growth follow up survey, Appendix XIII
- If applicable, MEDWATCH, Appendix XIV

APPENDIX VIII

ALOPECIA SELF REPORT

PATIENT STUDY NUMBER _____

SITE _____

DATE _____

CYCLE _____

HAIR LOSS

1. Please mark an **X** on the option that best describes your overall hair loss compared to the standardized photographs at this time:
- no hair loss
 - greater than 0 up to 25% hair loss
 - greater than 25 up to 50% hair loss
 - greater than 50 up to 75%
 - greater than 75% hair loss

USE OF HEAD COVER

2. Please place an **X** by the answer that most accurately describes your current use of wig, cap, scarf or other head cover because of hair loss:

Never _____

Sometimes _____

Always _____

SATISFACTION WITH PRESERVATION OF HAIR BECAUSE OF SCALP COOLING DURING CHEMOTHERAPY

3. Please place an **X** at the position on the scale that reflects your satisfaction with the quantity of your hair at this time.

0	10	20	30	40	50	60	70	80	90	100
Completely dissatisfied				Neither satisfied nor dissatisfied						Completely satisfied

4. Please place an **X** at the position on the scale that reflects your satisfaction with your decision to use scalp cooling during chemotherapy

0	10	20	30	40	50	60	70	80	90	100
Completely dissatisfied				Neither satisfied nor dissatisfied						Completely satisfied

HAIR QUALITY BECAUSE OF CHEMOTHERAPY/ SCALP COOLING

4. Please place an **X** by the statement(s) that most accurately describe the quality of your hair at this time.

Texture is coarse _____

Texture is unchanged _____

Hair has less body _____

Hair color has changed _____ (explain) _____

My hair is:

Thick _____

Medium _____

Thin _____

5. Please place an **X** on the scale that reflects your satisfaction with the quality of your hair at this time.

0	10	20	30	40	50	60	70	80	90	100
Completely dissatisfied				Neither satisfied nor dissatisfied						Completely satisfied

Please explain your satisfaction rating:

APPENDIX IX

SYMPTOMS SURVEY (To be filled out by the patient at the end of each chemotherapy treatment)

PATIENT STUDY NUMBER _____

SITE _____

DATE _____

CYCLE _____

1. In the past month have you experienced headache? _____yes _____no

If yes, how many headaches have you experienced in the past month?

1-2_____

3-4_____

5-6_____

> 6_____

More than usual? _____yes _____no

2. Did the scalp cooling treatment today trigger or exacerbate headache or migraine? ____yes ____no

3. If yes, please mark the location on the scale below that best describes the level of pain you experienced with headaches today.

(0= no pain 50= moderate pain 100= worst possible pain)

0 10 20 30 40 50 60 70 80 90 100

4. Please mark the point on the scale that best describes how chilled you felt during the cooling down period today.

(0=none, 100=as bad as it could be)

0 10 20 30 40 50 60 70 80 90 100

5. Please mark the point on the scale that best describes how chilled you felt with your overall cooling treatment today.

(0=none, 100=as bad as it could be)

0 10 20 30 40 50 60 70 80 90 100

6. Please mark the scale at the point that best describes any scalp pain you experienced with your treatment today.

(0= no pain 50= moderate pain 100= worst possible pain)

0 10 20 30 40 50 60 70 80 90 100

7- Did you take any pain killers today because of your scalp cooling treatment?

Yes No

Comment _____

APPENDIX X

EORTC-QLQ-BR23

Please see attachment.

PATIENT STUDY NUMBER _____

SITE _____

DATE _____

FOLLOW UP NUMBER _____



EORTC QLQ - BR23

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

During the past week:

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

During the past four weeks:

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

Please go on to the next page

During the past week:

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



APPENDIX XI**BODY IMAGE SCALE (BIS)****PATIENT STUDY NUMBER** _____**SITE** _____**DATE** _____**CYCLE OR FOLLOW-UP NUMBER** _____

In this questionnaire you will be asked how you feel about your appearance and about any changes that may have resulted from your disease or treatment. Please read each item carefully and place a checkmark on the line below the reply that best describes the way you have been feeling about yourself during the past week.

Have you been feeling self-conscious about your appearance?

Not at all	A little	Quite a bit	Very much
.....

Have you felt less physically attractive as a result of your disease or treatment?

Not at all	A little	Quite a bit	Very much
.....

Have you been dissatisfied with your appearance when dressed?

Not at all	A little	Quite a bit	Very much
.....

Have you been feeling less feminine/masculine as a result of your disease or treatment?

Not at all	A little	Quite a bit	Very much
.....

Did you find it difficult to look at yourself naked?

Not at all	A little	Quite a bit	Very much
.....

Have you been feeling less sexually attractive as a result of your disease or treatment?

Not at all	A little	Quite a bit	Very much
.....

Did you avoid people because of the way you felt about your appearance?

Not at all	A little	Quite a bit	Very much
.....

Have you been feeling that the cancer treatment has left your body less whole?

Not at all	A little	Quite a bit	Very much
.....

Have you felt dissatisfied with your body?

Not at all	A little	Quite a bit	Very much
---------------------	-------------------	----------------------	--------------------

Have you been dissatisfied with the appearance of your scar?

Not at all	A little	Quite a bit	Very much
---------------------	-------------------	----------------------	--------------------

HAIR APPERCEPTION

Please circle the statement that best reflects your opinion at this time:

a. My hair is important to me

1 Disagree Strongly	2 disagree somewhat	3 neutral	4 agree somewhat	5 agree strongly
---------------------------	---------------------------	--------------	------------------------	------------------------

b. My hair is important for my appearance

1 Disagree Strongly	2 disagree somewhat	3 neutral	4 agree somewhat	5 agree strongly
---------------------------	---------------------------	--------------	------------------------	------------------------

APPENDIX XII

IMPACT OF HAIR LOSS ON TREATMENT DECISIONS

PATIENT STUDY NUMBER _____

SITE _____

DATE _____

At baseline and at follow up 3 months after completion of chemotherapy:

Does/did hair loss affect your decisions about taking chemotherapy?

- Not at All
- A Little
- Quite a Bit
- Very Much

Did the availability of scalp cooling affect your decision?

Explain: _____

APPENDIX XIII

HAIR RE-GROWTH FOLLOW UP SURVEY

PATIENT STUDY NUMBER _____

SITE _____

DATE _____

FOLLOW UP NUMBER _____

1. Have you experienced visible hair re-growth?

No _____ Yes _____ Not applicable (Did not experience hair loss) _____

2. Please place an **X** by the answer that most accurately describes your current use of wig, cap, scarf or other head cover because of hair loss:

Never _____ Sometimes _____ Always _____

3. Please describe the texture of your hair since beginning chemotherapy.

- _____ hair is finer
- _____ hair is coarser
- _____ hair has re-grown but is curly now
- _____ hair has re-grown and is no different in texture than before chemotherapy
- _____ did not lose hair
- _____ hair has re-grown thicker
- _____ hair has re-grown but thinner

4. Please place an **X** by the statement(s) that most accurately describes the quality of your hair at this time.

- _____ Texture is coarse
- _____ Hair feels "dead"
- _____ Hair falls out more easily
- _____ Happy with hair quality
- _____ Unhappy with hair quality
- _____ Texture is unchanged
- _____ Hair color has changed (explain) _____
- _____ I like the way my hair feels
- _____ I do not like the way my hair feels

5. Please place an **X** on the scale that reflects your satisfaction with the quality of your hair because of chemotherapy/ scalp cooling at this time.

0	10	20	30	40	50	60	70	80	90	100
Completely dissatisfied				Neither satisfied nor dissatisfied						Completely satisfied

6. Please place an **X** on the scale that reflects your satisfaction with the quantity of your hair at this time.

0	10	20	30	40	50	60	70	80	90	100
Completely dissatisfied				Neither satisfied nor dissatisfied						Completely satisfied

Please explain your satisfaction rating:

6. Other comments on hair quality texture and satisfaction with hair:

APPENDIX XIV

MEDWATCH -please see attachment

U.S. Department of Health and Human Services
Food and Drug Administration

For use by user-facilities,
importers, distributors and manufacturers
for MANDATORY reporting

Mfr Report #
UF/Importer Report #
FDA Use Only

MEDWATCH

FORM FDA 3500A (6/10)

Page 1 of _____

A. PATIENT INFORMATION			
1. Patient Identifier In confidence	2. Age at Time of Event: or _____ Date of Birth:	3. Sex <input type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight ____ lbs or ____ kgs
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: _____ (mm/dd/yyyy)		<input type="checkbox"/> Disability or Permanent Damage	
<input type="checkbox"/> Life-threatening		<input type="checkbox"/> Congenital Anomaly/Birth Defect	
<input type="checkbox"/> Hospitalization - initial or prolonged		<input type="checkbox"/> Other Serious (Important Medical Events)	
<input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy)		4. Date of This Report (mm/dd/yyyy)	
5. Describe Event or Problem			
6. Relevant Tests/Laboratory Data, Including Dates			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1 _____			
#2 _____			
2. Dose, Frequency & Route Used		3. Therapy Dates (If unknown, give duration from/to (or best estimate))	
#1 _____		#1 _____	
#2 _____		#2 _____	
4. Diagnosis for Use (Indication)			5. Event Abated After Use Stopped or Dose Reduced? #1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
#1 _____			
#2 _____			#2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
6. Lot #		7. Exp. Date	
#1 _____		#1 _____	
#2 _____		#2 _____	
8. Event Reappeared After Reintroduction?			
#1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply		#2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
#1 _____			
#2 _____			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			

D. SUSPECT MEDICAL DEVICE			
1. Brand Name DigniCap System			
2. Common Device Name Dignicap			
3. Manufacturer Name, City and State Dignitana AB, Ruben Rausing's gata 9, SE-223 55 Lund, Sweden			
4. Model #		Lot #	
Catalog #		Expiration Date (mm/dd/yyyy)	
Serial #		Other #	
5. Operator of Device			
<input checked="" type="checkbox"/> Health Professional			
<input type="checkbox"/> Lay User/Patient			
<input type="checkbox"/> Other:			
6. If Implanted, Give Date (mm/dd/yyyy)		7. If Explanted, Give Date (mm/dd/yyyy)	
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No			
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor			
10. Device Available for Evaluation? (Do not send to FDA) <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Returned to Manufacturer on: _____ (mm/dd/yyyy)			
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			

E. INITIAL REPORTER			
1. Name and Address			Phone #
2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		3. Occupation	4. Initial Reporter Also Sent Report to FDA <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Unk.

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

PLEASE TYPE OR USE BLACK INK

MEDWATCH

FORM FDA 3500A (6/10) (continued)

Page 2 of _____

FDA USE ONLY

F. FOR USE BY USER FACILITY/IMPORTER (Devices Only)

1. Check One <input checked="" type="checkbox"/> User Facility <input type="checkbox"/> Importer		2. UF/Importer Report Number	
3. User Facility or Importer Name/Address			
4. Contact Person		5. Phone Number	
6. Date User Facility or Importer Became Aware of Event (mm/dd/yyyy)		8. Date of This Report (mm/dd/yyyy)	
		7. Type of Report <input type="checkbox"/> Initial <input type="checkbox"/> Follow-up # _____	
9. Approximate Age of Device		10. Event Problem Codes (Refer to coding manual)	
		Patient Code: [] - [] - [] Device Code: [] - [] - []	
11. Report Sent to FDA? <input type="checkbox"/> Yes _____ (mm/dd/yyyy) <input type="checkbox"/> No _____		12. Location Where Event Occurred <input type="checkbox"/> Hospital <input type="checkbox"/> Outpatient Diagnostic Facility <input type="checkbox"/> Home <input type="checkbox"/> Ambulatory Surgical Facility <input type="checkbox"/> Nursing Home <input type="checkbox"/> Outpatient Treatment Facility <input type="checkbox"/> Other: _____ (Specify)	
13. Report Sent to Manufacturer? <input type="checkbox"/> Yes _____ (mm/dd/yyyy) <input type="checkbox"/> No _____			
14. Manufacturer Name/Address			

G. ALL MANUFACTURERS

1. Contact Office - Name/Address (and Manufacturing Site for Devices)		2. Phone Number	
		3. Report Source (Check all that apply) <input type="checkbox"/> Foreign <input type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other: _____	
4. Date Received by Manufacturer (mm/dd/yyyy)		5. (A)NDA # _____ IND # _____ STN # _____ PMA/510(k) # _____ Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol #			
7. Type of Report (Check all that apply) <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input type="checkbox"/> 15-day <input type="checkbox"/> Follow-up # _____			
9. Manufacturer Report Number		8. Adverse Event Term(s)	

H. DEVICE MANUFACTURERS ONLY

1. Type of Reportable Event <input type="checkbox"/> Death <input type="checkbox"/> Serious Injury <input type="checkbox"/> Malfunction <input type="checkbox"/> Other: _____		2. If Follow-up, What Type? <input type="checkbox"/> Correction <input type="checkbox"/> Additional Information <input type="checkbox"/> Response to FDA Request <input type="checkbox"/> Device Evaluation	
3. Device Evaluated by Manufacturer? <input type="checkbox"/> Not Returned to Manufacturer <input type="checkbox"/> Yes <input type="checkbox"/> Evaluation Summary Attached <input type="checkbox"/> No (Attach page to explain why not) or provide code: _____		4. Device Manufacture Date (mm/yyyy)	
		5. Labeled for Single Use? <input type="checkbox"/> Yes <input type="checkbox"/> No	
6. Evaluation Codes (Refer to coding manual)			
Method [] - [] - [] - []			
Results [] - [] - [] - []			
Conclusions [] - [] - [] - []			
7. If Remedial Action Initiated, Check Type <input type="checkbox"/> Recall <input type="checkbox"/> Notification <input type="checkbox"/> Repair <input type="checkbox"/> Inspection <input type="checkbox"/> Replace <input type="checkbox"/> Patient Monitoring <input type="checkbox"/> Relabeling <input type="checkbox"/> Modification/Adjustment <input type="checkbox"/> Other: _____		8. Usage of Device <input type="checkbox"/> Initial Use of Device <input type="checkbox"/> Reuse <input type="checkbox"/> Unknown	
		9. If action reported to FDA under 21 USC 360(f), list correction/removal reporting number:	
10. <input type="checkbox"/> Additional Manufacturer Narrative and / or 11. <input type="checkbox"/> Corrected Data			

The public reporting burden for this collection of information has been estimated to average 66 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

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Please DO NOT RETURN this form to this address.

MEDWATCH

FORM FDA 3500A (6/10) (continued)

Page 3 of _____

B.5. Describe Event or Problem (continued)

B.6. Relevant Tests/Laboratory Data, Including Dates (continued)

B.7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)

Concomitant Medical Products and Therapy Dates (Exclude treatment of event) (For continuation of C.10 and/or D.11; please distinguish)

Other Remarks

APPENDIX XIX

TRAINING PROTOCOL

Please see attachment.

A decorative graphic consisting of several overlapping circles in various shades of blue (dark, medium, and light) and thin, light blue lines that intersect and extend across the page. One large circle is in the top left, a smaller one is on the right edge, and another large one is in the bottom right corner.

Training of personnel

Instructions for scalp cooling treatment using
the DigniCap™ System

Guide for training according to REC044 Training of nurses,
checklist.

Dignitana AB
TR-20111129-02-EN

Training of personnel:

Instructions for scalp cooling treatment using the DigniCap™ System

Introduction.....	2
Principle and procedure	2
Demonstration of the system	3
The caps and how they are used	3
DigniCap™ scalp cooling procedure.....	5
Preparing for scalp cooling.....	5
Wetting the hair	5
Hygienic inner cap	5
During Scalp Cooling	6
Movement.....	6
Comfort/discomfort	6
Pausing the treatment	6
Post-Infusion Cooling Time.....	7
After scalp cooling	7
Practical training.....	8
How to fit the silicon and neoprene cap properly.....	8
(Dis-)connecting couplings.....	12
Trouble-shooting.....	13
Review of alarm icons	13
Low level of DigniCool™	13
Temporary power failure	13
Couplings	13
Temperature out of range.....	13
Sensor issues.....	13
Maintenance	14
Cooling liquid (DigniCool™)	14
How to handle.....	14
Disposal considerations.....	14
Refilling the tank	14
Cleaning the system.....	14
Cleaning and handling/storage of caps	15
Air filter.....	15

Introduction

Principle and procedure

Figure 1: Scalp cooling prevents chemotherapy-induced alopecia in two ways:

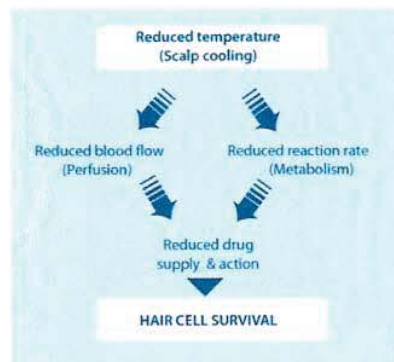


Fig.1

- Reduction of the blood flow to the scalp leads to reduced drug exposure
- Reduction of metabolism of the hair follicles leads to reduced drug uptake and action

Both mechanisms decrease the effect of the drug on the hair follicles and increase their chance of surviving chemotherapy, thereby preventing alopecia (Fig. 1).

To achieve good results, it is important to ensure efficient cooling of the scalp before (pre-infusion cooling), during (pre-infusion cooling), and for a certain time after (post-infusion cooling) the chemotherapy infusion time.

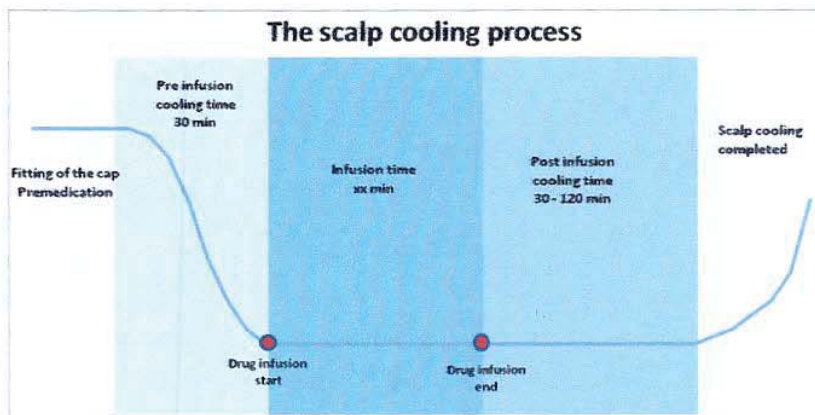


Fig.2

Cooling times in relation to medication during chemotherapy:

- Pre-infusion cooling: 30 minutes, including 20 minutes cooling-down period for the cap from room temperature to treatment temperature.
- Cooling during chemotherapy infusion.
- Post-infusion cooling: depending on the drugs and drug concentrations, recommended post-infusion cooling times are between 30 and 120 min. (Fig. 2).

Demonstration of the system

- Main menu & Settings menu
- How to start a treatment – brief overview, no details

The caps and how they are used

- Available sizes
 - The DigniCap™ is available in four different sizes and with tubes located on different sides of the cap (see Table 1).

DigniCap™ size	DigniCap™ colour	DigniTherm™ colour
Extra Small (XS) 1 (left)	Red	Red and black
Small (S) 1 and 2 (left and right)	Blue	Blue and black
Medium (M) 1 and 2 (left and right)	Green	Green and black
Large (L) 2 (right)	Yellow	Yellow and black

Table 1. Sizes and colours of DigniCap™ and corresponding DigniTherm™.

- The DigniCap™ is designed to cover the part of the head where the hair grows; it is not supposed to cover the forehead or the ears.
- Orientations of DigniCap™ and DigniTherm™
 - Please note the following when placing the DigniCap™ on the patient's head:
 - Always place the DigniCap™ on the patient's head in the right direction: The straight line of the cap (also marked with the text FRONT and an arrow) must be placed to the front of the patient's head and the rounded line must be located at the back (Fig. 2). The tubes which connect the cap to the instrument are then located behind the ear (Fig. 3).
 - For the patient's comfort and to minimise the risk of cap movement, always choose a DigniCap™ with the tubes oriented towards the cooling unit when placed on the patient's head.



Fig. 2 Orientations of DigniCap™



Fig. 3 Location of the tubes in relation to the patient's head.

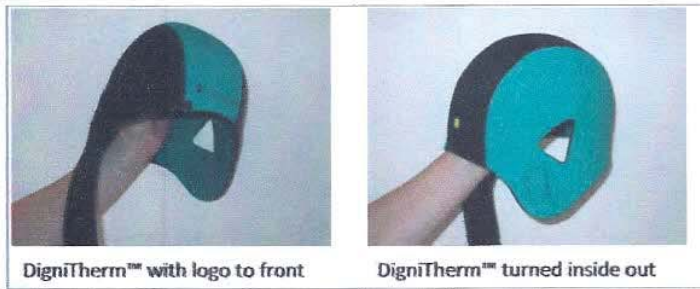


Fig. 4 Orientations of DigniTherm™.

The DigniCap™ is designed to cover the part of the head where the hair grows; it is not supposed to cover the forehead or the ears.

DigniCap™ scalp cooling procedure

Useful equipment (not supplied with the DigniCap™ System)

The following equipment is useful in preparing for the scalp cooling treatment:

- Access to a tap or water in a spray bottle
- Two towels
- Facial tissues
- Blanket

Ask the patient to bring:

- A comb or hair brush
- An extra cardigan
- Warm socks

Preparing for scalp cooling

- Efficient scalp cooling requires continuous and uniform cooling of the scalp. Please ensure that the DigniCap™ is in close contact with the scalp:
 - over the entire hair growth area
 - throughout the scalp cooling procedure
- Any air trapped between the scalp and the cap has an insulating effect, which will affect scalp cooling efficiency. As a result hair root cells will be exposed to the effects of the chemotherapy drugs. Alopecia will not be prevented on areas on the head which are not in close contact with the DigniCap™.
- Always place the DigniCap™ on the patient's head in cooperation with the patient. She/ he should be able to feel when the cap is positioned correctly and can provide valuable support during fitting of the cap.
- Ask the patient to tell you immediately if the cap is very uncomfortable or if it causes him/her any pain. The cap can then be taken off and re-fitted more comfortably.

Wetting the hair

1. Ask the patient to remove any hair band, hair pins etc. as well as earrings, studs or hearing aids.
2. Ask the patient to take off his/her glasses while the cap is being fitted.
NOTE Glasses may be worn during scalp cooling, but they have to be worn outside the DigniTherm™ or between the DigniCap™ and the DigniTherm™. Do **not** place the ear pieces **under** the DigniCap™.
3. Place a towel around the patient's shoulders to prevent the clothes becoming wet. If the patient has long hair, ensure that it is resting on the towel.
4. Ask the patient to wet his/her hair thoroughly under a tap or with a spray bottle, or provide assistance if required. It is important that the hair is completely saturated with water. When using a spray bottle, lift up areas of the hair and spray the water underneath to ensure it is completely wet and that the scalp is also wet (not just the surface of the hair).
NOTE Only the hair covering the scalp needs to be wet. If the patient's hair is longer than shoulder length, this part of the hair does not have to be wet.
5. Use a towel to lightly dab the hair (without rubbing) in order to avoid dripping.
6. Comb or brush all hair flat/ close to the head backwards /to the side to reveal the hairline.

Hygienic inner cap

7. Make sure that the hygienic inner cap covers the chin and the forehead.
8. The inner cap does not need to be wetted before being applied, as the wet hair will make it wet.

Wet the hair thoroughly – use a towel to dab the hair in order to avoid dripping

Ensure that the DigniCap™ is in close contact with the scalp on the whole area of hair growth

During Scalp Cooling

Movement

- Avoid any movement of the caps during the scalp cooling procedure. Instruct the patient not to move the cap during their treatment and to inform you if the cap has been moved accidentally. If this happens, make sure immediately that the cap is in its original position.
- When leaning back in the chair or bed, there is always a risk of slowly sliding downwards. This may cause the cap to be pushed up from the head, resulting in a loss of contact between the cap and the scalp. Please tell the patient to be aware of this.
- If the patient falls asleep during the scalp cooling treatment, check to see if the cap has moved. If it can be seen that the cap has moved, wake the patient in order to re-adjust the cap.

Ensure that the DigniCap™ is in close contact with the scalp throughout the scalp cooling procedure

Comfort/discomfort

- If the patient experiences discomfort when the temperature falls during the start of scalp cooling, it is very important to explain that this usually passes after 10 to 15 min. Support the patient while waiting for this time to pass, if it can be tolerated. For the next scalp cooling session, it might help if the patient takes painkillers (e.g. paracetamol) 30 minutes prior to scalp cooling.
- In order to prevent patients from feeling cold, please provide a blanket and, if possible, an electric blanket and hot drinks. You might also want to increase the room temperature. These measures are always most effective if they are started before the patient begins to feel cold.
- Shivering is not a common symptom of scalp cooling treatment, but it may occur as a result of a reaction to one of the cytostatic drugs, e.g. Taxol (anaphylactic reaction).
- The cap holders can be used to take the weight of the tubes off the shoulders.

Any discomfort usually passes after 10 to 15 minutes, once the temperature has stabilised

Pausing the treatment

- Pauses during treatment should be as few and as short as possible. The temperature of the scalp increases when the DigniCap™ is disconnected and this may affect the outcome of the scalp cooling treatment. Patients should therefore be asked to visit the toilet before starting treatment.
- If the DigniCap™ has to be disconnected for a short time (e.g. to visit the toilet), the patient must keep the cap on.
- To minimise pause times during scalp cooling treatment (e.g. for toilet visits)
 1. Ensure the toilet is vacant.
 2. Arrange infusions, a pump and other devices.
 3. Press the "Pause" button on the DigniCap™ System.
 4. Disconnect the DigniCap™ from the system.

When the patient returns:

5. Re-connect the DigniCap™.
 6. Press the flashing "Start" button.
 7. Re-arrange the infusion pump and other devices.
- The pause should be as short as possible, and an acoustic alarm will sound after 8 minutes as a reminder that a pause is still on-going.

As a result of the reduced scalp temperature, some patients may feel dizzy because when standing up and walking. The patient should be warned about this and it is advisable to walk alongside the patient to provide support if required.

Pauses during treatment should be as few and as short as possible

Post-Infusion Cooling Time

Post-Infusion Cooling Time is measured from the moment when the chemotherapy infusion is completed. Depending on drug and dose, the post-infusion cooling time will last for 30-120 minutes. Please see the document "Recommendations for Post-Infusion Cooling Times with DigniCap™".

After scalp cooling

1. Once the post-infusion cooling time is completed, undo the DigniTherm™ chin strap, but ensure that the patient keeps both caps on for another 10 to 15 minutes to allow the circulation and temperature in the scalp to slowly normalise thus keeping potential discomfort to a minimum.
2. Remove the DigniCap™ slowly by lifting it up and to the back.
3. Allow the patient's hair to dry naturally and do not use a hairdryer directly after the scalp cooling treatment.
4. Clean the DigniCap™ using soap or an alcohol-based detergent after every patient.

After the post infusion cooling time, leave both caps on for 10 to 15 minutes to allow the circulation and temperature to slowly normalise and to keep any discomfort to a minimum

Practical training

The team should try different sizes of DigniCap™ on each other. Note the different head shapes and how fitting of the cap can change according to size and how it is moved on the head. Make sure that everyone can put on the outer cap properly. If it is skewed, it must be removed and put on again.

How to fit the silicon and neoprene cap properly

1. Decide together with the patient which cap size should be tried first (usually small or medium size, see Tab. 1).
2. Ask the patient to sit upright with both feet on the floor and not leaning back.
3. If the tubes are not connected to the system, put them over your shoulder.
4. Stand in front of the patient.
5. Hold the cap with both hands with the front facing you.
6. Position the front edge of the cap in front of the patient's face; level with his/her nose/ eyes (Fig. 5).
7. Place the cap on the patient's head by tilting it from the front to the back and down onto the head.

NOTE Do not press the cap down when tilting to avoid pulling the patient's hair.

NOTE If the patient has long hair, leave it outside the cap as cooling is only required for the hair follicles. Placing lengths of the patient's hair under the cap would insulate the scalp from the cold and therefore reduce the efficiency of the scalp cooling treatment.

8. Use the ears as a reference to feel whether the cap is sitting straight or not. Ensure that ears are not bent over by the cap.

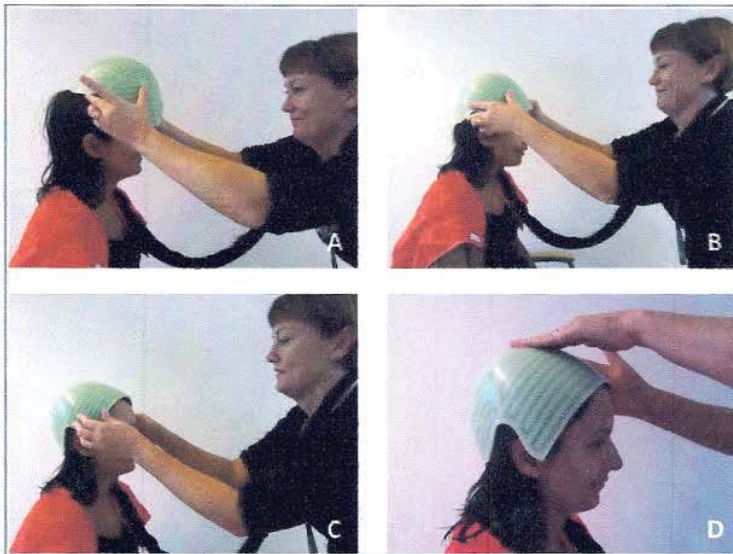


Fig. 5 Placing the DigniCap™ onto the head

9. To find the best position, move the cap backwards and forwards a little and from side to side (usually less than one centimetre in any direction). It is especially important to ensure good contact at the crown of the head. Also allow the patient to move the cap on his/her head to ensure a good fit, especially on the crown.
10. Check for good contact between the cap and the crown of the head by gently pressing on the cap at this position. Good contact is made when the cap cannot be pressed down at the crown.
11. Ask the patient to describe how the cap feels between the inside and the crown of the head. This will help you ensure the best position.
12. Depending on the outcome of steps 2 to 11, follow procedure A, B, C or D of Table 2.

13. Ensure that there are no air pockets between the patient's scalp and the DigniCap™. Lightly press on the cap at various places, especially on the crown and the back. If you are able to press the cap down significantly at any position, this indicates that there are air pockets between the cap and the head. Use padding at these positions.

NOTE Do not place anything under the DigniCap™ (between the hair and the DigniCap™).

14. To keep the cap in the right position, ask the patient to hold the cap in front of the ears with both hands (Fig. 6). The patient should hold the cap until you have reached step 19.

NOTE: As a precaution, always compare at least two different sizes of DigniCap™ by repeating steps 2 to 11 and choosing the cap with the best fit.



Fig. 6 Patient holding the DigniCap™ to keep it in the right position.

A close contact on the crown, back and sides is more important than completely covering the hair line

Always try comparing at least two different sizes of DigniCap™

If in doubt, choose the bigger DigniCap™ rather than using a DigniCap™ that is too small

A	B	C	D
The DigniCap™ is not in good contact with the crown of the head.	The DigniCap™ is in good contact with the crown of the head.		
The cap is too small.	<p>The edges of the cap do not reach the hairline (by > 1 cm). The cap might be too small.</p> <p>NOTE A close fit of the cap to the crown, back and sides is more important than completely covering the hair line.</p> <p>NOTE If in doubt, choose the next size of DigniCap™ rather than using DigniCap™ which is too small. A cap that is too small will move up during treatment and prevent adequate contact. If the best fitting DigniCap™ appears to be slightly too large, try to combine it with a DigniTherm™ of the next size down.</p>	The edges of the cap extend beyond the hair line and/ or the cap is not in contact with the back, front and/ or sides of the head. The cap may be too large.	<p>The sides of the cap are in good contact with the head and the edges are close to the hairline. The DigniCap™ seems to be the right size.</p> <p>NOTE A close contact on the crown, back and sides is more important than completely covering the hair line.</p>
Try a bigger cap, following steps 2 to 11.	Try the next size up, following steps 2 to 11.	Try the next size down, following steps 2 to 11.	Proceed to step 13.

Table 2. Instructions for choosing the best-fitting DigniCap™.

15. Choose the DigniTherm™ of the same size as the selected DigniCap™ (see Table 1 for the right size) and turn it inside out (Fig. 4).
16. Standing in front of the patient, place the middle of the front edge of the DigniTherm™ on the centre line of the patient's forehead. The front edge of the DigniTherm™ must extend beyond the front edge of the DigniCap™ by 2 cm (the upper line of the Dignitana logo is about 2 cm above the DigniTherm™ edge and therefore can be used for orientation) (Fig. 7).



Fig. 7 Placing the DigniTherm™ onto the DigniCap™. The edge of the DigniTherm™ extends beyond the edge of the DigniCap™.

17. Place the palm of your hand (the whole hand, including the fingers) on the crown (not front!) to hold the DigniTherm™ onto the patient's head. Keep your hand in this position until the DigniTherm™ covers the DigniCap™ (step 19) (Fig. 8A).
18. Use your other hand to spread the DigniTherm™ over the DigniCap™: Spread it bit by bit by moving your hand in a half circle backwards, downwards and from side to side until the cap is completely rolled down and covers the DigniCap™ (Fig. 8 B-D). This prevents the formation of air pockets between the DigniCap™ and the DigniTherm™.

NOTE Force should not be applied in order to avoid moving the DigniCap™ and for the patient's comfort.



Fig. 8 Placing the DigniTherm™ onto the DigniCap™

19. Ensure the DigniTherm™ is sitting straight and that it covers the DigniCap™.
If the DigniTherm™ is not in the right position, remove it by turning it inside-out beginning from the sides of the DigniTherm™, and then start again from step 14.
20. Fasten the chin strap of the DigniTherm™ under the patient's chin using the Velcro. The chin strap should be as tight as possible but still comfortable for the patient.

NOTE If the patient prefers, the strap can be placed in front of the chin as an alternative (Fig. 9).

NOTE Unless a hygienic inner cap is used, a facial tissue can be placed inside the chin strap before fastening it.



Fig. 9 Possibilities of placing the chin strap

21. Check again that the DigniCap™ and the DigniTherm™ are in the right position and comfortable for the patient.

- a. If the DigniCap™ is pushed upwards and loses contact with the scalp, this means that the DigniTherm™ is too small. Try the next larger size of DigniTherm™.
- b. If the DigniCap™ is slightly too large, a DigniTherm™ one size smaller than the DigniCap™ could be suitable (See Table 2 for further explanation).

22. If padding is used (step 13):

- There might still be air pockets between the scalp and the DigniCap™ after fitting the DigniTherm™. If this happens, ask the patient to hold the DigniCap™ in place (see step 14) and remove the DigniTherm™ by turning it inside out, starting from the sides of the DigniTherm.
- Air pockets might occur between the two caps around the edges of the padding. As long as the DigniCap™ is in direct contact with the scalp, this is okay.
- If you can feel air pockets between the two caps, try to remove the air by pressing the air with your hands to the edges of the DigniTherm™. If this does not work, ask the patient to hold the DigniCap™ in place (see step 20) and remove the DigniTherm™ by turning it inside out, starting from the sides of the DigniTherm™ and then starting again from step 16.

If the DigniTherm™ is not in the right position, remove it by turning it inside out starting from the sides, and then put it back on again. It cannot be adjusted once fitted onto the DigniCap™

(Dis-)connecting couplings

As all couplings have matching counterparts, incorrect connections are not possible.

The couplings do not have to be connected in any particular order.

Demonstration and practical training:

- Cooling liquid to the front/back of the cap
- Return for cooling liquid
- Sensor coupling
 - o note the red dot
 - o correct angle (horizontal) to the system
 - o careful and precise handling
 - o never press or pull with force



Trouble-shooting

Review of alarm icons

	Safety system, DigniCap™ 1
	Safety system, DigniCap™ 2
	Low level of DigniCool™
	Temperature out of range, DigniCap™ 1
	Temperature out of range, DigniCap™ 2
	DigniCap™ 1 not connected
	DigniCap™ 2 not connected
	Pause alarm
	DIGNICARD™ not inserted
	Desired temperature in tank not reached

Low level of DigniCool™

- The coolant liquid is not consumed but does vaporize over time. Refill only when the "Low level coolant" alarm icon is displayed.

Temporary power failure

- *Power failure for less than 30s:* The system will automatically continue with the treatment once power is restored.
- *Power failure for more than 30s:* The treatment has to be started again manually.

Couplings

The alarm "DigniCap™ 1/2 not connected" indicates that the return flow tube is not connected to Digni C3. As a result, the valves will not open and the temperature in the cap will increase.

Temperature out of range

This alarm appears if the set treatment temperature is not reached within time and/or if the temperature deviates by more than $\pm 2.0^{\circ}\text{C}$ from the set value. The system will automatically adjust for this. If it does not, check that:

- The **coupling** for cooling liquid to the cap is connected.
- The hoses to the cap are straight and with no kinks which could affect circulation of the coolant.
- The **air filter** is clean.
- Nothing is blocking the air outlet from Digni C3 (on the back).

Sensor issues

- If the temperature sensors for the back and front show "---" in the Main menu, there is something wrong with the sensor connection.
 - Make sure that the sensor cable is connected to the Digni C3.
 - Make sure that the connection on the cable, close to DigniCap™, is connected properly.
- If the sensors show $> 40^{\circ}\text{C}$, there is something wrong with the sensors.
 - Check that the treatment is running (the cap on the screen must be green).
 - Make sure that there is no mechanical damage to the temperature sensors or to the cable.

If the error persists, replace the cap.

Refill DigniCool™ only when the alarm icon "Low level coolant" is displayed

If **temperature** problems occur, always check that:

- All couplings are connected
- Treatment has started and is running
- There are no kinks in the hoses
- The air filter is clean
- Nothing is blocking the airflow

Maintenance

Cooling liquid (DigniCool™)

DigniCool™ is a cooling liquid consisting of diluted monpropylene glycol (MPG5).

The product is classified as *non*-hazardous to the environment and to health.

The product does *not* require fire or health hazard labeling.

The product is *not* covered by the Transportation of Dangerous Substances Act.

How to handle

Wash your hands with water and soap after contact with the product. Provide good ventilation. If clothes have been exposed, remove to avoid further contact.

Disposal considerations

The product must not be disposed of down the drain.

If DigniCool™ spills on the floor, be aware of slip hazard.


Refilling the tank

The coolant is not consumed but does vaporize over time. Refill only when the alarm icon "Low coolant level"

 is displayed.

NOTE DigniCool™ is always supplied in the correct concentration. Do not use any other coolant for filling the Digni C3 tank.



1. Open the lid.
2. Remove the coolant tank plug under the lid.
3. Measure ½ liter (500ml/17oz.) and refill. Continue to pour even when  is no longer displayed in the alarm panel. *Always refill with exactly ½ liter (500ml/17oz.) – no less and no more.*
4. Replace the coolant tank plug.
5. Close the lid.

When the coolant level is low and the alarm is displayed in the alarm panel, it is possible to complete an ongoing treatment but not to start a new one.

Cleaning the system

Make sure that the power is switched off, pull out the mains cable and extend the cap holders before cleaning.

- Clean the surfaces with alcohol surface detergent.
- Clean the touch screen regularly with a damp cloth (make sure it is not too wet) or alcohol wipes to prevent contamination and to remove dust.
- Remove any spilled DigniCool™ with water.

Cleaning and handling/storage of caps

Clean the DigniCap™ carefully with surface alcohol after each patient. Wipe gently around the temperature sensors and avoid pulling the cables attached to the sensors. Leave the DigniCap™ to air-dry after cleaning. The DigniCap™ should be handled carefully and stored individually in a dry and well-ventilated place. Be sure not to damage the sensors. The boxes in which the caps are delivered are not suitable for storage.

Inspect the DigniCap™ including cables and temperature sensors, cooling hoses and couplings from time to time to ensure that no damage or leakage has occurred which could affect the scalp cooling treatment. Dried DigniCool™ on couplings can be rinsed or wiped off with water.

The neoprene insulation on the tubes tends gradually to leave an uncovered part of the silicon tubes close to the cap. This will cause a loss of cooling effect and might influence the scalp cooling treatment. Loosen the Velcro and adjust the neoprene insulation when needed.

The DigniTherm™ can be washed in lukewarm soap water. Leave to air dry after cleaning.

NOTE Avoid exposing the DigniCap™ to direct sunlight and extreme temperatures in order to avoid discoloring and/or damage to silicon parts and/or temperature sensors.

Air filter

Location and cleaning.

Dusty air filters have a negative effect on the system's performance.

Replace or clean the air filter once a month.

Open the front air filter lid and remove the filter.

If the filter is not to be replaced, shake it to remove dust.

Place the air filter lid in its correct position.

NOTE The lamellas (behind the air filters) are very sharp, so be careful to avoid cuts.

NOTE The DigniCap™ System should not be used unless the air filter is in place.



Refill with DigniCool™ only when the alarm icon "Low level coolant" is displayed

Clean the DigniCap™ with surface alcohol after each patient

The DigniCap™ should be handled carefully and stored separately

Replace or clean the air filter once a month

APPENDIX XX

Checklist Training of Nurses

Hospital/clinic: _____

Introduction

Scalp cooling – principle and procedure

Demonstration of the system,

- menus
- how to start a treatment

The caps and how they are used

- The sizes of the silicon and neoprene caps.

DigniCap™ scalp cooling procedure

- Preparation for scalp cooling
- During scalp cooling treatment – movements, comfort/discomfort
- Pause the treatment.
- Post-cooling.
- Stop the treatment and what to consider after post-cooling (temperature increasing, no hair dryer).

Practical training

- Fitting of the cap How to fit the silicon and neoprene cap properly.
- Connecting and disconnecting the couplings.

Trouble shooting

- Review of alarm icons.
- Trouble-shooting:
 - low level of coolant
 - brownout
 - couplings
 - temperature out of range
 - sensors
 - air filter

Maintenance

- Cooling agent.
 - How to handle.
 - Disposal considerations.
 - Refilling the tank.
- Cleaning the system.
- Cleaning and handling/storage of the caps
- Air filter. Localization and cleaning

Training of nurses is made according to the Appendix XXVII “Training - Instructions for scalp cooling treatment using the DigniCap™ System”.

Education received/ Signature	
Date	
Name	
Title	

Training performed and effectiveness verified (Dignitana representative/Responsible for education)	Date/Sign
--	-----------

Record No. and title	Issue	Pages
REC 044 Training of nurses checklist	5	1(2)

Hospital/clinic: _____

Introduction.

- Hair loss
- Scalp cooling

Using the system.

- Cooling agent. How to handle. Filling and refilling the tank.
- Cleaning the system.
- Air filter. Localization and cleaning.
- Cap holders.
- Touch screen. Review of menus.
- Review of alarm icons.
- Back-up battery function and charging procedure

The caps and how they are used.

- The sizes of the silicon and neoprene caps.
- How to fit the cap properly.
- Cleaning and handling/storage of the caps.

DigniCap® scalp cooling procedure.

- Start a scalp cooling treatment.
- Change of pre cooling time.
- Change of temperature.
- Damp the hair.
- Caring during scalp cooling treatment.
- Pause the treatment.
- Trouble-shooting:
 - low level of coolant
 - brownout
 - couplings
 - sensors
 - air filter
- Post-cooling.
- Stop the treatment and what to consider after post-cooling (temperature increasing, no hair dryer).

Practical training.

- Fitting of the cap
- Start a scalp cooling treatment.
- Connecting and disconnecting the couplings.

Training of nurses is made according to the document “Training - Instructions for scalp cooling treatment using the DigniCap® System”.

Education received/ Signature	
Date	
Name	
Title	

Training performed and effectiveness verified (Dignitana representative/Responsible for education)	Date/Sign
--	-----------

If many nurses receive training in the same clinic, please sign the list page 2.

Training received by:

Name	Signature	Date

Ref. SOP 021

APPENDIX XXI

GUIDELINES FOR STUDY PHOTOGRAPHS

- Preferably all photographs should be taken in the same place with as little impact from daylight as possible.
- Minimize background complexity by choosing a blank, pale or white coloured wall as background.
- Photographs shall be taken at a distance of 5 feet from the patient. If at all possible, always use the same place to take the photographs. Mark the distance with tape on the floor.
- It is important that the lens is parallel to the floor and at the height of the patient's eyes; a tripod may be used to stabilize the camera.

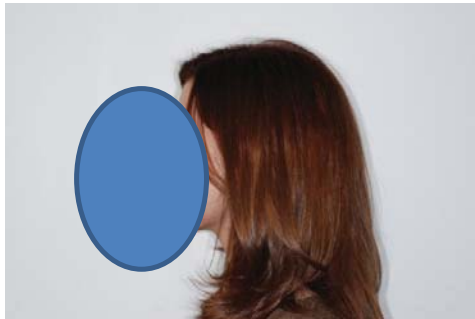
The photographs should be taken using a Nikon D90 digital camera with a 60mm fixed focal length lens and a Canfield Twin Flash attachment .Cameras will be supplied by the Sponsor/CRO

Picture size should be set to Small and JPEG setting to Normal.

Camera Settings

- The camera should be set on Autofocus (Green auto)
- On the lens, the Lens Focus mode should be set to A.
- Focus mode switch should be set to AF (Auto Focus)
- Once the subject is positioned, lightly depress the Photo capture button, Then take the photograph. You should take 3 photos of each required position. Use the same settings for all five photographs:
 - Front - bangs should be held back so that the hairline is visible.
 - Back
 - Right
 - Left
 - Top – hair divided in the midline with both hands
 - For the front and side photographs, the subject should hold the provided mask to conceal their identity.

Front



Left



Right



Back



Top

APPENDIX XXII**DEVICE ACCOUNTABILITY LOG**

Art. No	Product	Serial/Batch number	Receiving date	Signature	First used date	Signature
10032	Digni C3 115VAC					
13201	DigniCap™ (silicon cap) XS 1 (Left) red					
13401	DigniCap™ (silicon cap) Small 1 (Left) blue					
13501	DigniCap™ (silicon cap) Small 2 (Right) blue					
13601	DigniCap™(silicon cap) Medium 1 (Left) green					
13701	DigniCap™(silicon cap) Medium 2 (Right) green					
13901	DigniCap™(silicon cap) Large 2 (Right) yellow					
11320	DigniTherm™ (neoprene cap) XS red					
11340	DigniTherm™ (neoprene cap) S blue					
11340	DigniTherm™ (neoprene cap) S blue					
Art. No	Product	Serial/Batch	Receiving	Signature	First used	Signature

		number	date		date	
11360	DigniTherm™ (neoprene cap) M green					
11360	DigniTherm™ (neoprene cap) M green					
11380	DigniTherm™ (neoprene cap) L yellow					
11000	DigniCool™					
11000	DigniCool™					
11000	DigniCool™					
11100	DIGNICARD™					
11200	DIGNISTICK™					

APPENDIX XXIII

CASE REPORT FORM FOR DEVICE USE

FILL OUT ONE CRF FOR EACH CYCLE OF CHEMOTHERAPY.

PATIENT STUDY NUMBER _____

SITE _____

DATE _____

CHEMOTHERAPY REGIMEN _____

CYCLE

NUMBER _____ **DOSE** _____

DIGNICAP™ SYSTEM (COOLING UNIT) s/n _____

SIZE	DIGNICAP™ (SILICON) no
X-SMALL (RED)	
SMALL (BLUE)	
MEDIUM (GREEN)	
LARGE (YELLOW)	

PADDING COMMENT _____

TIME SCHEDULE

Cold cap on.....
 Chemotherapy infusion starts.....
 Chemotherapy infusion ends.....
 Cooling turned off.....
 Cold cap off.....

Additional cooling after the chemotherapy infusions ends (post cooling) is 120 minutes for all the chemotherapy regimens in this study protocol, except for Paclitaxel every 2 weeks, where the post cooling is 90 minutes.

PAUSES

NUMBER OF PAUSES DURING TREATMENT _____

WAS THE PAUSE(S) ALARM ACTIVATED?

- YES
- NO

IF YES, HOW MANY TIMES? _____

COMMENTS _____

SIGNATURE _____

APPENDIX XXIV

GUIDE TO DEVICE LABELING

Label on Digni C3/box label/ DigniCool label/labels for Cooling Cap Set / Clinical Investigation Only label: see attached pdf files

DIGNICARD™



DIGNISTICK™

■ 281C
■ 200C



APPENDIX XXV**DIGNICOOL™ HAZARDS INFORMATION AND MATERIAL SAFETY DATA****1. IDENTIFICATION OF THE SUBSTANCE AND OF THE COMPANY****Product information*****Product name:*** DigniCool™***Active substance:*** monopropylene glycol MPG5

DigniCool™ is a cooling agent consisting of diluted monypropylene glycol (MPG5). The dilution is made by Dignitana AB to serve the DigniCap™ System optimally.

This Safety Data Sheet refers to non-diluted MPG5.

Manufactured by:**Dignitana AB**

PO Box 24022

SE- 224 21 Lund

Sweden

www.dignitana.se

Phone +46 (0) 46 16 30 90

2. HAZARDS IDENTIFICATION**General**

Classified as non hazardous to environment or health. The product does not require fire or health hazard labeling.

3. COMPOSITION / INFORMATION ON INGREDIENTS

Ingredient name	EC No.	CAS No.	Classification
1,2-propandiol	2003380	57-55-6	No classification required
<i>Explanation of classification symbols:</i> T+=highly toxic, T=toxic, C=corrosive, Xn=harmful, Xi= irritant E=Explosive, O=Oxidising, F+=ExtremelyFlammable, F=Highly flammable, N=Dangerous for the environment, Cancer=Carcinogenic, Mut=Mutagenic, Rep=Toxic for reproduction, Conc.=Concentration			

4. FIRST AID MEASURES**Inhalation**

Breathe fresh air, rest and keep warm. Rinse nose, mouth and throat with water. Seek medical advice if symptoms persist.

Skin contact

Wash with soap and water. If clothes have been exposed, remove to avoid further contact. Seek medical advice if symptoms persist.

Eye contact

Flush with plenty of water for 10-15 minutes. Seek medical advice if symptoms persist.

Ingestion

Small amount: rinse the mouth with water and then drink water or milk.

Large quantities: seek medical advice.

5. FIRE-FIGHTING MEASURES

Extinguishing media

CO₂, dry chemical, alcohol resistant foam, water mist.

Improper extinguishing media

Water.

Fire and explosion media

Heated product can form flammable vapors. Combustion can produce irritating fumes. Carbon monoxide (CO) may be formed in the event of incomplete combustion.

Protective equipment for fire fighters

Use respiratory protection.

Other information

Fire in closed areas should only be extinguished by trained personal. Containers near a fire must be moved and/or cooled with water.

6. ACCIDENTAL RELEASE MEASURES

Personal precautions

Use personal protection as stated in section 8. Mark the spillage.

Safety actions to protect external environment

MPG-5 is completely miscible with water.

Contain the spillage with e.g. sand, soil or other suitable material. Avoid seepage into the drains. If the spillage escapes into the drains or waterways, inform concerned parties.

Immediately remove spillage with cloths or absorption material. Be aware of slippery surface.

7. HANDLING AND STORAGE

Handling precautions

Handle the product suitable to avoid spillage.

Storage

Store the product in room temperature.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Exposure control

Wash hands with water and soap after contact with the product. Provide good ventilation. If clothes have been exposed, remove to avoid further contact.

If the risk of direct contact or splashes is considered high while handling larger quantities, wear face visor or goggles, protective gloves and clothing.

Eye protection

Use suitable glasses or goggles.

Hand protection

Use protective gloves of Viton or nitrile rubber.

Other information

For more information contact a supplier of protection equipment.

9. PHYSICAL AND CHEMICAL PROPERTIES

Physical state: Liquid.

Color: Green.

Odor: Characteristic.

Solubility: Soluble in water and polar solvents.

Physical and chemical parameters

Parameter	Value/unit	Method/reference
pH in solution	6,5 - 8,5	50% / 20°C
Melting point	< -50°C	
Boiling point	> 150°C	
Flash point	> 100°C	
Explosion limits	2,6 - 12,6 %	
Vapor pressure	2 mbar	20°C
Density	1060 kg/m ³	20°C
Viscosity	70 mm ² /s	20°C

10. STABILITY AND REACTIVITY

Stability

Stable if handled normally.

Materials to avoid

Reacts violently with oxidizers.

Hazardous decomposition products

When heated, or during combustion, carbon monoxide (CO) and other health hazardous compounds may be formed.

11. TOXICOLOGICAL INFORMATION

Acute toxic test results

1,2-propandiol		
Route of exposure	Value / unit	Species
LD50 (Dermal)	20 800 mg/kg	Rabbit
LD50 (oral)	20 - 34 g/kg	Rat

General

Not known or expected to be harmful to health in normal use. Used product may contain harmful contaminants.

Skin contact

Repeated exposure over a longer period of time might cause irritation.

12. ECOTOXICOLOGY INFORMATION

Acute aquatic test results

LC50 (fish, mg/L) : >10000

Eco toxicity

Not harmful to aquatic organisms.

Mobility

Dissolves in water.

Degradability

>70% (OECD 302B)

Accumulation

Does not bioaccumulate.

Other information

At correct supply in low concentrations to adapted biological sewage treatment works, no disorders are to expect. The product adsorbs to organic bound halogens. Does not contain any organic bound halogen.

13. DISPOSAL CONSIDERATIONS

General regulations

Product must not be flushed into the drain. If the product is introduced into the drain, alert concerned parties.

Waste must be collected and delivered to destruction if the amount exceeds 1 kg annually.

Product should be disposed or destroyed according to local regulations.

Category of waste

EWC (European Waste Catalogue) -code 070101.

Clean, not contaminated containers can be reused. Containers that can not be cleaned are to be destroyed in the same way as its content.

14. TRANSPORT INFORMATION

Not Classified as Dangerous Goods

Other information

Not covered by the transportation of dangerous substances act.

15. REGULATORY INFORMATION

EC-Label: No

16. OTHER INFORMATION

Information source

Information from the supplier of Thermfluid MPG5, version 1.0.0 (2009-09-29).

APPENDIX XXVI
LIST OF HAZARDS

Hazard No	Hazardous situation (failure mode)	Effect of hazard (severity)	Sequence of event (Cause of Failure Mode)
Electricity	Spillage (<2dl) and/or other liquids in contact with electrical parts inside the system	electrical shock, death	disconnected earth
	damaged external power cord	electrical shock, death	inflicted damage, damage or ageing
	high temp of hardware inside system (e.g. pump)	Melting plastic could generate poisonous gases that cause nausea.	defected thermal fuse, incorrect connections, not following environmental recommendation(s), too low temperature tolerance
	high temp of hardware inside system (e.g. pump)	no treatment, hair loss	Too low temperature tolerance of the pump, environmental recommendation(s)
	High temp (extreme heat) of hardware inside system (e.g. pump or fan)	burn	defected thermal fuse, incorrect connections, not following environmental recommendation(s)
	influence/damage the functionality of other devices (1500VA)	Other devices effected/stops, death	power failure (same outlet)
	influence/damage the functionality of other devices (1500VA)	Infusion pump or other devices malfunction.	EMC requirements not fulfilled, rebuilding of the device by MTA
	System does not start	No treatment, hair loss	Damaged, worn out, not connected or broken power supply, fuses inside system, compressor, blue screen (C2-3), card, hard drive (C2-3), flash memory (C3) or similar
	fire of hardware	burn	shortcut, defected electrical component

	Electrical malfunction that generates main power transfer to applied part (cap and/or hoses to cap). Or parts that could come in contact with the patient through an operator.	electrical shock, death	Damage to internal electrical system.
Temperature	Insufficient cooling	no treatment, hair loss	defected cooling unit, tank sensor, pump, compressor, valves, etc.
	Insufficient cooling	no treatment, hair loss	Software inflicted problem, screen hangs, regulation, no recurring notification if silenced (as with C2-3)
	Insufficient cooling	no treatment, hair loss	Dignicard non functional
	Insufficient cooling	no treatment, hair loss	Wrong diluted DigniCool
	Insufficient cooling	no treatment, hair loss	Effectuated cooling unit due to environmental factors such as RH, temperature, space, dirty air filter, bad insulation
	Insufficient cooling	no treatment, hair loss	defected cap; sensors, sensor cable, connector(s)
	Over cooling	reversible skin irritation and/or numbness on the scalp	defected cap, malfunctioning SW
Dimensions	transportation the system, (un-)packing system, lifting the system, moving the system	physical damage to person handling the system	not following the instructions, lack of education (emphasizing on the importance), time-issue (e.g. Stress/hurry)
Labeling	manual not available or wrong language or version	no treatment, hair loss	lack of education, loss of manual by Dignitana/customer/partner, lack of follow-up by Dignitana/partner

	Misinterpretation of symbols, notifications, labels, colors.	no treatment, hair loss	language, cultural differences, education, description of work-instructions
	incorrect or missing label (VAC, s/n)	no treatment, hair loss	labeling by manufacturer
Chemical leakage	Exposure to CFC free R404A refrigerant	irritation of skin and eyes, nausea	Self-inflicted damage, insufficient quality control, maintenance
	exposure to liquid(s); Cooling agent Dignicool	irritation of skin and eyes	defected hoses, hole in the DigniCap, connectors/couplings, bad gluing of components, self-inflicted damage, insufficient quality control, maintenance
	Leakage of DigniCool, overfilling	Physical damage (slipping)	Lack of education, sensor not working, tap not closed
	Leakage of DigniCool, tube loosened unexpected inside system (Maximum volume is 9 liters)	Physical damage (slipping)	Bad manufacturing, bad transportation.
	exposure to material and process aids	irritation of skin and eyes, change of skin (eczema), nausea	change of material, added products to existing material, non-biocompatible material,
Mechanical parts	Circulation in the cap	no treatment, hair loss	Gluing
	(Dis-)connecting couplings	surface cut, squeezed/pinched	normal use (e.g. dis-connecting couplings) and maintenance
	(Dis-)connecting couplings	no treatment, hair loss	Abnormal use (problems with connecting sensor cable), rough handling
	(Dis-)connecting couplings	no treatment, hair loss	Not correctly adjusted induction sensor for return coupling
	(Dis-)connecting couplings, leakage of DigniCool	Physical damage (slipping)	Bad assembly, abnormal use (problems with connectors), rough handling

	(Dis-)connecting couplings, leakage of DigniCool	Physical damage (slipping)	Bad assembly, abnormal use (problems with connectors), rough handling
	Cleaning/replacing airfilter	cut	service/maintenance/repair
	Cleaning/replacing particle filter	surface cut, squeezed/pinched	service/maintenance/repair
Moving parts	Unintended movement of the system	surface cut, squeezed/pinched	forget to use the brake(s)
	front cover/back chassis removal	surface cut, squeezed/pinched	maintenance
	front cover/back chassis removal	no treatment, hair loss	Broken screws back chassis, screws not possible to remove, thread damaged
	Unwanted material in the DigniCool	no treatment, hair loss	Damage or loss of plug or lid, bad manufacturing, insulation/particles material stuck in connections
	Defected caps	no treatment, hair loss	caps placed wrong on capholders, design of cap holders
	Power cable	Physical damage (tripping)	Placement of the system
	Cap holders	discomfort	Placement of the holders, adjusting
	Fan	cut	service/maintenance/repair
Power Supply	power failure in the hospital (brown-out)	no treatment, hair loss	no functional memory system / malfunction of battery

	System does not start	no treatment, hair loss	Fuses blown in the wall or in the system
	unstable/fluctuation of voltage	no treatment, hair loss	supplier (energy company/hospital) unable to deliver/distribute stable power
	incorrect specs in relation to the VAC	no treatment, hair loss	insufficient research as to the specifications
Microorganism	contamination between patients	infection	not being hygienic, following hygienic recommendations
Other	Misuse: Use of scalp cooling when local chemotherapy treatment of the scalp area is intended.	Reduced intended effect of chemotherapy, potential irreversible harm to patient.	During cooling of the scalp blood vessels constrict and the blood flow and the concentration of chemotherapy in the scalp is reduced.
	Misuse: Use of scalp cooling when of importance to obtain equal systemic concentration of the chemotherapy treatment.	Reduced intended effect of chemotherapy, potential irreversible harm to patient.	During cooling of the scalp blood vessels constrict and the blood flow and the concentration of chemotherapy in the scalp is reduced.
	Patients who are sensitive to receive scalp cooling.	Allergy, cold agglutinins or other hypersensitivity	Patient history not known.
	Patients who are sensitive to acoustic energy and vibration	Hypersensitivity	Patient history not known.

*Not applicable for ETL-certified systems.

The information above is extracted from the Dignitana Risk analysis dated 2/26/2013. The conclusion is that the overall residual risks area acceptable and the benefits to the patient with the use of the product are higher than any risk.

APPENDIX XXVII**Annual Safety Follow-Up Visits**

What is the current status of the subject's breast cancer?

- No evidence of disease
- Recurrent disease

If recurrent,

- Local/regional Specify site(s): _____
- Distant Specify site(s): _____

- Scalp metastases:

- Yes
- No

If yes,

- Number and size of metastatic lesions: _____
- How were scalp metastases detected? (eg: physical exam, imaging (CT, MRI, PET): _____
- Specify if scalp metastases are presumed or biopsy proven?

- Specify any local therapy for scalp metastases:

Since the subject's last visit, has she been diagnosed with any **new** cancer(s)?

- Yes
- No

If yes, please specify whether cancer(s) is/are primary or metastatic:

- Primary Location: _____ Stage at Diagnosis: _____
- Metastatic

Please provide survival status of the subject:

- Alive
- Expired Date: _____

Source of Information

- Chart review
- Subject
- Friend or family member
- Other , specify (e.g., newspaper, etc): _____

Clinical Performance, Efficacy and Safety of the DigniCap™ System, a Scalp Hypothermia System, in Preventing Chemotherapy Induced Alopecia in Patients with Early Stage Breast Cancer

Clinical Investigational Plan (CIP)

CIP version: *April 16, 2013. Issue 2.*

Amended June 13, 2013, August 7, 2013, October 18, 2013, December 17, 2013, 21 March 2014

DETAILED CHANGES

Principal Investigator(s):

University of California San Francisco (UCSF)

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Susan Melin, MD

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Tessa Cigler, MD

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Study Statistician:

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This Amendment to Protocol DIG-001 was written to extend safety follow up to a total of 5 years for evaluation of risk of scalp metastases.

Protocol Wording Changes

Synopsis, Objectives, Secondary Objectives

Add the following Secondary Objective:

To assess the incidence of scalp metastases in women who used the DigniCap™ System annually for a total of five years after completion of chemotherapy

Synopsis, Study Endpoints, Secondary Endpoints

Add the following Secondary Endpoint:

Safety defined as the number of scalp metastases over a 5-year period, compared to the incidence in an untreated control group.

Synopsis, Study Design

Old Wording

This is a prospective, non-randomized, concurrent age- and treatment-matched control, clinical trial. The control group will establish whether a similar group of women based on disease, age, and treatment regimen will experience an expected high percentage of hair loss. An interim analysis will be conducted and if at least 12 out of the first 15 control group women have a Dean score of 4 (lose greater than 75% of their hair) at any chemotherapy visit, enrollment of the control group will be discontinued.

New Wording

This is a prospective, non-randomized, concurrent age- and treatment-matched control, clinical trial. The control group will establish whether a similar group of women based on disease, age, and treatment regimen will experience an expected high percentage of hair loss. An interim analysis will be conducted and if at least 12 out of the first 15 control group women have a Dean score of 4 (lose greater than 75% of their hair) at any chemotherapy visit, enrollment of the control group will be discontinued. The primary efficacy outcome will be based on graded photographs 4 weeks after the last chemotherapy. The incidence of scalp metastases will be based on a 5-year follow up.

2.2 Secondary Objective

Add the following secondary objective:

- To assess the incidence of scalp metastases in women who used the DigniCap™ System annually for a total of five years after chemotherapy

3.2 Secondary Endpoints

Add the following Secondary Endpoint:

Safety defined as the number of scalp metastases over a 5-year period, compared to the incidence in an untreated control group.

4. TREATMENT PLAN

4.1 Schedule of Investigational Events for Treatment and Control Group

Old Wording

Assessments	Baseline ¹	Each Chemotherapy cycle	1 month (3-6 weeks) after last chemotherapy infusion	Follow-up Visit (3 months ± 2 weeks)	Follow-up Visit (6 months ± 2 weeks)
Chemotherapy treatment		X			
Scalp cooling ⁵		X			
Signed Informed Consent, Appendix III	X				
Eligibility checklist, Appendix I	X				
Baseline Case Report Form, Appendix IV	X				
Case Report Form for all chemotherapy cycles, Appendix V		X			
Treatment follow-up form at 3 months after chemotherapy completion, Appendix VI				X	
Treatment follow-up form at 6 months after chemotherapy completion, Appendix VII				X	X
Photographs of hair/scalp (Section 8.1; Appendix XXI)	X	X ³	X		
Alopecia self-report, Appendix VIII	X	X	X	X	X
Patient symptoms survey ^{2,5} , Appendix IX		X			

EORTC-QLQ-BR233, Appendix X	X	X ⁴	X	X	X
Body Image Scale (BIS), Appendix XI	X	X ⁴	X	X	X
Impact of hair loss on treatment decision, Appendix XII					X
Hair Re-growth Follow Up Survey, Appendix XIII				X	X
Medwatch, Appendix XIV		X	X	X	X
Case Report Form for Device Use ⁵ , Appendix XXIII		X			
Screening Log- Non Enrolled Patients, (If applicable), Appendix II	X				

New Wording

Assessments	Baseline ¹	Each Chemotherapy cycle	1 month (3-6 weeks) after last chemotherapy infusion	Follow-up Visit (3 months ± 2 weeks)	Follow-up Visit (6 months ± 2 weeks)	<u>Annual Follow-up Visits at 1, 2, 3, 4 and 5 years (± 2 weeks)</u>
Chemotherapy treatment		X				
Scalp cooling ⁵		X				
Signed Informed Consent, Appendix III	X					
Eligibility checklist, Appendix I	X					

Baseline Case Report Form, Appendix IV	X					
Case Report Form for all chemotherapy cycles, Appendix V		X				
Treatment follow-up form at 3 months after chemotherapy completion, Appendix VI				X		
Treatment follow-up form at 6 months after chemotherapy completion, Appendix VII				X	X	
Photographs of hair/scalp (Section 8.1; Appendix XXI)	X	X ³	X			
Alopecia self-report, Appendix VIII	X	X	X	X	X	
Patient symptoms survey ^{2,5} , Appendix IX		X				
EORTC-QLQ-BR233, Appendix X	X	X ⁴	X	X	X	
Body Image Scale (BIS), Appendix XI	X	X ⁴	X	X	X	
Impact of hair loss on treatment decision, Appendix XII					X	
Hair Re-growth Follow Up Survey, Appendix XIII				X	X	
<u>Case Report Form for safety follow up visits, Appendix XV</u>				<u>X</u>	<u>X</u>	<u>X</u>
Medwatch, Appendix XIV		X	X	X	X	<u>X</u>
Case Report Form for Device Use ⁵ , Appendix XXIII		X				

Screening Log- Non Enrolled Patients, (If applicable), Appendix II	X					
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7 STUDY DESIGN

Old Wording

Patients will be ~~informed that an extension protocol will be implemented to follow this protocol and that they will be asked to participate in the extension protocol~~ in order to obtain long term follow up information on the risk of scalp metastases.

New Wording

Patients will be followed annually for 5 years in order to obtain long term follow up information on the risk of scalp metastases.

8 ASSESSMENTS

Old Wording

8.5 Assessments At The Follow-Up Visit 3 Months (± 2 Weeks) After The Completion Of Study Treatment

Vital signs, medical history, physical examination, examination for cutaneous metastases of the scalp will be carried out in the treatment group patients. ~~The use of concomitant medication and any adverse events will be reported.~~ The patient will assess hair re-growth using the Hair Re-growth Follow Up Survey. Quality of life questionnaires including EORTC-QLQ-BR23 scale and BIS will be assessed.

New Wording

8.5 Assessments At The Follow-Up Visit 3 Months (± 2 Weeks) After The Completion Of Study Treatment

Vital signs, medical history, physical examination, examination for cutaneous metastases of the scalp will be carried out in the treatment group patients. The patient will assess hair-re-growth using the Hair Re-growth Follow Up Survey. Quality of life questionnaires including EORTC-QLQ-BR23 scale and BIS will be assessed.

Old Wording

8.6 Assessments At The Follow-Up Visit 6 Months (± 2 Weeks) After The Completion Of Study Treatment

~~The use of concomitant medication and any adverse events will be reported.~~ The patient will assess hair re-growth using the Hair Re-growth Follow Up Survey. Quality of life questionnaires

including EORTC-QLQ-BR23 scale and BIS will be assessed. The impact of hair loss on treatment decision will be evaluated.

New Wording

8.6 Assessments At The Follow-Up Visit 6 Months (± 2 Weeks) After The Completion Of Study Treatment

The patient will assess hair re-growth using the Hair Re-growth Follow Up Survey. Quality of life questionnaires including EORTC-QLQ-BR23 scale and BIS will be assessed. The impact of hair loss on treatment decision will be evaluated.

Add the following new section

8.7 Assessments at the Follow-Up Visits 1, 2, 3, 4 and 5 Years (± 2 Weeks) After Completion of Study Treatment

The incidence of scalp metastases will be determined by contacting the patient annually (12 months ± 2 weeks) following the 6 month follow up visit of Protocol DIG-001. The investigator will determine whether scalp metastases have occurred through best efforts using the following information sources:

- Examination of the patient
- Patient provided history
- Patient medical records
- Patient personal physician or other health professional

Supporting information will be additional history of recurrence of breast cancer, metastases in other body systems, other cancers and other medical conditions.

8 ADVERSE EVENTS (AE)

9.9.3 Toxicity Reporting

Old Wording

All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded with details regarding duration, severity of each episode and outcome. The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to investigational product or their clinical significance. The

description of the AE will include the onset date, duration, date of resolution, severity, seriousness, etiology, and the likelihood of relationship of the AE to study treatment.

Information regarding AEs will be collected from the time the patient signs the informed consent form up to 30 days after the ~~last dose of investigational product is administered.~~

New Wording

All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded with details regarding duration, severity of each episode and outcome. The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to investigational product or their clinical significance. The description of the AE will include the onset date, duration, date of resolution, severity, seriousness, etiology, and the likelihood of relationship of the AE to study treatment.

Information regarding AEs will be collected from the time the patient signs the informed consent form up to 30 days after the patient's last scalp cooling.

Add the following new section

10.2.3 Incidence of Scalp Metastases

The incidence of scalp metastases will be determined by contacting the patient annually. The investigator will determine whether scalp metastases have occurred through best efforts using the following information sources:

- Examination of the patient
- Patient provided history
- Patient medical records
- Patient personal physician or other health professional

Supporting information will be additional history of recurrence of breast cancer, metastases in other body systems, other cancers and other medical conditions.

13. STATISTICAL CONSIDERATIONS

13.1 Objectives

Old Wording

This study is designed to assess the ability of scalp hypothermia using the DigniCap™ System to prevent chemotherapy induced alopecia. 'Activity' will be quantified using alopecia grading scales as described above, which will be used to define the proportion of responders among all evaluable patients. The primary goal of this study is to assess the efficacy of this system. To

assess efficacy, the primary endpoint will be grade of alopecia 1 month after the last chemotherapy treatment as assessed by the patient with photographic documentation (digital photos), comparing current hair loss versus baseline.

Comparisons of the primary endpoint will be made with a concurrent non-randomized control group and also with a pre-defined level of clinical efficacy.

A secondary objective is to examine the safety of the system, in terms of adverse symptoms and adverse device effects reported by patients during use of the DigniCap™ System and during the follow-up period 3 and 6 months after completion of treatment will be examined.

New Wording

This study is designed to assess the ability of scalp hypothermia using the DigniCap™ System to prevent chemotherapy induced alopecia. ‘Activity’ will be quantified using alopecia grading scales as described above, which will be used to define the proportion of responders among all evaluable patients. The primary goal of this study is to assess the efficacy of this system. To assess efficacy, the primary endpoint will be grade of alopecia 1 month after the last chemotherapy treatment as assessed by the patient with photographic documentation (digital photos), comparing current hair loss versus baseline. The primary endpoint analysis for the purpose of seeking approval for marketing will be conducted when all enrolled subjects have completed the primary outcome visit at 4 weeks after the last chemotherapy or withdrawn from the study. Patients will continue follow-up at 3 and 6 months and then annually for 5 years after the last chemotherapy. After the last patient has completed the 5 year follow up, a final safety analysis will be performed.

Comparisons of the primary endpoint will be made with a concurrent non-randomized control group and also with a pre-defined level of clinical efficacy.

A secondary objective is to examine the safety of the system, in terms of adverse symptoms and adverse device effects reported by patients during use of the DigniCap™ System and during the follow-up period 3 and 6 months after completion of treatment will be examined.

The incidence of scalp metastases at annual examinations during a 5-year follow-up is a secondary objective.

13.6 Analysis

Add the following analysis:

2. Safety assessed by a summary of the incidence of scalp metastases during a 5-year follow up.

Appendix XV: CASE REPORT FORM FOR LONG TERM SAFETY FOLLOW UP

New.

Clinical Performance, Efficacy and Safety of the DigniCap™ System, a Scalp Hypothermia System, in Preventing Chemotherapy Induced Alopecia in Patients with Early Stage Breast Cancer

Clinical Investigational Plan (CIP)

CIP version: *April 16, 2013. Issue 2.*

Amended June 13, 2013, August 7, 2013, October 18, 2013, December 17, 2013

DETAILED CHANGES

Principal Investigator(s):

University of California San Francisco (UCSF)

Hope S. Rugo, MD

Wake Forest University School of Medicine

Susan Melin, MD

Weill Cornell Medical College

Tessa Cigler, MD

Beth Israel Comprehensive Cancer Center

Paula Klein, MD

UCLA Jonsson Comprehensive Cancer Center

Sara Hurvitz, MD

Study Statistician:

Wake Forest University School of Medicine

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This Amendment to Protocol DIG-001 was written to modify the time of post-infusion cooling, to add a new investigator, and to include an additional chemotherapy regimen based on a recently FDA approved treatment.

Protocol Wording Changes

Cover Page, Principal Investigators

New Wording

UCLA Jonsson Comprehensive Cancer Center

Sara Hurvitz, MD

Synopsis, Treatment Group, Inclusion Criteria

Old Wording

3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens:
 - Doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 2 - 3 weeks
 - Docetaxel 75 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 3 weeks
 - Paclitaxel 80 mg/m² weekly IV x at least 12 weeks with or without IV trastuzumab
 - Paclitaxel 175 mg/m² IV every 2 weeks x 4 – 6 cycles (without an anthracycline)
 - Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks
 - Docetaxel 75 mg/m² and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks
 - Targeted agents such as trastuzumab or lapatinib are allowed

New Wording

3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens:
 - Doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 2 - 3 weeks
 - Docetaxel 75 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 3 weeks
 - Paclitaxel 80 mg/m² weekly IV x at least 12 weeks with or without IV trastuzumab
 - Paclitaxel 175 mg/m² IV every 2 weeks x 4 – 6 cycles (without an anthracycline)
 - Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks
 - Docetaxel 75 mg/m² and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks

- Pertuzumab, trastuzumab, and docetaxel every 3 weeks (in the neoadjuvant setting) for 3-6 cycles
- Targeted agents such as trastuzumab or pertuzumab are allowed

Synopsis, Control Group, Inclusion Criteria

Old Wording

3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens:
 - Doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 2 - 3 weeks
 - Docetaxel 75 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 3 weeks
 - Paclitaxel 80 mg/m² weekly IV x at least 12 weeks with or without IV trastuzumab
 - Paclitaxel 175 mg/m² IV every 2 weeks x 4 – 6 cycles (without an anthracycline)
 - Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks
 - Docetaxel 75 mg/m² and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks
 - Targeted agents such as trastuzumab or ~~lapatinib~~ are allowed

New Wording

3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens:
 - Doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 2 - 3 weeks
 - Docetaxel 75 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 3 weeks
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 - Docetaxel 75 mg/m² and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks
 - Pertuzumab, trastuzumab, and docetaxel every 3 weeks (in the neoadjuvant setting) for 3-6 cycles
 - Targeted agents such as trastuzumab or pertuzumab are allowed

5.1.1 Inclusion Criteria (Treatment Group)

Old Wording

3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens:

- Doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 2 - 3 weeks
- Docetaxel 75 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 3 weeks
- Paclitaxel 80 mg/m² weekly IV x at least 12 weeks with or without IV trastuzumab
- Paclitaxel 175 mg/m² IV every 2 weeks x 4 – 6 cycles (without an anthracycline)
- Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks
- Docetaxel 75 mg/m² and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks
- Targeted agents such as trastuzumab or lapatinib are allowed

New Wording

3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens:
 - Doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 2 - 3 weeks
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 - Paclitaxel 80 mg/m² weekly IV x at least 12 weeks with or without IV trastuzumab
 - Paclitaxel 175 mg/m² IV every 2 weeks x 4 – 6 cycles (without an anthracycline)
 - Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks
 - Docetaxel 75 mg/m² and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks
 - Pertuzumab, trastuzumab, and docetaxel every 3 weeks (in the neoadjuvant setting) for 3-6 cycles
 - Targeted agents such as trastuzumab or pertuzumab are allowed

5.2.1 Inclusion Criteria (Control Group)

Old Wording

3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens:
 - Doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 2 - 3 weeks
 - Docetaxel 75 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 3 weeks
 - Paclitaxel 80 mg/m² weekly IV x at least 12 weeks with or without IV trastuzumab
 - Paclitaxel 175 mg/m² IV every 2 weeks x 4 – 6 cycles (without an anthracycline)
 - Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks
 - Docetaxel 75 mg/m² and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks
 - Targeted agents such as trastuzumab or lapatinib are allowed

New Wording

3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens:
 - Doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 2 - 3 weeks
 - Docetaxel 75 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 3 weeks
 - Paclitaxel 80 mg/m² weekly IV x at least 12 weeks with or without IV trastuzumab
 - Paclitaxel 175 mg/m² IV every 2 weeks x 4 – 6 cycles (without an anthracycline)
 - Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks
 - Docetaxel 75 mg/m² and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks
 - Pertuzumab, trastuzumab, and docetaxel every 3 weeks (in the neoadjuvant setting) for 3-6 cycles
 - Targeted agents such as trastuzumab or pertuzumab are allowed

7.1 Study Treatment

Old Wording

Patients will receive scalp hypothermia as delivered by the DigniCap™ System. Scalp cooling will begin 30 minutes prior to administration of chemotherapy. Scalp temperature will be maintained at +3°C (37°F) throughout drug administration and for ~~60-90~~ minutes after discontinuing the infusion, depending on the chemotherapy regimen as outlined in Section 7.2.

New Wording

Patients will receive scalp hypothermia as delivered by the DigniCap™ System. Scalp cooling will begin 30 minutes prior to administration of chemotherapy. Scalp temperature will be maintained at +3°C (37°F) throughout drug administration and for 90-120 minutes after discontinuing the infusion, depending on the chemotherapy regimen as outlined in Section 7.3.

7.3 Chemotherapy Regimen and Cooling Times

Old Wording

Chemotherapy Regimen	Dose	Post Infusion Cooling Time (minutes)
AC x 4 or 6 cycles, every 2-3 weeks	Doxorubicin: 60 mg/m ² , Cyclophosphamide 600 mg/m ²	90
TC x 4 or 6 cycles,	Docetaxel 75 mg/m ² ,	90

every 3 weeks	Cyclophosphamide 600 mg/m ²	
Paclitaxel x at least 12 cycles every week	Paclitaxel 80 mg/m ²	90
Paclitaxel and Carboplatin x 6 cycles, 3 on/ 1 off	Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks	90
Paclitaxel x 4 – 6 cycles every 2 weeks	Paclitaxel 175 mg/m ² IV every 2 weeks (without an anthracycline)	90
TCH x 6 cycles every 3 weeks	Docetaxel 75mg/m ² , Carboplatin AUC 6, Trastuzumab weekly or every 3 weeks	90

Targeted therapeutics not associated with hair loss are allowed (including trastuzumab, lapatinib, etc.).

New Wording

Chemotherapy Regimen	Dose	Post Infusion Cooling Time (minutes)
AC x 4 or 6 cycles, every 2-3 weeks	Doxorubicin: 60 mg/m ² , Cyclophosphamide 600 mg/m ²	120
TC x 4 or 6 cycles, every 3 weeks	Docetaxel 75 mg/m ² , Cyclophosphamide 600 mg/m ²	120
Paclitaxel x at least 12 cycles every week	Paclitaxel 80 mg/m ²	90
Paclitaxel and Carboplatin x 6 cycles, 3 on/ 1 off	Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks	120
Paclitaxel x 4 – 6 cycles every 2 weeks	Paclitaxel 175 mg/m ² IV every 2 weeks (without an anthracycline)	<u>120</u>
TCH x 6 cycles every 3 weeks (<u>pertuzumab is allowed in the neoadjuvant setting</u>)	Docetaxel 75mg/m ² , Carboplatin AUC 6, Trastuzumab weekly or every 3 weeks	<u>120</u>

<u>Pertuzumab, trastuzumab, and docetaxel every 3 weeks (in the neoadjuvant setting) for 3-6 cycles</u>	<u>Pertuzumab initial dose of 840 mg, followed by 420 mg 603 every 3 weeks, Trastuzumab initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks, Docetaxel 75 mg/m²</u>	<u>120</u>
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Targeted therapeutics not associated with hair loss are allowed (including trastuzumab, pertuzumab, etc.).

Appendix I

Replaced to modify inclusion criteria list

Appendix XXIII: CASE REPORT FORM FOR DEVICE USE

Replaced to modify cooling times.

Clinical Performance, Efficacy and Safety of the DigniCap™ System, a Scalp Hypothermia System, in Preventing Chemotherapy Induced Alopecia in Patients with Early Stage Breast Cancer

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DETAILED CHANGES

Principal Investigator(s):

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This Amendment to Protocol DIG-001 was written to modify the inclusion criteria for the Control Group to include Stage I and II breast cancer only.

Protocol Wording Changes

Synopsis, Control Group, Inclusion Criteria

Old Wording

2. Documented diagnosis of stage I to III breast cancer.

New Wording

2. Documented diagnosis of stage I or II breast cancer.

5.2.1 Inclusion Criteria (Control Group)

Old Wording

2. Documented diagnosis of stage I to III breast cancer.

New Wording

2. Documented diagnosis of stage I or II breast cancer.

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Amendment 2 to Protocol DIG-001 was written to make the following changes to the protocol:

1. Modify the recruitment of control group patients to specify that each patient will be matched to a treatment group patient at the same site.
2. Modify the follow up of the control group patients to the same duration of follow up as the treatment group patients.
3. To correct inconsistencies in the protocol related to:
 - 3.1 The Hair Re-growth Follow Up Survey timing and questions
 - 3.2 The timing of the assessment of the impact of hair loss on treatment decisions to occur only at 6 months after completion of chemotherapy
 - 3.3 The timing of the Quality of Life and Body Image Scale assessments
 - 3.4 Secondary Objectives in the Statistical section 13.6 Analysis

In addition, typographical errors were corrected, but not detailed below.

Protocol Wording Changes

Synopsis, Objectives

Old Wording

To evaluate hair re-growth at 3 and 6 months after completion of chemotherapy ~~compared to the greatest hair loss~~ as assessed by the patient using the hair regrowth follow up survey.

New Wording

To evaluate hair re-growth at 3 and 6 months after completion of chemotherapy as assessed by the patient using the Hair Re-growth Follow Up Survey.

Synopsis, Patient Population and Sample Size

Old Wording

An age- and treatment regimen-matched control group of up to 30 patients will be enrolled; hair loss will be assessed during treatment using the same procedures as the treatment group.

New Wording

At each site an age- and treatment regimen-matched control group of up to 30 total patients will be enrolled; hair loss will be assessed during treatment using the same procedures as the treatment group.

Synopsis, Patient Selection Criteria, Control Group

Add the following Inclusion Criterion

9. Willing to enroll in an extension protocol for follow up for 5 years following the end of chemotherapy treatment

Add the following Exclusion Criterion

10. Participation in any other clinical investigation or exposure to other investigational agents, drugs, device or procedure that may cause hair loss

2.2 Secondary Objective

Old Wording

- To evaluate hair re-growth at 3 and 6 months after completion of chemotherapy ~~compared to the greatest hair loss~~ as assessed using the hair regrowth follow up survey.

New Wording

- To evaluate hair re-growth at 3 and 6 months after completion of chemotherapy as assessed using the Hair Re-growth Follow Up Survey.

4. Treatment Plan

Deleted Section 4.2 and incorporated control group follow up information into Section 4.1 table.

5.2 Control Group

Add the following Inclusion Criterion

9. Willing to enroll in an extension protocol for follow up for 5 years following the end of chemotherapy treatment

7. Study Design

Old Wording

Patients who choose not to undergo scalp cooling during chemotherapy are eligible to enrol in the study as part of the concurrent control group. The control group is being enrolled to determine whether the expected frequency of almost total hair loss will occur using the criteria of this study. The control patients will be matched by disease (breast cancer), age (± 5 years) and chemotherapy treatment regimen. If at least 12 out of the first 15 control patients have a Dean score of 4, or lose greater than 75% of their hair, enrolment of the control group will be discontinued. Otherwise, a total of 30 control patients will be recruited.

New Wording

Patients who choose not to undergo scalp cooling during chemotherapy are eligible to enrol in the study as part of the concurrent control group. The control group is being enrolled to determine whether the expected frequency of almost total hair loss will occur using the criteria of this study. The control patients will be matched to a patient at the same investigative site by disease (breast cancer), age (± 5 years) and chemotherapy treatment regimen. If at least 12 out of the first 15 control patients have a Dean score of 4, or lose greater than 75% of their hair, enrolment of the control group will be discontinued. Otherwise, a total of 30 control patients will be recruited.

8.2 Assessments at Baseline

Old Wording

Eligible patients who consent to this study will have the following baseline assessments: Medical history, physical examination, vital signs, and Karnofsky Performance status. Each patient will be examined for cutaneous metastases of the scalp. The use of concomitant medication will also be assessed at baseline. Hair will be photographed before initiation of the first cycle of chemotherapy by the physician or study personnel as detailed above. Patients will be asked to assess their current hair status by comparing the photographs against standardized photographs using of the quantitative Dean scale ~~and to assess the impact of hair loss on treatment decision~~. Quality of Life questionnaires including the EORTC-QLQ-BR23 scale and BIS will be filled out by the patient.

New Wording

Eligible patients who consent to this study will have the following baseline assessments: Medical history, physical examination, vital signs, and Karnofsky Performance status. Each patient will be examined for cutaneous metastases of the scalp. The use of concomitant medication will also be assessed at baseline. Hair will be photographed before initiation of the first cycle of chemotherapy by the physician or study personnel as detailed above. Patients will be asked to assess their current hair status by comparing the photographs against standardized photographs using of the quantitative Dean scale. Quality of Life questionnaires including the EORTC-QLQ-BR23 scale and BIS will be filled out by the patient.

8.4 Assessments at 4 Weeks (3-6 Week Window) Following Last Chemotherapy Cycle

Old Wording

Evaluation of the last chemotherapy cycle will take place 4 (± 1 week) weeks after the last cycle of chemotherapy. The medical history of the patient and the use of concomitant medication will be reassessed, and a physical examination will be performed. Hair will be photographed by the physician or study personnel. Patients (treatment and control) will be asked to assess their current hair loss by examination of the photograph set using the quantitative Dean scale. Use of any head cover such as wig, scarves or cap will be documented as “never”, “sometimes”, or “always”. Patients will also fill out the quality of life questionnaires including the EORTC-QLQ-BR23 scale and BIS. ~~Control group patients will end participation in the study at this visit.~~

New Wording

Evaluation of the last chemotherapy cycle will take place 4 weeks (3-6 weeks) after the last cycle of chemotherapy. The medical history of the patient and the use of concomitant medication will be reassessed, and a physical examination will be performed. Hair will be photographed by the physician or study personnel. Patients (treatment and control) will be asked to assess their current hair loss by examination of the photograph set using the quantitative Dean scale. Use of any head cover such as wig, scarves or cap will be documented as “never”, “sometimes”, or “always”. Patients will also fill out the quality of life questionnaires including the EORTC-QLQ-BR23 scale and BIS.

8.5 Assessments At The Follow-Up Visit 3 Months (± 2 Weeks) After The Completion Of Study Treatment

Old Wording

Vital signs, medical history, physical examination, examination for cutaneous metastases of the scalp will be carried out in the treatment group patients. The use of concomitant medication and any adverse events will be reported. The patient will ~~compare her hair status as compared to baseline~~ in the Hair Re-growth Follow-Up Survey ~~using the quantitative Dean scale~~. Quality of life questionnaires including EORTC-QLQ-BR23 scale and BIS will be assessed.

~~Use of any head cover such as wig, scarves or cap will be documented as “never”, “sometimes” or “always”. The impact of hair loss on treatment decision will be evaluated.~~

New Wording

Vital signs, medical history, physical examination, examination for cutaneous metastases of the scalp will be carried out in the treatment group patients. The use of concomitant medication and any adverse events will be reported. The patient will assess hair re-growth using the Hair Re-growth Follow Up Survey. Quality of life questionnaires including EORTC-QLQ-BR23 scale and BIS will be assessed.

8.6 Assessments At The Follow-Up Visit 6 Months (± 2 Weeks) After The Completion Of Study Treatment

Old Wording

Assessment at 6 Months

The use of concomitant medication and any adverse events will be reported. ~~The patient will compare her own hair status as compared to baseline in the Hair Re-growth Follow-Up Survey using the quantitative Dean scale.~~ Quality of life questionnaires including EORTC-QLQ-BR23 scale and Body Image will be assessed.

~~Use of any head cover such as wig, scarves or cap will be documented as “never”, “sometimes” or “always”.~~

The presence of any cutaneous metastases of the scalp will be documented.

New Wording

The use of concomitant medication and any adverse events will be reported. The patient will assess hair re-growth using the Hair Re-growth Follow Up Survey. Quality of life questionnaires including EORTC-QLQ-BR23 scale and BIS will be assessed. The impact of hair loss on treatment decision will be evaluated.

The presence of any cutaneous metastases of the scalp will be documented.

10.2.3 Quality of Life in Women Using the Dignicap™ System

Old Wording

Quality of Life measured by the EORTC-QLQ-BR23 scale and BIS at Baseline, Cycle 4 of chemotherapy and 4 weeks after the last cycle of chemotherapy.

New Wording

Quality of Life measured by the EORTC-QLQ-BR23 scale and BIS at Baseline, Cycle 4 of chemotherapy, 4 weeks after the last cycle of chemotherapy and at 4 weeks and 3 and 6 months after the completion of chemotherapy.

10.2.5 Impact of Hair Loss on Treatment Decisions

Old Wording

Information regarding the perceived impact of hair loss on treatment decisions will be collected at ~~baseline and 3 months~~ after completion of chemotherapy.

New Wording

Information regarding the perceived impact of hair loss on treatment decisions will be collected at Month 6 after completion of chemotherapy.

13.1 Objectives

Old Wording

The secondary endpoints also include tolerability of the DigniCap™ System, quality/quantity of hair re-growth at follow-up visits at 3 and 6 months, quality of life measures assessed using the EORTC-QLQ-BR23 scale and BIS during chemotherapy and follow-up visits, the 5-level Dean score measured on a continuous scale and the impact of hair loss on treatment decisions ~~assessed at follow up using a 4-level ordered categorical measure~~. These secondary outcomes will be evaluated in all patients, whether or not they are evaluable for response.

New Wording

The secondary endpoints also include tolerability of the DigniCap™ System, ~~hair loss at each chemotherapy~~, quality/quantity of hair re-growth at follow-up visits at 3 and 6 months, quality of life measures assessed using the EORTC-QLQ-BR23 scale and BIS during chemotherapy and follow-up visits, and the impact of hair loss on treatment decisions. These secondary outcomes will be evaluated in all patients, whether or not they are evaluable for response.

13.6 Analysis

Old Wording

The secondary endpoints will be reported with descriptive statistics (means, medians, and measures of variability, including 95% confidence intervals for continuous measures and counts and percents, with corresponding 95% confidence intervals for categorical variables):

1. Safety assessed by a summary of the incidence and severity of adverse events and summary of scalp changes identified during physical examination.

2. Tolerability defined as the percentage of patients who complete all planned cycles of chemotherapy using the DigniCap™ System.
3. Assessment of hair loss by the patient using alopecia self-report at each chemotherapy.
4. Assessment of hair regrowth by the patient using the Hair Regrowth Follow Up Survey.
5. Assessment of Quality of life during and after treatment with the DigniCap™ System by the patients using the EORTC-QLQ-BR23 scale and BIS.
6. Assessment of the impact of hair loss on treatment decisions in patients offered therapy with the DigniCap™ System at the follow up visit 3 months after completion of treatment.
- ~~7. Assessment of quality of treatment response in terms of quality/ quantity of hair re-growth from baseline during follow up period 3, 6, and 12 months after completion of treatment. Patients will grade the hair in terms of texture, manageability and color variation from baseline.~~
- ~~8. Assessment of the scalp for the occurrence of scalp metastases at 3 and 6 months.~~

New Wording

The secondary endpoints will be reported with descriptive statistics (means, medians, and measures of variability, including 95% confidence intervals for continuous measures and counts and percents, with corresponding 95% confidence intervals for categorical variables):

1. Safety assessed by a summary of the incidence and severity of adverse events and summary of scalp changes identified during physical examination.
2. Tolerability defined as the percentage of patients who complete all planned cycles of chemotherapy using the DigniCap™ System.
3. Assessment of hair loss by the patient using alopecia self-report at each chemotherapy.
4. Assessment of hair re-growth by the patient using the Hair Re-growth Follow Up Survey.
5. Assessment of Quality of life during and after treatment with the DigniCap™ System by the patients using the EORTC-QLQ-BR23 scale and BIS.
6. Assessment of the impact of hair loss on cancer treatment decisions at 6 months after completion of chemotherapy.

Clinical Performance, Efficacy and Safety of the DigniCap™ System, a Scalp Hypothermia System, in Preventing Chemotherapy Induced Alopecia in Patients with Early Stage Breast Cancer

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DETAILED CHANGES

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Amendment 1 to Protocol DIG-001 was written to make the following changes to the protocol:

1. Modify the target temperature of the DigniCap™ System from 5°C to 3°C. In practice, clinicians will modify the temperature to ensure adequate cooling and lower the temperature if the cap is not fitted well to the scalp because of the shape of the head or thickness of the hair. Lowering the temperature for all subjects will ensure that all receive adequate cooling without the need for individual subject decisions.
2. Reduced the patient burden for photographs in those patients receiving the weekly paclitaxel infusions so that photographs will be taken only at weeks 1, 2, 4, 6, 8, 10, and 12.
3. Clarified the wording to be used for the Dean scale categories for patient self assessment.
4. Modified cooling times to 90 minutes after completion of chemotherapy to 90 minutes for all regimens.
5. Correct a typographical error in the sample size calculation.
6. Correct the description of secondary endpoints in the statistical section to make them consistent with the secondary endpoints in Section 3.2 of the protocol.

Protocol Wording Changes

4.1 Schedule of Investigational Events for Treatment Group

4.2 Schedule of Investigational Events for Control Group

8.1 Photographic Documentation

8.3 Assessments at Each Cycle of Chemotherapy

10.2.1 Alopecia Report Assessment by the Patient

The following statement was added: Patients receiving weekly paclitaxel treatment will have photographs taken at weeks 1, 2, 4, 6, 8, 10, and 12.

7.1 Study Treatment

Old Wording

No study specific assessments or treatments will commence prior to obtaining written signed informed consent from the patient.

Patients will receive scalp hypothermia as delivered by the DigniCap™ System. Scalp cooling will begin 30 minutes prior to administration of chemotherapy. Scalp temperature will be maintained at +5°C (41°F) throughout drug administration and for 60-90 minutes after discontinuing the infusion, depending on the chemotherapy regimen as outlined in Section 7.2.

New Wording

No study specific assessments or treatments will commence prior to obtaining written signed informed consent from the patient.

Patients will receive scalp hypothermia as delivered by the DigniCap™ System. Scalp cooling will begin 30 minutes prior to administration of chemotherapy. Scalp temperature will be

maintained at $+3^{\circ}\text{C}$ (37°F) throughout drug administration and for 60-90 minutes after discontinuing the infusion, depending on the chemotherapy regimen as outlined in Section 7.2.

7.3 Chemotherapy Regimens and Cooling Times

The third column "Post Infusion Cooling Time (minutes) was modified to 90 minutes for all regimens.

10.1 Criteria for Response Assessment

Old Wording

Criteria for grading of alopecia will be assessed using the Dean scale [22].

- Grade 0: no hair loss
- Grade 1: up to 25% hair loss
- Grade 2: between 25 and 50% hair loss
- Grade 3: between 50 and 75%
- Grade 4: greater than 75% hair loss

New Wording

Criteria for grading of alopecia will be assessed using the Dean scale [22].

- Grade 0: no hair loss
- Grade 1: greater than 0 up to 25% hair loss
- Grade 2: greater than 25 up to 50% hair loss
- Grade 3: greater than 50 up to 75% hair loss
- Grade 4: greater than 75% hair loss

13.3 Sample Size and Power Estimation

Old Wording

For the comparison within the treated group only, using a one group chi-square test for proportions, with type I error of 5% (2-sided), for a sample size of 100 patients, there is 92% power to detect the difference between the null hypothesis proportion of less than 40% versus an alternative proportion of 56% (or greater).

New Wording

For the comparison within the treated group only, using a one group chi-square test for proportions, with type I error of 5% (2-sided), for a sample size of 110 patients, there is 92% power to detect the difference between the null hypothesis proportion of less than 40% versus an alternative proportion of 56% (or greater).

13.6 Analysis

Old Wording

The secondary endpoints will be reported with descriptive statistics (means, medians, and measures of variability, including 95% confidence intervals for continuous measures and counts and percents, with corresponding 95% confidence intervals for categorical variables):

1. Tolerability defined as the percentage of patients who complete all planned cycles of chemotherapy using the DigniCap™ System.
2. Assessment of hair loss by the patient using the quantitative Dean scale.
3. Assessment of hair re-growth at the 3 and 6 month follow-up visits compared to hair status after completion of chemotherapy, by a three person independent panel. Hair re-growth is defined by an improvement in the Dean scale by at least one level.
4. Assessment of hair regrowth by the patient using the Hair Regrowth Follow Up Survey.
5. Assessment of Quality of life during and after treatment with the DigniCap™ System by the patients using the EORTC-QLQ-BR23 scale and BIS.
6. Assessment of the impact of hair loss on treatment decisions in patients offered therapy with the DigniCap™ System at the follow up visit 3 months after completion of treatment.
7. Assessment of quality of treatment response in terms of quality/ quantity of hair regrowth from baseline during follow-up period 3, 6, and 12 months after completion of treatment. Patients will grade the hair in terms of texture, manageability and color variation from baseline.
8. Assessment of the scalp for the occurrence of scalp metastases at 3 and 6 months.

New Wording

The secondary endpoints will be reported with descriptive statistics (means, medians, and measures of variability, including 95% confidence intervals for continuous measures and counts and percents, with corresponding 95% confidence intervals for categorical variables):

1. Safety assessed by a summary of the incidence and severity of adverse events and summary of scalp changes identified during physical examination.
2. Tolerability defined as the percentage of patients who complete all planned cycles of chemotherapy using the DigniCap™ System.
3. Assessment of hair loss by the patient using alopecia self-report at each chemotherapy.
4. Assessment of hair regrowth by the patient using the Hair Regrowth Follow Up Survey.
5. Assessment of Quality of life during and after treatment with the DigniCap™ System by the patients using the EORTC-QLQ-BR23 scale and BIS.

6. Assessment of the impact of hair loss on treatment decisions in patients offered therapy with the DigniCap™ System at the follow up visit 3 months after completion of treatment.
7. Assessment of quality of treatment response in terms of quality/ quantity of hair re-growth from baseline during follow-up period 3, 6, and 12 months after completion of treatment. Patients will grade the hair in terms of texture, manageability and color variation from baseline.
8. Assessment of the scalp for the occurrence of scalp metastases at 3 and 6 months.

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SIGNATURE PAGE

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Signature of Study Statistician:

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SYNOPSIS

TITLE	Clinical Performance, Efficacy and Safety of the DigniCap™ System, a Scalp Hypothermia System, in Preventing Chemotherapy Induced Alopecia in Patients with Early Stage Breast Cancer
PHASE	IDE PMA Study
BACKGROUND	<p>Alopecia is a non-life threatening complication of the majority of effective adjuvant chemotherapy regimens for early stage breast cancer. It has a significant impact on quality of life and affects decisions regarding the risks and benefits of treatment.</p> <p>Scalp cooling prevents hair loss through vasoconstriction, and thus a lower concentration of chemotherapy is delivered to the scalp. Scalp cooling also decreases cellular uptake of drugs and decreases the intra-follicular metabolic rate.</p> <p>We propose to study the safety and efficacy of the DigniCap™ System in women undergoing standard adjuvant chemotherapy for early stage breast cancer at 5 centers in the United States. The study design is a two arm study with a non-randomized active arm and a concurrent non-randomized control group. We believe that scalp cooling, now commonly used around the world outside of the U.S., is an important tool that should be studied in American women.</p>
OBJECTIVES	<p>The overall objective is to assess the clinical performance, efficacy and safety of a Scalp Hypothermia System in breast cancer patients receiving specific chemotherapy treatments that, unless counteracted by simultaneous hypothermia treatment, result in hair loss.</p> <p>Primary Objective: To assess the ability of the DigniCap™ System to prevent hair loss in women receiving specific chemotherapy regimens for early stage breast cancer. Efficacy will be measured by assessment of hair loss up to 4 weeks (3-6 week window) after the completion of the last chemotherapy cycle by patient self-assessment of standardized photographs using the Dean scale by patients in the treatment and control groups</p> <p>Secondary Objectives: To assess safety of the DigniCap™ System in women receiving specific chemotherapy regimens for early stage breast cancer.</p> <p>To assess tolerability of the Digni-Cap™.</p>

	<p>To evaluate hair loss and recovery as assessed by the patient during and following chemotherapy using the alopecia self-report.</p> <p>To evaluate hair re-growth at 3 and 6 months after completion of chemotherapy compared to the greatest hair loss as assessed by the patient using the hair regrowth follow up survey.</p> <p>To assess patient quality of life and satisfaction with hair during and after treatment with the DigniCap™ System.</p> <p>To assess the impact of hair loss on treatment decisions.</p>
STUDY ENDPOINTS	<p>Primary endpoint: Success of the DigniCap™ System to prevent hair loss, defined as a maximum Dean score of ≤ 2 using standardized photographs graded by the patient up to 4 weeks after the last chemotherapy treatment, in at least 50% of patients enrolled in the treatment group with a lower bound of the 95% CI greater than 40%, and statistical superiority over a concurrent control group.</p> <p>Secondary endpoints: Safety as determined by spontaneous reporting of adverse events and as negative scalp changes determined by physical examination.</p> <p>Tolerability is defined as the percentage of patients who complete all planned cycles of chemotherapy do so using the DigniCap™ System.</p> <p>Patient assessment of hair loss by the alopecia self-report at each chemotherapy.</p> <p>Hair re-growth assessed by the patient using the hair regrowth follow up survey.</p> <p>Quality of life as measured by the EORTC-QLQ-BR23 quality of life questionnaire and a Body Image Scale.</p> <p>Assessment of the impact of hair loss on breast cancer treatment decisions at 6 months after completion of chemotherapy.</p>
PATIENT POPULATION AND SAMPLE SIZE	110 women with stage I or II breast cancer scheduled to receive at least 4 cycles of specific anthracycline or taxane based chemotherapy regimens in the adjuvant or neoadjuvant setting

	<p>will be enrolled to ensure a sample size of at least 100 patients that complete the study.</p> <p>An age- and treatment regimen-matched control group of up to 30 patients will be enrolled; hair loss will be assessed during treatment using the same procedures as the treatment group.</p>
INVESTIGATIONAL PRODUCTS:	The DigniCap™ System
PATIENT SELECTION CRITERIA Treatment Group	<p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. Female patients \geq 18 years of age 2. Documented diagnosis of stage I or II breast cancer. 3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens: <ul style="list-style-type: none"> • Doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 2 - 3 weeks • Docetaxel 75 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 3 weeks • Paclitaxel 80 mg/m² weekly IV x at least 12 weeks with or without IV trastuzumab • Paclitaxel 175 mg/m² IV every 2 weeks x 4 – 6 cycles (without an anthracycline) • Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks • Docetaxel 75 mg/m² and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks • Targeted agents such as trastuzumab or lapatinib are allowed 4. Plan to complete chemotherapy within 6 months 5. At least two years out from the last chemotherapy causing hair loss with complete recovery of hair 6. Karnofsky performance status \geq 80% 7. Willing and able to sign informed consent for protocol treatment 8. Willing to participate in study procedures including having photographs of the head before each cycle of chemotherapy and 1 month after the last chemotherapy 9. Willing to enroll in an extension protocol for follow up for 5 years following the end of chemotherapy treatment
	<p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. Patients with female pattern baldness resembling picture I-3 or higher on the Savin scale (Appendix IB)

	<ol style="list-style-type: none"> 2. Autoimmune disease affecting hair; e.g. alopecia areata, systemic lupus with associated hair loss 3. A history of whole brain radiation 4. Plans to use a chemotherapy regimen other than those specified in the inclusion criteria. Specifically, patients receiving a regimen including both an anthracycline and a taxane are not eligible for this trial (AC/T, EC/T, TAC, etc.) 5. Concurrent hormone therapy with chemotherapy. Hormone therapy should be used as indicated following completion of chemotherapy 6. Underlying clinically significant liver disease including active viral hepatitis with abnormal liver function tests >1.5 times the upper limit of normal, including alkaline phosphatase, AST, and total bilirubin. Patients with Gilbert's disease (elevated indirect bilirubin only) will be eligible for participation. 7. Clinically significant renal dysfunction defined as serum creatinine > the upper limit of normal. 8. A serious concurrent infection or medical illness that would jeopardize the ability of the patient to complete the planned therapy and follow-up 9. A history of persistent grade 2 (or higher) alopecia induced by prior chemotherapeutic regimens 10. Participation in any other clinical investigation or exposure to other investigational agents, drugs, device or procedure that may cause hair loss 11. Intercurrent life-threatening malignancy 12. A history of cold agglutinin disease or cryoglobulinemia 13. Evidence of untreated or poorly controlled hyper- or hypothyroidism 14. A history of silicon allergy 15. American Society of Anesthesiologist Class ≥ 3 (Appendix IV.A)
<p>PATIENT SELECTION CRITERIA Control Group</p>	<p>Inclusion Criteria:</p> <ol style="list-style-type: none"> 1. Female patients ≥ 18 years of age 2. Documented diagnosis of stage I to III breast cancer. 3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens: <ul style="list-style-type: none"> • Doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 2 - 3 weeks • Docetaxel 75 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 3 weeks • Paclitaxel 80 mg/m² weekly IV x at least 12 weeks with or without IV trastuzumab • Paclitaxel 175 mg/m² IV every 2 weeks x 4 - 6 cycles

	<p>(without an anthracycline)</p> <ul style="list-style-type: none"> • Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks • Docetaxel 75 mg/m² and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks • Targeted agents such as trastuzumab or lapatinib are allowed <ol style="list-style-type: none"> 4. At least two years out from the last chemotherapy causing hair loss with complete recovery of hair 5. Karnofsky performance status \geq 80% 6. Willing and able to sign informed consent for protocol treatment 7. Willing to participate in study procedures including having photographs of the head before each cycle of chemotherapy and 1 month after the last chemotherapy 8. Chooses not to use scalp cooling during chemotherapy
	<p>Exclusion Criteria:</p> <ol style="list-style-type: none"> 1. Patients with female pattern baldness resembling picture I-3 or higher on the Savin scale (Appendix IB) 2. Autoimmune disease affecting hair; e.g. alopecia areata, systemic lupus with associated hair loss 3. A history of whole brain radiation 4. Plans to use a chemotherapy regimen other than those specified in the inclusion criteria. Specifically, patients receiving a regimen including both an anthracycline and a taxane are not eligible for this trial (AC/T, EC/T, TAC, etc.) 5. Concurrent hormone therapy with chemotherapy. Hormone therapy should be used as indicated following completion of chemotherapy 6. Underlying clinically significant liver disease including active viral hepatitis with abnormal liver function tests >1.5 times the upper limit of normal, including alkaline phosphatase, AST, and total bilirubin. Patients with Gilbert's disease (elevated indirect bilirubin only) will be eligible for participation. 7. Clinically significant renal dysfunction defined as serum creatinine $>$ the upper limit of normal. 8. A serious concurrent infection or medical illness that would jeopardize the ability of the patient to complete the planned therapy and follow-up 9. A history of persistent grade 2 (or higher) alopecia induced by prior chemotherapeutic regimens 10. Intercurrent life-threatening malignancy 11. Evidence of untreated or poorly controlled hyper- or

	hypothyroidism 12. American Society of Anesthesiologist Class ≥ 3 (Appendix IV.A)
STUDY DESIGN	This is a prospective, non-randomized, concurrent age- and treatment-matched control, clinical trial. The control group will establish whether a similar group of women based on disease, age, and treatment regimen will experience an expected high percentage of hair loss. An interim analysis will be conducted and if at least 12 out of the first 15 control group women have a Dean score of 4 (lose greater than 75% of their hair) at any chemotherapy visit, enrollment of the control group will be discontinued.

1. BACKGROUND AND RATIONALE

1.1 Chemotherapy Induced Hair Loss

Chemotherapy acts on cells with a high proliferation rate, targeting not only tumor cells but also benign proliferating cells, including those comprising the hair follicles. One previously unavoidable and emotionally distressing side effect from chemotherapy is chemotherapy-induced hair loss, or alopecia.

Chemotherapy is commonly utilized as adjuvant therapy for potentially curable malignancies such as breast cancer; the majority of patients with early stage disease will receive some sort of adjuvant chemotherapy. Different chemotherapy agents as well as variations in dose and schedule of administration result in varied effects on hair follicles. However, the most effective and most commonly administered adjuvant chemotherapy regimens for breast cancers include those that cause complete alopecia, anthracyclines and/or taxanes [1]. In contrast, some agents used primarily in the metastatic setting are not associated with significant hair loss, such as capecitabine and vinorelbine. Despite improvements in supportive care, and new chemotherapy regimens with less systemic toxicity, hair loss remains universal in the early stage setting.

Although genomic assays that predict chemotherapeutic benefit are an exciting approach that already are helping to determine which patients are most likely to benefit from adjuvant chemotherapy, hair loss remains a major issue in decision making for many patients. Patients with cancer rate chemotherapy induced alopecia as one of the most distressing side effects of treatment [2]. Complete alopecia is a constant reminder for the patient and others of their disease. This side effect is mostly, but not always, reversible [3]. It takes months to a year after completion of chemotherapy for the hair to recover, and it may be different in quality, color, and thickness, and baldness is a public declaration of illness. Cranial prostheses, or wigs, are helpful but uncomfortable, and often readily identifiable.

1.2 Methods Of Preventing Chemotherapy Induced Hair Loss

Chemotherapy induced hair loss potentially can be prevented by various methods, including minoxidil, CDK2 (cell division protein kinase) inhibitors, and scalp cooling. However, the efficacy of minoxidil and CDK2 inhibitors to prevent chemotherapy induced hair loss has not been very successful [4]. The most widely used and successful method today is scalp cooling.

1.2.1 Scalp Cooling Rationale

Scalp cooling prevents hair loss through vasoconstriction, and thus a lower concentration of chemotherapy is delivered to the scalp. Scalp cooling also decreases cellular uptake of drugs and decreases the intra-follicular metabolic rate. Cooling is normally initiated 30 minutes prior to the chemotherapy infusion, then continues during the infusion and for a period of time after the infusion is completed. The post infusion cooling time depends on the chemotherapy regimen and dose that is administered, but cooling normally continues for 60-90 minutes after termination of the infusion.

1.2.2 Scalp Cooling Development

Scalp cooling was first performed using ice packs that were placed on the patient's head, but with unsatisfactory results. The ice packs were subsequently replaced with ice caps. The most

common system of this type is called the Penguin Cold Cap [5]. The caps are frozen when placed on the patient's head and then thaw over time. The caps therefore have to be replaced frequently (approximately every 20 minutes). Numerous caps are required for a chemotherapy session. Every time a cap has been used it needs a certain time (12-24h) in the freezer before it can be used again. In order for a center to support the use of these ice caps, a large freezer as well as refrigerated storage are required, and each patient needs multiple caps for a single chemotherapy session. The frequent changing of caps is labor-intensive and requires a caregiver or health care worker. In addition, the fluctuation of temperature could potentially affect efficacy. This led to the development of cooling systems that could provide continuous cooling of the scalp.

1.2.3 Continuous Scalp Cooling

The DigniCap™ System has been available since 1999. The scalp is cooled by a liquid coolant that is flowing from a refrigeration unit through tubes into the channels of the DigniCap™ and then back to the cooling system. The DigniCap™ is a silicone cap that fits uniformly to the scalp, with internal automatic temperature regulation. The cap is available in four different sizes and is specifically designed not to cover the patient's ears for comfort. Each cap contains two cooling compartments and the temperature in both compartments is monitored and automatically adjusted by a security sensor to prevent side effects from excessive cooling. Two patients can be treated at the same time using one refrigeration unit. Default time and temperature settings can easily be altered for patient comfort. In September 2009, the new generation of the DigniCap™ System was introduced: the Digni C3/DigniCap™ System. This new generation device offers a number of improvements in design, potentially improving both tolerance and efficacy.

The competing scalp cooling system on the European market is the Paxman hair loss prevention system [6]. In analogy with the DigniCap™ System, the Paxman system offers continuous scalp cooling and consists of a refrigeration unit, cooling caps and a liquid coolant. On the contrary, Paxman does not measure the temperature on the head and has only one cooling circuit.

1.3 The Efficacy Of Scalp Cooling To Prevent Chemotherapy Induced Hair Loss

1.3.1 Efficacy Determinants

The efficacy of scalp cooling depends on several factors [7-9]: chemotherapy regimen and dose, dose interval, performance status of the patient, scalp cooling temperature, post cooling time, and the scalp cooling system. The optimal scalp cooling system can maintain a constant low temperature of the scalp and comes with a snug fitted cap. 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.

1.3.2 Efficacy Measures

Hair preservation is generally evaluated by assessing hair loss. Assessments are performed either by the patient herself and/or by the clinician. Clinicians assess hair loss either directly, when meeting with the patient, or afterwards when looking at photographs. Different scales for assessing hair loss are used: the modified WHO scale, the Dean scale and the visual analogue scale (VAS) [39]. The modified WHO scale and the Dean scale are both 5-grade scales but with different cut-points for the grades. The VAS is a continuous scale used for patient assessment of, in this case, hair loss.

Another way to measure efficacy of scalp cooling is wig use. This is a subjective method that may or may not reflect efficacy but rather patient satisfaction with their hair. Another method is the Cohen's Cross Section Trichometer, a device for measuring hair quantity. This is a new promising method that has not yet been evaluated in scalp cooled patients [10]. Clearly a number of methods to measure hair loss exist, without clear superiority to one method. However, the Dean scale is a validated measure of hair quantity that can be graded based on photographs taken at 5 angles, and may be the most reproducible measure for use in multicenter studies.

1.3.3 Literature Review

In the extensive review by Breed in 2011 [9], the efficacy of scalp cooling was evaluated. 57 studies and 3 personal communications involved over 6000 patients were treated with scalp cooling were included. The author states that scalp cooling is effective, but not for all patients. In the review by Poder et al. [11] it is concluded that, "scalp cooling seems to get good performance in its aim to prevent hair loss in patients receiving chemotherapy."

The efficacy and safety of the DigniCap™ System has been evaluated in a number of studies [12-17]. These studies are described in detail in the Dignitana Clinical Evaluation Report [18]. Overall the data demonstrates the ability of the system to prevent chemotherapy induced hair loss in a number of settings. There is an ongoing evaluation of the DigniCap™ System in Japan [16]. The latest report was presented in St. Gallen in 2011, in 359 women diagnosed with early stage breast cancer. Photographs were taken and hair loss was evaluated using VAS. 70% of the patients were treated with weekly dose paclitaxel 60 mg/m² plus cyclophosphamide 400 mg/m², 8% were treated with paclitaxel plus trastuzumab, 15% were treated with epirubicin 40 mg/m² and cyclophosphamide 400 mg/m² biweekly, and 7% were treated with combinations including fluorouracil, irinotecan, vinorelbine or capecitabine. 48% of the patients did not lose any hair, 33% experienced a little hair loss, and 16% experienced mild hair loss. Only 4% experienced moderate hair loss and reported using a wig.

The clinical experience regarding efficacy and safety was reviewed in the Dignitana Post Market Surveillance Report [19]. Data was collected through phone calls and clinic visits. From 2001 until August 2011, more than 6000 patients have used the DigniCap™ System in Sweden, Norway, Denmark, Finland, England, Germany, Greece, Turkey, Russia, Japan, Singapore, Chile and Venezuela. The majority of patients in the report are breast and ovarian cancer patients. The overall success rate in terms of patient satisfaction is approximately 83%. Since most of the clinics do not log the number of patients or the results of scalp cooling, the numbers presented are conservative estimations by the treating nurse. Taken together, the DigniCap™ System has been evaluated in a variety of chemotherapy regimens, both in the adjuvant and in the palliative setting.

1.4 Safety Of Scalp Cooling

1.4.1 Short Term Side Effects

Based on published accounts of more than 2000 patients, it is concluded that scalp cooling is generally very well tolerated [20] with infrequent and mild side effects that rarely result in stopping cooling. 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 [8]. Uncomfortable cold sensations and headaches were especially pronounced in

studies where pre-cooled caps, which are usually chilled to -15°C to -25° , were used. Patients also complain about a heavy feeling of the head, and transient light-headedness following cap removal [1]. In addition, patients experienced neck pain due to heavy weight of some cooling caps [1]. Frostbite or freezing of skin has never been reported. There are only a few small, older studies in which more than 10% of the patients reported that side effects were a reason for stopping scalp cooling [8].

Side effects reported specifically from the use of the DigniCap™ System are limited. In a pilot study of 26 patients, it was reported that the side effects and the extra time required for scalp cooling was acceptable [13]. When evaluating discomfort during scalp cooling using a 10 point graded visual analogue scale (VAS) (0=none, 10=as bad as it could be), the discomfort was modest among the entire group (median value 1.5; range 0.5–8). In a larger study, only two out of 74 patients discontinued the treatment, one because of discomfort and one due to hair loss and discomfort [14]. Interestingly, side effects from chemotherapy such as uncomfortable scalp itching and distinctive scalp pain, and dermatitis (including hyperemia and skin flaking), appeared to be less frequent in the patients treated with the DigniCap™ System as compared to non-cooled patients [15].

1.4.2 Long Term Side Effects

Scalp cooling prevents hair loss through vasoconstriction, decreases cellular uptake of drugs, and decreases the intra-follicular metabolic rate. A theoretical increased risk of scalp metastases among breast cancer patients has been of concern since breast tumors may metastasize to the scalp. However, scalp metastases are rare in breast cancer, occurring in approximately 1% of all patients and almost always occurring in the presence of additional sites of disease[21]. Only a fraction of patients (0.025%), experience scalp metastasis as the first site of recurrence [22].

In the Dignitana Post Market Surveillance [19] including 6000 patients scalp cooled with the DigniCap™ system, only two patients have been reported with scalp metastases. Both patients had multiple sites of metastatic disease at the time of diagnosis with scalp involvement.

Breed et al. concluded, regarding scalp metastases, that “for breast cancer patients the theoretical risk of scalp cooling during adjuvant chemotherapy seems to be minimal” [9]. A recent extensive literature review has been conducted and the conclusion is that scalp cooling has not been shown to increase the incidence of scalp metastases in patients with both early and late stage breast cancer [23]. The author’s opinion is that scalp cooling can and should be offered to breast cancer patients who will be treated with adjuvant chemotherapy, and also to those who are offered palliative chemotherapy associated with a significant risk of alopecia. The risks involved in scalp cooling 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 [23].

1.5 Scalp Cooling In Relation To Well Being

Well-being has been evaluated in breast cancer patients treated with and without scalp cooling [24]. Patients completed questionnaires (including the EORTC QLQ-C30 and EORTC-QLQ-BR23, and BIS) before, during, and after completion of the last cycle of chemotherapy. At all three times of measurement, alopecia was considered among the most distressing problems. The

study showed a positive trend towards higher well-being in successfully scalp-cooled patients as indicated by a general better health-related quality of life and better body image.

1.6 Scalp Cooling: Available To Cancer Patients World Wide

Scalp cooling has been used for decades in Europe, and is now also under evaluation in the United States, Japan, the Middle East, Canada and South America.

Previously, scalp cooling was not available in the U.S. In 1991 the FDA stopped the approval of scalp cooling because of lack of documentation about efficacy and safety [25]. There has been increasing interest in scalp cooling in the United States, with increasing numbers of websites, TV shows and articles that discuss scalp cooling [26-37], and development of an advocacy group.

At this time, outside of a clinical trial, only Penguin Cold Caps are available to patients in the U.S. and are marketed by a group in Southern California and shipped from the U.K. directly to patients. Outside of the setting of a clinical investigation, patients generally investigate the caps through online research and chat rooms, then coordinate and pay themselves for the cap rental. Sharing of caps orchestrated by the company is quite common, allowing patients to obtain the caps with short notice. As of late 2010, BreastCancer.org had more than 1500 posts related to cold cap therapy, and seven medical centers in the U.S. currently or will soon have freezers dedicated to cooling Penguin Cold Caps on site (37).

A study on scalp cooling using the Penguin Cold Caps was presented at the San Antonio Breast Cancer Symposium, but has not yet been published [38]. The objective of the study was to determine the effectiveness of scalp hypothermia in patients with stage I-IIIc breast cancer receiving either anthracycline (n=22) or non-anthracycline based adjuvant chemotherapy (n=12). For patients who used scalp hypothermia through chemotherapy, the median incidence of alopecia was 10% for those treated with the combination of docetaxel-cyclophosphamide and docetaxel-carboplatin-trastuzumab. In patients treated with doxorubicin-cyclophosphamide, doxorubicin-cyclophosphamide followed by paclitaxel, and docetaxel-doxorubicin-cyclophosphamide combined, the median incidence of alopecia was 50%. Hair loss was thus reduced in those receiving anthracyclines and almost completely prevented in the group receiving non-anthracycline based chemotherapy. These data document existing use of scalp cooling in the U.S., and use is clearly increasing (personal communication, Frank Fronza).

1.7 Feasibility Study Of Scalp Cooling With The Dignicap™ System In The US

A pilot study was conducted in the United States at the University of California San Francisco, and Wake Forest University, evaluating the feasibility of use of the DigniCap™ System in patients with breast cancer receiving adjuvant chemotherapy known to cause significant alopecia. Eligible patients included women diagnosed with stage I breast cancer planning to receive chemotherapy in the adjuvant or neo-adjuvant setting. 20 patients were enrolled. The majority (80%) received docetaxel and cyclophosphamide (TC) every three weeks for four to six doses. Other chemotherapy regimens included 12 cycles of weekly paclitaxel with trastuzumab (10%), and docetaxel and carboplatin with trastuzumab every three weeks for six cycles (10%).

The primary endpoint of the pilot study was to determine the feasibility of use of the DigniCap™ System in this setting. Feasibility was defined as less than 50% of patients discontinuing use of

the cap due to cap-associated toxicity. Nineteen of 20 patients (95%) completed all chemotherapy using the DigniCap™ System, indicating that this system is feasible for use by women with breast cancer receiving adjuvant chemotherapy.

Secondary endpoints included prevention of hair loss, assessed by an independent panel as well as by patients. The Dean scale was used to grade extent of hair loss, with up to grade 2 (\leq 50% hair loss) considered successful prevention of hair loss. Using these criteria, the independent panel assessed that 75% of patients had no more than grade 2 alopecia at any time during their treatment and follow-up. The patient-reported hair loss using the Dean scale was also considered a success, as 55% of patients experienced grade 2 or less alopecia throughout their entire treatment and follow-up.

Overall, scalp cooling was well tolerated, with 68% and 32% of patients experiencing grade 1 and 2 toxicity respectively. With a median follow-up under two years, no scalp metastases have been observed.

The most common side effects experienced by patients using the DigniCap™ System were head pain, scalp pain, and feeling chilled. The majority of patients took over-the-counter pain medications as prophylaxis before starting the cooling process to counteract the initial headache. Head pain was experienced by 65% of patients during only one treatment (31%) or at most during three treatments (31%). More patients (50%) reported head pain during their second treatment than during any other treatment. The average level of head pain ranged from 39 (Cycle 2) to 46 (Cycle4) as assessed on a scale from 0-100.

Scalp pain was experienced by 95% of patients during at least one treatment. More patients (80%) reported scalp pain during their third treatment than during any other treatment. Most patients (65%) experienced scalp pain during 2 or 3 treatments, and this symptom was most prevalent during the third treatment, as 80% of patients reported scalp pain at this time. The average level of scalp pain ranged from 38 (Cycle 2) to 46 (Cycle1) as assessed on a scale from 0-100.

Chill was experienced by 80% of patients. Of these patients, 40% felt chilled during every treatment. The third treatment caused the most number of patients to feel chilled (80%). the average level of chill during treatment ranged from 42 (Cycle 1) to 54 (Cycle 3), as assessed on a scale from 0-100.

Overall, average patient satisfaction with hair was 85% at baseline, and 82% three months after the completion of chemotherapy. This pilot study demonstrated both feasibility and success of the DigniCap™ System in terms of preventing significant hair loss in the majority of women receiving non-anthracycline based adjuvant chemotherapy. These data support the planned pivotal trial to better evaluate the use of scalp cooling in women with early stage breast cancer receiving adjuvant chemotherapy.

1.8 The Need For A Prospective Study Of Scalp Cooling

Alopecia is a non-life threatening complication of the majority of effective adjuvant chemotherapy regimens for early stage breast cancer, but has a significant impact on quality of life and affects decisions regarding the risks and benefits of treatment. A safe and well tolerated system to prevent the majority of hair loss would be a powerful addition to our expanding

armamentarium of tools for supportive care, and would improve quality of life for women undergoing adjuvant therapy for these common malignancies.

2. OBJECTIVES

The overall objective is to assess the clinical performance, efficacy and safety of a Scalp Hypothermia System in breast cancer patients receiving specific chemotherapy treatments that, unless counteracted by simultaneous hypothermia treatment, result in hair loss.

2.1 Primary Objective

To assess the ability of the DigniCap™ System to prevent hair loss in women receiving specific chemotherapy regimens for early stage breast cancer. Efficacy will be measured by assessment of hair loss up to 4 weeks (3-6 week window) after the completion of the last chemotherapy cycle by patient self-assessment of standardized photographs using the Dean scale by patients in the treatment and control groups.

2.2 Secondary Objective

- To assess safety of the DigniCap™ System in women receiving specific chemotherapy regimens for early stage breast cancer.
- To assess tolerability of the DigniCap™ System
- To evaluate hair loss and recovery as assessed by the patient during and following chemotherapy using the alopecia self-report.
- To evaluate hair re-growth at 3 and 6 months after completion of chemotherapy compared to the greatest hair loss as assessed using the hair regrowth follow up survey.
- To assess patient quality of life and satisfaction with hair during and after treatment with the DigniCap™ System.
- To assess the impact of hair loss on treatment decisions.

3. TREATMENT ENDPOINTS

3.1 Primary Endpoint

Success of the DigniCap™ System to prevent hair loss, defined as a maximum Dean score of ≤ 2 using standardized photographs graded by the patient up to 4 weeks after the last chemotherapy treatment, in at least 50% of patients enrolled in the treatment group with a lower bound of the 95% CI greater than 40%, and statistical superiority over a concurrent control group.

3.2 Secondary Endpoints

Safety as determined by spontaneous reporting of adverse events and as negative scalp changes determined by physical examination.

Tolerability is defined as the percentage of patients who complete all planned cycles of chemotherapy do so using the DigniCap™ System.

Patient assessment of hair loss by the alopecia self-report at each chemotherapy.

Hair re-growth assessed by the patient using the hair regrowth follow up survey.

Quality of life as measured by the EORTC-QLQ-BR23 quality of life questionnaire and a Body Image Scale.

Assessment of the impact of hair loss on breast cancer treatment decisions at 6 months after completion of chemotherapy.

4. TREATMENT PLAN**4.1 Schedule Of Investigational Events for Treatment Group**

Assessments	Baseline ¹	Each Chemo-therapy cycle	1 month after last chemo-therapy infusion	Follow-up Visit (3 months)	Follow-up Visit (6 months)
Chemotherapy treatment		X			
Scalp cooling		X			
Signed Informed Consent, Appendix III	X				
Eligibility checklist, Appendix I	X				
Baseline Case Report Form, Appendix IV	X				
Case Report Form for all chemotherapy cycles, Appendix V		X			
Treatment follow-up form at 3 months after chemotherapy completion, Appendix VI				X	
Treatment follow-up form at 6 months after chemotherapy completion, Appendix VII				X	X
Photographs of hair/scalp (Section 8.1.1; Appendix XXI)	X	X	X		
Alopecia self-report, Appendix VIII	X	X	X	X	X
Patient symptoms survey ² , Appendix IX		X			
EORTC-QLQ-BR233, Appendix X ³	X	X ³	X	X	X
Body Image Scale (BIS) ³ , Appendix XI	X	X ³	X	X	X
Impact of hair loss on treatment decision, Appendix XII					X
Hair re-growth follow-up survey, Appendix XIII				X	X
Medwatch, Appendix XIV		X	X	X	X
Case Report Form for Device Use, Appendix XXIII		X			

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DIGNITANA AB
16 April 2013

Screening Log- Non Enrolled Patients, (If applicable), Appendix II	X				
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¹All baseline measurements must be done prior to treatment administration unless otherwise specified.

²This survey should be administered at the end of each chemotherapy session.

³QOL (EORTCQLQ-BR233 and BIS) to be completed at Cycle 4 only during Chemotherapy and at the last Chemotherapy Visit if the patient is discontinued early because of hair loss

4.2 Schedule Of Investigational Events for Control Group

Assessments	Baseline ¹	Each Chemo-therapy cycle	1 month after last chemo-therapy infusion
Chemotherapy treatment		X	
Signed Informed Consent, Appendix III	X		
Eligibility checklist, Appendix I	X		
Baseline Case Report Form, Appendix IV	X		
Case Report Form for all chemotherapy cycles, Appendix V		X	
Photographs of hair/scalp (Section 8.1.1; Appendix XXI)	X	X	X
Alopecia self-report, Appendix VIII	X	X	X
EORTC-QLQ-BR233, Appendix X ³	X	X ³	X
Body Image Scale (BIS) ³ , Appendix XI	X	X ³	X
Medwatch, Appendix XIV		X	X
Screening Log- Non Enrolled Patients, (If applicable) Appendix II	X		

¹All baseline measurements must be done prior to treatment administration unless otherwise specified.

²This survey should be administered at the end of each chemotherapy session.

³QOL (EORTCQLQ-BR233 and BIS) to be completed at Cycle 4 only during Chemotherapy and at the last Chemotherapy Visit if the patient is discontinued early because of hair loss

5. PATIENT SELECTION CRITERIA

5.1 Treatment Group

5.1.1 Inclusion Criteria

In order to be eligible for the study, patients should fulfil all of the following inclusion criteria:

1. Female patients ≥ 18 years of age
2. Documented diagnosis of stage I or II breast cancer.
3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens:
 - Doxorubicin 60 mg/m^2 and cyclophosphamide $600 \text{ mg/m}^2 \times 4 - 6$ cycles IV every 2 - 3 weeks
 - Docetaxel 75 mg/m^2 and cyclophosphamide $600 \text{ mg/m}^2 \times 4 - 6$ cycles IV every 3 weeks
 - Paclitaxel 80 mg/m^2 weekly IV x at least 12 weeks with or without IV trastuzumab
 - Paclitaxel 175 mg/m^2 IV every 2 weeks x 4 – 6 cycles (without an anthracycline)
 - Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles and trastuzumab IV weekly or every 3 weeks
 - Docetaxel 75 mg/m^2 and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles and trastuzumab IV weekly or every 3 weeks
 - Targeted agents such as trastuzumab or lapatinib are allowed
4. Plan to complete chemotherapy within 6 months
5. At least two years out from the last chemotherapy causing hair loss with complete recovery of hair
6. Karnofsky performance status $\geq 80\%$
7. Willing and able to sign informed consent for protocol treatment
8. Willing to participate in study procedures including having photographs of the head before each cycle of chemotherapy and 1 month after the last chemotherapy
9. Willing to enroll in an extension protocol for follow up for 5 years following the end of chemotherapy treatment

5.1.2 Exclusion Criteria

1. Patients with female pattern baldness resembling picture I-3 or higher on the Savin scale (Appendix IB)
2. Autoimmune disease affecting hair; e.g. alopecia areata, systemic lupus with associated hair loss
3. A history of whole brain radiation
4. Plans to use a chemotherapy regimen other than those specified in the inclusion criteria. Specifically, patients receiving a regimen including both an anthracycline and a taxane are not eligible for this trial (AC/T, EC/T, TAC, etc.)
5. Concurrent hormone therapy with chemotherapy. Hormone therapy should be used as indicated following completion of chemotherapy
6. Underlying clinically significant liver disease including active viral hepatitis with abnormal liver function tests >1.5 times the upper limit of normal, including alkaline phosphatase, AST, and total bilirubin. Patients with Gilbert's disease (elevated indirect bilirubin only) will be eligible for participation.

7. Clinically significant renal dysfunction defined as serum creatinine > upper limit of normal.
8. A serious concurrent infection or medical illness which would jeopardize the ability of the patient to complete the planned therapy and follow-up
9. A history of persistent grade 2 (or higher) alopecia induced by prior chemotherapeutic regimens
10. Participation in any other clinical investigation or exposure to other investigational agents, drugs, device or procedure that may cause hair loss
11. Intercurrent life-threatening malignancy
12. A history of cold agglutinin disease or cryoglobulinemia.
13. Evidence of untreated or poorly controlled hyper or hypothyroidism
14. A history of silicon allergy
15. American Society of Anesthesiologist Class ≥ 3 (Appendix IV.A)

5.2 Control Group

5.2.1 Inclusion Criteria

In order to be eligible for the study, patients should fulfil all of the following inclusion criteria:

1. Female patients ≥ 18 years of age
2. Documented diagnosis of stage I to III breast cancer.
3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens:
 - Doxorubicin 60 mg/m^2 and cyclophosphamide $600 \text{ mg/m}^2 \times 4 - 6$ cycles IV every 2 - 3 weeks
 - Docetaxel 75 mg/m^2 and cyclophosphamide $600 \text{ mg/m}^2 \times 4 - 6$ cycles IV every 3 weeks
 - Paclitaxel 80 mg/m^2 weekly IV x at least 12 weeks with or without IV trastuzumab
 - Paclitaxel 175 mg/m^2 IV every 2 weeks x 4 – 6 cycles (without an anthracycline)
 - Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles and trastuzumab IV weekly or every 3 weeks
 - Docetaxel 75 mg/m^2 and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles and trastuzumab IV weekly or every 3 weeks
 - Targeted agents such as trastuzumab or lapatinib are allowed
4. At least two years out from the last chemotherapy causing hair loss with complete recovery of hair
5. Karnofsky performance status $\geq 80\%$
6. Willing and able to sign informed consent for protocol treatment
7. Willing to participate in study procedures including having photographs of the head before each cycle of chemotherapy and 1 month after the last chemotherapy
8. Chooses not to use scalp cooling during chemotherapy

5.2.2 Exclusion Criteria

1. Patients with female pattern baldness resembling picture I-3 or higher on the Savin scale (Appendix IB)
2. Autoimmune disease affecting hair; e.g. alopecia areata, systemic lupus with associated hair loss

3. A history of whole brain radiation
4. Plans to use a chemotherapy regimen other than those specified in the inclusion criteria. Specifically, patients receiving a regimen including both an anthracycline and a taxane are not eligible for this trial (AC/T, EC/T, TAC, etc.)
5. Concurrent hormone therapy with chemotherapy. Hormone therapy should be used as indicated following completion of chemotherapy
6. Underlying clinically significant liver disease including active viral hepatitis with abnormal liver function tests >1.5 times the upper limit of normal, including alkaline phosphatase, AST, and total bilirubin. Patients with Gilbert's disease (elevated indirect bilirubin only) will be eligible for participation.
7. Clinically significant renal dysfunction defined as serum creatinine > upper limit of normal.
8. A serious concurrent infection or medical illness which would jeopardize the ability of the patient to complete the planned therapy and follow-up
9. A history of persistent grade 2 (or higher) alopecia induced by prior chemotherapeutic regimens
10. Participation in any other clinical investigation or exposure to other investigational agents, drugs, device or procedure that may cause hair loss
11. Intercurrent life-threatening malignancy
12. Evidence of untreated or poorly controlled hyper or hypothyroidism
13. American Society of Anesthesiologist Class ≥ 3 (Appendix IV.A)

6. INVESTIGATIONAL DEVICE

6.1 The Dignicap™ System

The DigniCap™ System consists of the digitized system for controlled scalp cooling (Digni C3) in conjunction with the soft, tight-fitting silicon cap (DigniCap™), the neoprene outer cap (DigniTherm™), and the liquid coolant (DigniCool™). DIGNISTICK™ is prepared to log data from a treatment when inserted in the slot. DIGNICARD™ is a key card which has to be inserted in order to start a treatment.

The liquid coolant circulates from the cooling unit to and through the channels of the cap and back to the cooling unit again. The scalp temperature is monitored by three separate thermometers. Deviations from the pre-set temperature are immediately and automatically adjusted by the system (scalp temperature can be controlled with an accuracy of $\pm 2.0^{\circ}\text{C}$).

6.2 Dignicap™

6.2.1 Composition

The silicon cap has two separate cooling circuits, one for the front of the head and one for the back of the head (as the front of the head is warmer than the back of the head). Two sensors for controlling the cooling circuits, plus one for the safety system are attached.

6.2.2 Product Safety

Minimal risk associated with rare incidence of silicon allergy.

6.2.3 Storage Requirements

Product should be protected from non-operator handling and cleaned with alcohol swabs after each use.

6.2.4 Biocompatibility

Silicon is tested < 24h contact with intact skin without any remarks (cytotoxicity, sensitization, intracutaneous reactivity).

6.3 Dignitherm™

An outer neoprene cap that insulates and keeps the inner cap in place.

6.4 Digni C3

6.4.1 Specifications

Voltage 115 VAC 50-60 Hz.

Maximum Volt ampere 1500 VA.

Digni C3 weighs approximately 76 kg.

6.4.2 Temperature Control

The temperature in the DigniCap™ is kept at $\pm 2.0^{\circ}\text{C}$ from the set value. The safety system controls that the temperature never goes below 0°C . The unit is fully hermetically sealed and is using CFC-free R404A refrigerant.

6.5 Dignicool™

6.5.1 Product Name

Monopropylene Glycol diluted with water. DigniCool™ Hazards Information and Material Safety Data, Appendix XXV.

6.6 Labeling

Guide to Device Labeling, please see Appendix XXIV.

6.7 Investigational Device Accountability

When a device shipment is received at the site, a designee of the investigational team at each site should verify the contents, sign the packing invoice provided with the shipment, and maintain the original copy for review by the study monitor.

Each shipment of investigational supplies will contain an accountability log to allow maintaining current and accurate inventory records covering receipt, dispensing, and disposition of the investigational device. During the study, the following information must be noted in the accountability log: the identification number(s), initials of patient(s) to whom device is dispensed, the date(s) that the investigational device is dispensed, and the initials of the designee who dispensed it.

The study monitor will examine the inventory during the study. Additionally, the inventory records must be readily available and may be subject to regulatory authorities, the local regulatory agency, or an independent auditor's inspection at any time. At the completion of the study, to satisfy regulatory requirements regarding device accountability, all remaining investigational device items, used as well as unused, should be found in the inventory, reconciled and retained or destroyed according to applicable state and federal regulations.

Device Accountability Log, Appendix XXII.

6.8 Training And Experience For The Use Of The Device

Dignitana AB is responsible for installation of the DigniCap™ System and instruction and training of dedicated medical personnel.

Appropriate training on the hardware, software and fitting of the caps and communication with patients are ensured through a 3 day training program. Supplementary training can be performed in case of need. Education in handling and maintenance for dedicated medical personnel is performed at sufficient level to ensure correct experience and knowledge to carry out recommended use and maintenance.

Training of personnel will be performed according to Training Protocol, Appendix XIX, and is to be documented in the Checklist Training of Personal, Appendix XX.

7. STUDY DESIGN

This trial will be conducted in compliance with the GCP, Declaration of Helsinki and applicable regulatory requirements.

Only patients receiving chemotherapy treatment that may result in hair loss by the completion of chemotherapy will be included in the study.

Patients who choose not to undergo scalp cooling during chemotherapy are eligible to enrol in the study as part of the concurrent control group. The control group is being enrolled to determine whether the expected frequency of almost total hair loss will occur using the criteria of this study. The control patients will be matched by disease (breast cancer), age (± 5 years) and chemotherapy treatment regimen. If at least 12 out of the first 15 control patients have a Dean score of 4, or lose greater than 75% of their hair, enrolment of the control group will be discontinued. Otherwise, a total of 30 control patients will be recruited.

Patients will be informed that an extension protocol will be implemented to follow this protocol and that they will be asked to participate in the extension protocol in order to obtain long term follow up information on the risk of scalp metastases.

7.1 Study Treatment

No study specific assessments or treatments will commence prior to obtaining written signed informed consent from the patient.

Patients will receive scalp hypothermia as delivered by the DigniCap™ System. Scalp cooling will begin 30 minutes prior to administration of chemotherapy. Scalp temperature will be maintained at $+5^{\circ}\text{C}$ (41°F) throughout drug administration and for 60-90 minutes after discontinuing the infusion, depending on the chemotherapy regimen as outlined in Section 7.2.

7.2 Point Of Enrollment

Patients must be recruited and sign informed consent before initiation of treatment in order to be checked for eligibility and enrolled in the study. The Eligibility Checklist (Appendix I) should be completed prior to enrolment. If the patient meets all eligibility criteria and treatment must be started over a weekend or during a holiday, a maximum of 72 hours may elapse between the initiation of treatment and enrolment of the patient.

Eligible patients must be scheduled to receive either anthracyclines or taxanes as outlined in Section 5.1.

Patients found to be ineligible following study enrolment will be replaced in order to guarantee a 110-patient study population enrolment. Ineligible patients who have received treatment using the DigniCap™ System will be monitored for potential device-associated toxicity for 30 days following treatment. Upon determination of ineligibility, these patients will not have any more photographs taken nor will they be asked to complete any more protocol-mandated surveys.

Any patients who elect to discontinue study treatment prior to chemotherapy completion will also be monitored for potential device-associated toxicity for 30 days following treatment and will be followed for recurrence and survival. Upon study withdrawal, these patients will not have

any more photographs taken nor will they be asked to complete any more protocol mandated surveys.

7.3 Chemotherapy Regimens and Cooling Times

Chemotherapy Regimen	Dose	Post Infusion Cooling Time (minutes)
AC x 4 or 6 cycles, every 2-3 weeks	Doxorubicin: 60 mg/m ² , Cyclophosphamide 600 mg/m ²	60
TC x 4 or 6 cycles, every 3 weeks	Docetaxel 75 mg/m ² , Cyclophosphamide 600 mg/m ²	60
Paclitaxel x at least 12 cycles every week	Paclitaxel 80 mg/m ²	60
Paclitaxel and Carboplatin x 6 cycles, 3 on/ 1 off	Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks	60
Paclitaxel x 4 – 6 cycles every 2 weeks	Paclitaxel 175 mg/m ² IV every 2 weeks (without an anthracycline)	90
TCH x 6 cycles every 3 weeks	Docetaxel 75mg/m ² , Carboplatin AUC 6, Trastuzumab weekly or every 3 weeks	60

Targeted therapeutics not associated with hair loss are allowed (including trastuzumab, lapatinib, etc.).

Dose reductions if required for patient safety or toxicity are allowed but full dose therapy should be planned at treatment start.

Patients should receive standard supportive care including myeloid growth factors as indicated.

Concomitant use of hormone therapy is not allowed. Hormone therapy should be started following completion of chemotherapy.

8. ASSESSMENTS

8.1 Photographic Documentation

Photographic documentation for all treatment and control patients will be performed before initiation of the first cycle of chemotherapy, each subsequent cycle of chemotherapy, and at a visit 4 weeks (3-6 week window) after the last cycle of chemotherapy. At each time point, 5 photographs should be taken: from the front (bangs should be held back), behind, both sides and the top with the hair divided in the midline with both hands (See Guidelines for Study Photographs, Appendix XXI). Hair loss will be assessed by comparing the photographs against standardized photographs to estimate the percentage of hair lost according to the Dean scale.

8.2 Assessments At Baseline

Eligible patients who consent to this study will have the following baseline assessments: Medical history, physical examination, vital signs, and Karnofsky Performance status. Each patient will be examined for cutaneous metastases of the scalp. The use of concomitant medication will also be assessed at baseline. Hair will be photographed before initiation of the first cycle of chemotherapy by the physician or study personnel as detailed above. Patients will be asked to assess their current hair status by comparing the photographs against standardized photographs using of the quantitative Dean scale and to assess the impact of hair loss on treatment decision. Quality of Life questionnaires including the EORTC-QLQ-BR23 scale and BIS will be filled out by the patient.

8.3 Assessments At Each Cycle Of Chemotherapy

Before infusion:

The medical history of the patients and the use of concomitant medication will be reassessed and a physical examination will be performed. Hair will be photographed by the physician or study personnel. Patients (treatment and control) will be asked to assess their current hair loss by examination of the photographs using the quantitative Dean scale compared to standardized photographs. Any patient with a Dean score of 4 at any visit will be considered to have met the study definition of “treatment failure” and will not have additional photographs. Treatment and control patients with a Dean score of 3 or lower will continue to be followed with photographic documentation until 4 weeks after the last chemotherapy visit. Use of any head cover such as wig, scarves or cap will be documented as “never”, “sometimes”, or “always”. Patients will fill out the quality of life questionnaires including the EORTC-QLQ-BR23 scale and BIS before cycle 4 of chemotherapy, or at the visit that they are considered to have failed because of hair loss.

At the end of the infusion:

Discomforts such as headache, being chilled, and scalp pain will be assessed using a visual analogue scale. Any adverse events will also be reported.

Device use parameters will be reported in the Device Use Log.

8.4 Assessment 4 Weeks (3-6 Week Window) Following The Last Cycle Of Chemotherapy

Evaluation of the last chemotherapy cycle will take place 4 (± 1 week) weeks after the last cycle of chemotherapy. The medical history of the patient and the use of concomitant medication will be reassessed, and a physical examination will be performed. Hair will be photographed by the physician or study personnel. Patients (treatment and control) will be asked to assess their current hair loss by examination of the photograph set using the quantitative Dean scale. Use of any head cover such as wig, scarves or cap will be documented as “never”, “sometimes”, or “always”. Patients will also fill out the quality of life questionnaires including the EORTC-QLQ-BR23 scale and BIS. Control group patients will end participation in the study at this visit.

8.5 Assessments At The Follow-Up Visit 3 (± 2 Weeks) Months After The Completion Of Study Treatment

Vital signs, medical history, physical examination, examination for cutaneous metastases of the scalp will be carried out in the treatment group patients. The use of concomitant medication and any adverse events will be reported. The patient will compare her hair status as compared to baseline in the Hair Re-growth Follow-Up Survey using the quantitative Dean scale. Quality of life questionnaires including EORTC-QLQ-BR23 scale and BIS will be assessed.

Use of any head cover such as wig, scarves or cap will be documented as “never”, “sometimes” or “always”. The impact of hair loss on treatment decision will be evaluated.

8.6 Assessments At The Follow-Up Visit 6 Months (± 2 Weeks) After The Completion Of Study Treatment

Assessment at 6 Months

The use of concomitant medication and any adverse events will be reported. The patient will compare her own hair status as compared to baseline in the Hair Re-growth Follow-Up Survey using the quantitative Dean scale. Quality of life questionnaires including EORTC-QLQ-BR23 scale and Body Image will be assessed.

Use of any head cover such as wig, scarves or cap will be documented as “never”, “sometimes” or “always”.

The presence of any cutaneous metastases of the scalp will be documented.

9. Adverse Events (AE)

An *Adverse Event* is any untoward medical occurrence in a patient treated with an investigational product but which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not associated to the investigational treatment.

9.1 Adverse Device Events (ADE)

An *Adverse Device Event* is any untoward and unintended response to a medical device, including any event resulting from insufficiencies or inadequacies in the instructions for use of the device, and/or any event that is a result of a user error.

All conditions that are pre-existing to treatment with the study device should be recorded on the Medical History section within the patient's Baseline Case Report Form (CRF), Appendix IV.

9.2 Recording Of Adverse Events Any Adverse Device Events

Solicited adverse events/adverse device events will be asked for and will be recorded in the CRF.

Adverse events/adverse device events already documented in the CRF, e.g. at a previous visit, and were classified as "ongoing", should be reviewed at subsequent visits. If resolved or changed severity, this should be documented in the CRF accordingly.

9.3 Assessment Of Severity

The severity of an adverse event/adverse device event will be recorded according to the following guidelines;

0	None	
1	Mild	An event, which is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
2	Moderate	An event, which is sufficiently discomforting to interfere with everyday activities.
3	Severe	An event, which prevents normal everyday activities and requires medical treatment.

9.4 Assessment Of Causality

Causal relationship, if any, to treatment with the investigational product/device should be assessed according to the following categories:

NR	Not related	The event is definitely not causally related to treatment with the investigational product/device.
UL	Unlikely	There are other, more likely causes and treatment with the investigational product/device is not suspected as a cause.
SU	Suspected (<i>reasonable possibility</i>):	A direct cause and effect relationship between the treatment with the investigational product/device and the event has not been demonstrated but there is a reasonable possibility that the event was caused by treatment with the investigational product/device.
PB	Probable	There probably is a direct cause and effect relationship between the event and treatment with the investigational product/device.

9.5 Follow-Up Of Adverse Events And Assessment Of Outcome

The investigator should follow patients with non-serious adverse events, until symptoms resolve or has stabilized and advise the monitor of the final outcome.

The duration in days, or in hours, (if applicable) of the adverse event should be assessed.

The outcome of the adverse event will be assessed as:

- 1 = Resolved
- 2 = Improved
- 3 = Unchanged
- 4 = Worse
- 5 = Fatal
- 6 = Not available

The action taken as a result of the adverse event will be assessed as:

- 1 = None
- 2 = Therapy required
- 3 = Procedure discontinued due to AE
- 4 = Hospitalization required or prolonged

9.6 Unexpected Adverse Event

An “*unexpected*” adverse event is one not identified in nature, severity, or frequency in the Investigator’s Brochure or the product package insert for the investigational product/device.

9.7 Serious Adverse Event

A “*serious*” adverse event is one that results in any of the following:

- fatal (leading to death)
- life threatening, i.e. placing the patient at immediate risk of death in the judgment of the investigator
- permanently disabling or impairing a body structure or a body function
- requiring inpatient hospitalization or prolongation of existing hospitalization
- requiring medical or surgical intervention to prevent permanent impairing a body structure or a body function
- leads to a congenital anomaly or birth defect, fetal distress or fetal death.

9.8 Relationship To Study Intervention

9.8.1 Probably Related

The event occurs within a reasonable time period following the intervention and cannot be reasonably explained by known patient characteristics (including use of concomitant medications) at the associated chemotherapy.

9.8.2 Unknown Relationship

The etiology of the event is not known and the event does not occur within a reasonable time period following the intervention and does not follow a known response pattern for chemotherapy.

9.8.3 Definitely Not Related

The event is known not to be related to the study intervention.

9.9 Foreseeable Investigational Treatment Related Adverse Events

9.9.1 Hypersensitivity Reactions

Allergic reactions or urticaria from contact with silicon are extremely rare, but have been reported in some patients receiving silicone gel breast augmentation. If severe hypersensitivity reactions thought to be due to silicon occur, remove the patient from protocol therapy.

9.9.2 Pain Or Discomfort Reactions

Transient cephalgia, scalp pain, has been reported in patients treated with the DigniCap™ System for systemic cytotoxic chemotherapy. Patients who report pain or discomfort will have all complaints documented and treated symptomatically if thought to not be severe. Treatment interruption will not be indicated unless the patient requires it due to patient reported severe symptoms.

9.9.3 Toxicity Reporting

Toxicity Criteria: Skin toxicity will be determined using the revised NCI Common Toxicity Criteria (CTC) version 4.0 for Toxicity and Adverse Event Reporting.

All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded with details regarding duration, severity of each episode and outcome. The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to investigational product or their clinical significance. The description of the AE will include the onset date, duration, date of resolution, severity, seriousness, etiology, and the likelihood of relationship of the AE to study treatment.

Information regarding AEs will be collected from the time the patient signs the informed consent form up to 30 days after the last dose of investigational product is administered.

9.10 Reporting Adverse Events

9.10.1 Immediate Reporting By Investigator To Sponsor

Any AE considered serious by the Principal Investigator or Sub-investigator or which meets the previous criteria must be entered as an SAE on the adverse event form and communicated to Dignitana AB within one business day (24 hours) from the time that the site personnel first becomes aware of the serious adverse event.

The written SAE report must consist of the Serious Adverse Event Report Form (MEDWATCH) (Appendix XIV) and data not entered in the CRF (e.g. lab reports, ECG reports, etc.). If the patient is hospitalized because of or during the course of an SAE, then a copy of the hospital discharge summary should be faxed to Dignitana AB as soon as it becomes available. Withdrawal from the study and all therapeutic measures will be at the discretion of the Principal Investigator or Sub-investigator. All reported SAEs (related or not to the investigational product) will be followed until satisfactory resolution or until the Principal Investigator or Sub-investigator deems the event to be chronic or the patient to be stable.

This will be documented on a MEDWATCH form (Appendix XIV). The form must be completed and supplied to Dignitana AB within 24 hours/one business day at the latest on the following working day. The initial report must be as complete as possible, including details of

the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational intervention.

9.10.2 Non Expedited Reporting

In the event of any other types of events not requiring expedited reporting, the investigator will notify Dignitana AB within 7 business days. If at any time that the events noted in this category changes (i.e. is upgraded), the investigator should notify Dignitana AB accordingly as noted in the section above.

9.10.3 Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA and GCP safety reporting requirements. All adverse experience reports must include the patient number, age, sex, severity of reaction (mild, moderate, severe), relationship to study intervention (probably related, unknown relationship, definitely not related), date and time of administration of intervention and all concomitant medications, and medical treatment provided. The investigator will record this information on the MEDWATCH form (Appendix XIV) and will provide reports of adverse experiences on a regular basis during the study. The investigator is responsible for evaluating all adverse events to determine whether criteria for “serious” and “unexpected” as defined above are present. The investigator is responsible for reporting adverse events to Dignitana AB as described under “Immediate reporting by investigator to sponsor” and “Non Expedited Reporting” above.

Dignitana AB’s business fax number is: 46(0)46 16 30 99 and business telephone number is 46(0)46 16 30 90.

The Address of Dignitana is:

DIGNITANA AB

Ruben Rausings Gata 9, SE-223 55 Lund

PO Box 240 22, SE-224 21 Lund Sweden

9.10.4 Sponsor Reporting Responsibilities

Dignitana AB will report to FDA without any delay.

9.10.5 Deviations From The CIP And/Or Amendments

Any deviation from the CIP and/or amendments must be reported to Dignitana and will be reviewed by Dignitana AB and principle investigators.

9.11 Data Safety Monitoring Board

The Data Safety Monitoring Board will be constituted by charter to review safety and to assess the interim analysis of the concurrent control group.

10. PATIENT EVALUATION CRITERIA

10.1 Criteria For Response Assessment

Criteria for grading of alopecia will be assessed using the Dean scale [22].

- Grade 0: no hair loss
- Grade 1: up to 25% hair loss
- Grade 2: between 25 and 50% hair loss
- Grade 3: between 50 and 75%
- Grade 4: greater than 75% hair loss

Quantitative Grade 0-2 will be considered adequate protection from alopecia. Grade 3 and 4 will be considered study treatment failure.

10.2 Endpoint Variables

10.2.1 Alopecia Report Assessment by the Patient

Hair loss will be assessed by the patient review of digital photographs taken of their hair/scalps at baseline, at each chemotherapy visit, and 4 weeks (3-6 weeks window) after the last chemotherapy treatment. The photographs will include 5 views and will be graded by the quantitative Dean scale as above (Appendix VIII). A Dean score of 4 at any evaluation will be considered essentially complete hair loss and the patient will not have additional photographs.

The patient will also complete the Alopecia Self Report, Appendix VIII.

10.2.2 Adverse Events Related to Use of the Dignicap™ System

Adverse events related to use of the DigniCap™ System are to be reported by the patient using the Symptoms Survey, Appendix IX.

The scalp of the patient will be thoroughly examined by the physician prior to each chemotherapy session, at one month after completion of chemotherapy, and at the follow-up visits at 3 and 6 months after completion of treatment using the corresponding CRFs.

10.2.3 Quality Of Life in Women Using the Dignicap™ System

Quality of Life measured by the EORTC-QLQ-BR23 scale and BIS at Baseline, Cycle 4 of chemotherapy and 4 weeks after the last cycle of chemotherapy.

10.2.4 Hair Re-Growth

Hair re-growth will be evaluated at the Month 3 and 6 visits. Information regarding quality of treatment response defined as patient reported grading of quality of hair in terms of texture, manageability, and color variation from baseline will be collected.

10.2.5 Impact of Hair Loss on Treatment Decisions

Information regarding the perceived impact of hair loss on treatment decisions will be collected at baseline and 3 months after completion of chemotherapy.

10.3 Criteria and Procedures for Withdrawal from Protocol Treatment

Patients may withdraw from this study under the following conditions:

- The patient withdraws consent to participate in the study.
- The investigator feels that it is in the best interest of the patient.
- During study treatment patient experiences severe hypersensitivity reaction due to silicon.
- During study treatment patient reports severe symptoms of cephalgia or of severe pain/discomfort.
- The patient has a serious or life-threatening adverse event.
- Disease Progression: In the event of documented disease progression, significant clinical decline resulting in discontinuation or prolonged treatment which effect alopecia the patient will be withdrawn.
- The patient develops scalp metastases during the chemotherapy treatment.

Any patients who elect to discontinue use of the cap prior to completing their prescribed chemotherapy regimen will be considered to have entered study follow-up at the time of stopping cap use. They will have hair/scalp photographs taken and will complete surveys according to the protocol-mandated follow-up schedule. If study consent is withdrawn, patients will be monitored for potential device-associated Serious Adverse Events (SAEs) for 30 days following treatment.

10.3.1 Hypersensitivity Reactions

Allergic reactions or urticaria from contact with silicon are extremely rare, but have been reported in some patients receiving silicone gel breast augmentation. If severe hypersensitivity reactions thought to be due to silicon occur, remove the patient from protocol therapy.

10.3.2 Pain or Discomfort Reactions

Transient cephalgia, scalp pain, has been reported in patients treated with the DigniCap™ system for systemic cytotoxic chemotherapy. Patients who report pain or discomfort will have all complaints documented and treated symptomatically if thought to not be severe. Treatment interruption will not be indicated unless the patient requires it due to patient reported severe symptoms.

10.4 Early Termination or Suspension of the Investigation

See section 12.4.

11. DEVICE RISK ANALYSIS AND RISK ASSESSMENT

List of hazards (see Appendix XXVI).

12. DATA quality

12.1 Original Data

Original data, also known as source data/records, are those data elements that represent the first recording of study data. Original data contain all the information that is necessary for the reconstruction and evaluation of the study. Examples of original data are 1) subject's information used in a clinical trial whether collected on paper or electronically at the time of the subject's visit, 2) certified copies of original records, 3) observations, and 4) laboratory data from clinical laboratories. Clinical investigators maintain control over source data from inception and until the end of the regulatory retention period. The Investigator must permit access to these data during sponsor monitoring visits, audits, IRB reviews and regulatory inspections.

In addition to original records maintained by the clinical site as part of their standard practices of patient care, this study will use direct data entry of clinical trial data into the Target e*CRF[®] (EDC) system, using the Target e*CTR[™] (Target e*Clinical Trial Record) process. This process enables clinical study site personnel to perform data entry of original data directly into Target e*CRF[®] at the time of the subject's office visit. This process stores the original data, along with transcribed data, in PDF format in the Target e*CTR data repository, access to which is controlled by the clinical Investigator. Authorized users can review these PDF documents using the Target e*CTR Viewer. In this data flow, the system stores all of the entered data first in the Target e*CTR repository (as PDF documents) before transmitting them to the Target e*CRF[®] database. At any point during the study or after completion of the study, each site can generate, or the system host will provide them with, an electronic file containing all of the records and audit trail, in PDF format, for all subjects at their site.

12.2 Target e*CRF[®] (Electronic Data Capture)

Personnel at the investigative site will enter all required clinical trial data into Target e*CRF[®], a validated 21 CFR Part 11 compliant Internet-based EDC system. Site personnel similarly manage all changes to the clinical trial data, through the EDC system's change management functionality that is subject to a full audit trail.

Target Health personnel will train investigator and site staff on the use of Target e*CRF[®] prior to enrollment of the first subject. Target Health maintains a list of authorized users and grants role-based access to the EDC system only after ensuring that site personnel have received system training. Target Health restricts access to the e*CRF database only to authorized personnel.

At the end of the study, the clinical investigator or authorized sub-investigator electronically signs the completed online eCRF. A certification must be obtained from all authorized persons in order to sign electronically, indicating that their electronic signature is equivalent to their hand-written signature. In order to sign electronically, the signer must log in with his or her username and password and then reenter this password on the page(s) requiring a signature(s). At the end of the trial, Target Health will provide each site with an electronic file containing all of the eCRF records for all subjects at their site.

12.3 Target e*CTR[®] Viewer (Target e*Clinical Trial Record Viewer)

Target e*CTR Viewer is a validated 21 CFR Part 11 compliant Internet-based software system. The PDF documents, representing both original and transcribed subject data, reside in a read-only environment. Authorized personnel at the investigative site control users' access to the Target e*CTR[®] Viewer. The Investigator can download a bookmarked PDF copy of records of individual subjects or all subjects at his/her site, including an audit trail of changes and electronic signatures. At the end of the study, the system host will provide each investigator with an electronic file containing all of the records and audit trail for all subjects at his/her site. Target Health personnel will train investigator and site staff on the use of Target e*CTR prior to enrollment of the first subject.

12.4 Certified Copies of Original Data

In the event that site personnel find that they are unable to perform direct data entry at the time of the study visit, they will record original data using paper records or equivalent media. Certified copies of these original data can be created, for example, by creating an exact copy of a paper record by scanning the paper or taking a photograph and storing it electronically. In order to do this, each site must have an SOP supporting this process. These scanned documents must be available to Target Health personnel during monitoring visits and during regulatory review.

12.5 Quality by Design (QbD)

12.5.1 Data Management

Target Health Data Management personnel create the data management plan (DMP) to specify data management activities for the study. The following summarizes the DMP:

Target Health hosts and manages the clinical database (i.e., Target e*CRF EDC system) during the lifetime of the study. At the conclusion of the study, Target Health provides a database extract to the sponsor for analysis and reporting to regulatory authorities. Target e*CRF will be used for online edit checks, batch edit checks and query management. Sponsor or authorized representatives capture the EDC specifications in an Application Setup Instructions (ASI) document. The ASI document contains the specific instructions for both the EDC development and data management (DM) staff.

The Data Validation Plan (DVP) provides specifications for the edit-checks. Within the DVP, there are three types of automated validation checks:

- Online edit-checks – Performed by the EDC system during data entry. Target Health personnel are responsible for programming and resolving any hits based on these checks.
- Batch edit-checks – Target Health personnel are responsible for programming and resolving any hits based on these checks.
- Manual checks – Performed by the monitor and data manager (DM). The DM is responsible for providing the listings if used by the monitors for manual checks.

Monitors manage queries within the Target e*CRF[®] application. Authorized site personnel (e.g., study coordinator) respond to and resolve queries. All changes to the database require a “Reason for Change” and are subject to an audit trail. The audit trail identifies the changed data,

reason(s) for change, who changed the data and the time and date of the change (based on the Target e*CRF[®] server's time).

EDC management reports are also available to view the data for consistency. Standard reports include:

- Overall Data Entry Status (By Site/Subject)
- Investigator Signature Status (By Site/Subject)
- Query Age Report (by Site)
- Query Report (by Site/Subject)
- Query Frequency by Site
- Query Frequency by Edit Check
- Query Frequency by Form
- Subject Visit Status Report (by Site / Subject)
- AE Report (By Site/Subject)
- Concomitant Medication Report (By Site/Subject)
- Serious AE Report (by Site/Subject)
- Subject Status Report (by Site)
- Protocol Violation Report (by Site / Subject)
- Treated (by Site / Subject)
- Subject Tracking Report (Individual)

Monitors and reviewers can request and specify changes to existing reports as well as additional management reports during the course of the study. Management of these requests fall under Change Control SOPs.

12.5.2 Centralized Monitoring

Study monitors carry out centralized (i.e., remote) monitoring of entered data daily or at an agreed-upon frequency, as defined in the Clinical Data Monitoring Plan (CDMoP). The following are samples of reports that assist in the centralized monitoring process. Study specific reports are found in Target e*CRF.

1. Time from subject visit to data entry
2. Online edit checks
3. Batch edit checks
4. Data listings

At the QbD meetings, monitoring findings are discussed. Clinical research and DM personnel meet to review and discuss data quality and data management issues, and capture relevant observations and decisions in meeting minutes. When necessary, the DMP and CDMoP are revised and corrective actions are implemented.

12.6 Record Retention

All study records will be retained for a period of time defined by the regulatory authority for the country in which the investigation is conducted. In general, this period is at least 2 years following the date on which the drug receives regulatory approval. In other situations (e.g., where the investigation is not in support of or as part of an application for a research or marketing permit), the retention period is 2 years following the date on which the entire clinical program is completed, terminated or discontinued, or the investigational application under which the investigation is being conducted is terminated or withdrawn by the regulatory authorities.

In the event the Investigator retires, relocates or for any other reason withdraws from the responsibility for maintaining records for the time period required, custody of the records may be transferred to any other person who will accept responsibility for the records. Notice of such a transfer must be given in writing to the sponsor. The Investigator must contact the sponsor prior to disposal of any records related to this study.

12.7 Confidentiality of Subject Data

The Investigator will preserve the confidentiality of the subjects' data. CRFs and other documents submitted to the sponsor will reference subjects only by an anonymized subject ID, which uniquely identifies the subject in the context of the study. The Investigator will maintain documents not meant for submission to the sponsor, e.g., the confidential subject identification code and the signed informed consent forms, in strict confidence. All data are subject to monitoring, audits and inspection.

12.8 Clinical Data Monitoring Plan (CDMoP)

The CDMoP identifies the monitoring schedule and the rationale for the frequency and type of monitoring visits. Since this study is using Direct Data Entry (DDE), in addition to agreed-upon source data verification (SDV), on-site monitoring visits will be limited to: assuring that the sites understand and are following the protocol, are adequately monitoring subject safety, and are managing the drug supply. The CDMoP also provides details with regard to the use of risk-based monitoring and source document verification. If the monitor is not allowed access to any e-source records during source document verification, certified printouts provided by sites can be used. In addition to on-site monitoring, monitors will perform central (i.e., remote) monitoring, electronically reviewing data in near real-time.

Communication	Timeframe
Site initiation visit (SIV)	All sites will have a SIV. The investigator meeting may serve as the SIV.
First on-site monitoring visit	See CDMoP.
Interim monitoring visits (IMV)	As specified in the CDMoP
Closeout visit (COV)	All sites must have a COV. Non-enrolling sites may have a COV over the telephone as permitted by the sponsor.

Communication	Timeframe
Site Update and Monitoring Calls	Monitors will contact sites as needed via email or telephone, based on review of site activity and the quality of data entry.
Teleconferences between the sites and CRO	Monitors will schedule teleconferences as appropriate to discuss the overall study status and to discuss study-wide related issues.
Initiation, Monitoring and Closeout Visit Reports	<p>Interim monitoring visits can be performed on-site or online. On-site visits are preceded by a confirmation letter sent to the site. The confirmation letter must outline the date, time and purpose of the monitoring visit</p> <p>Monitors will route all online Qualification, Monitoring and Closeout Visit Reports for signature to their supervisor(s). The supervisor will review the report and enter comments if needed.</p> <p>Following the completion of an on-site monitoring visit report, the monitor provides feedback to the site, identifying any outstanding issues from the visit.</p>
Study updates, Protocol Amendments, etc.	Will be forwarded to sites during study.
Adverse Events (AE) and Serious Adverse Events (SAE)	The primary method for reporting the event consists of entering data into the AE and Pharmacovigilance forms in Target e*CRF [®] .

12.9 Site Qualification Visit

Sites will undergo a qualification visit prior to the site initiation visit. The qualification of the site must include:

- The experience of the site personnel
- Availability of the population under investigation
- The suitability of the site facilities and equipment
- The suitability of the site for IMP storage
- Assurance that site personnel are not on the FDA debarment list

Sponsor or Target Health may waive the qualification visit if the study site has been previously qualified within a 12-month period of the site initiation visit for the same or similar indication. The Project Manager will document any such waivers in the project file (eTMF). Acceptable forms of documentation of previous qualification include previous approved site qualification reports from THI or similar documentation from the sponsor or their representatives.

12.10 Site Initiation Visit

The purpose of the study initiation visit is to train Investigators and site personnel on the specific requirements and procedures needed to satisfy the study protocol. This training may occur at the

Investigator site, during a joint Investigator Meeting, or via Internet-based training or teleconference.

The site initiation visit will include the following elements:

- Review of the protocol
- Review of the IMP handling procedures
- Training of appropriate staff on GCP regulations (including SAE reporting requirements)
- Training of the Investigator on the Investigator responsibilities listed on the FDA Form 1572
- Training of appropriate staff on maintenance of the Trial Master File in Target Document
- Training of appropriate staff on eCRF completion and expectations
- Training on eSource and access to the Target e*CTR Viewer

Task	Protocol-Specific Requirements
Prior to the site initiation visit, the following documents should be collected and uploaded into the Target Document electronic Trial Master File (TMF)	<ol style="list-style-type: none"> 1. Signed Confidentiality Agreement (CDA) 2. Mutually signed Clinical Trial Agreement (CTA) 3. Signed Statement of Investigator (Form 1572) 4. CV's of the Investigator and sub-Investigators (including current medical licenses). 5. Disclosure of Financial Interests and Financial Arrangements of staff listed on the 1572 (Form 3455). 6. IRB approval letter of protocol and Informed Consent Form
At the time of the site initiation visit, the following items will be available for the site personnel	<ol style="list-style-type: none"> 1. Personnel Signature Logs 2. Documentation of sponsor personnel participating in on-site visits 3. Training Records (GCP, protocol training)

12.11 First On-Site Monitoring Visit

During the first on-site monitoring visit, monitors will check:

- Adherence to the study protocol, with special focus on subject eligibility, IMP management and titration-related activities
- Informed consent process
- Medical histories and protocol eligibility, and verify transcription into Target e*CRF
- Drug accountability and storage
- SDV of paper source of questionnaires (if applicable) and verify transcription into Target e*CRF®
- Outstanding questions or issues with Investigator and study coordinator

12.12 Interim Monitoring

Monitoring of the clinical trial will occur both by on-site visits as well as by central (i.e., remote or in-house) review of eCRF forms, data management reports and the electronic Trial Master

File (eTMF). Monitors document the results of their monitoring assessments, both on-site and central, via online monitoring report functionality integrated into the EDC (eCRF) system.

The purpose of interim monitoring is to ensure protection of the rights and well-being of each subject, that the site understands and is following the protocol, that trial data are accurate, complete and verifiable, that the site is following ICH GCP guidelines, and that the trial site and staff remain qualified.

Interim monitoring activities typically include:

- Review of study and enrollment status (on-site or central)
- Review of consent forms, source documents and the eCRFs (on-site only)
- Review of study conduct and protocol adherence (on-site or central)
- Review of adverse events and that all Serious Adverse Events have been accurately been reported to the sponsor and IRB (on-site or central)
- Review of IRB approval and essential documents (on-site or central)
- IMP documentation and reconciliation (on-site only)
- Review of facility, personnel and delegation (on-site only)
- Personnel Signature Logs and delegation of authority (on-site only)
- Training Records (on-site only)
- Follow-up of outstanding issues (on-site or central)
- Documentation of sponsor personnel participating in on-site visits (on-site only)

When findings indicate that retraining is required, this must occur within 3 working days and if necessary the site will be informed not to enroll additional subjects until successful completion of the training.

It is the responsibility of the monitor to inform his/her supervisor of any issues that suggest the need for increased scrutiny across sites. The project manager will coordinate cross-site review and remediation, where warranted, to avoid or minimize repetition of the behaviors that led to the findings. Online management reports will support these cross-site reviews. These reports and all entered eCRF forms must be reviewed daily at the beginning of the study, defined as the first visit of the first subject, and corrective action reports generated as appropriate. It is critical that monitors document and share all findings that have an impact on the sites and study performance with the project manager and other study monitors.

Initially, the project manager will schedule Quality by Design meetings weekly, to review monitoring procedures and study progress. Based on findings from these meetings, the project manager will adjust the frequency of the meetings as appropriate. As well, the findings will drive remediation efforts as warranted. The project manager will document the results of each meeting and the decisions and the rationale for changing any of the procedures in the Quality by Design report.

The Monitor must immediately inform the Clinical Project Manager if he/she suspects fraud/misconduct at the site. The Clinical Project Manager will notify the sponsor of suspected fraud/misconduct and will propose an investigational action plan for approval by the sponsor.

12.13 Site Closeout

The purpose of the closeout visit is to bring to official completion all trial-related activities at the site.

During the visit, the monitor performs the following:

- Final resolution of outstanding data queries and verification of completeness of eCRFs.
- Final review for completeness of the eTMF.
- Reconciliation and disposition of the IMP.
- Review with the PI notification to the IRB that the study is closed. The correspondence should include the number of subjects enrolled, discontinued, and completed.
- Review with the site personnel the document retention requirements.

12.14 Audits

The Investigator will make all trial-related source data and records available at any time to a quality assurance auditor mandated by the sponsor or to domestic/foreign regulatory inspectors or representatives from IECs, who will audit/inspect the trial..

13. STATISTICAL CONSIDERATIONS

13.1 Objectives

This study is designed to assess the ability of scalp hypothermia using the DigniCap™ System to prevent chemotherapy induced alopecia. ‘Activity’ will be quantified using alopecia grading scales as described above, which will be used to define the proportion of responders among all evaluable patients. The primary goal of this study is to assess the efficacy of this system. To assess efficacy, the primary endpoint will be grade of alopecia 1 month after the last chemotherapy treatment as assessed by the patient with photographic documentation (digital photos), comparing current hair loss versus baseline.

Comparisons of the primary endpoint will be made with a concurrent non-randomized control group and also with a pre-defined level of clinical efficacy.

A secondary objective is to examine the safety of the system, in terms of adverse symptoms and adverse device effects reported by patients during use of the DigniCap™ System and during the follow-up period 3 and 6 months after completion of treatment will be examined.

The secondary endpoints also include tolerability of the DigniCap™ System, quality/quantity of hair re-growth at follow-up visits at 3 and 6 months, quality of life measures assessed using the EORTC-QLQ-BR23 scale and BIS during chemotherapy and follow-up visits, the 5-level Dean score measured on a continuous scale and the impact of hair loss on treatment decisions assessed at follow up using a 4-level ordered categorical measure. These secondary outcomes will be evaluated in all patients, whether or not they are evaluable for response.

13.2 Statistical Hypothesis and Model

The primary goal of this study is determine the success rate for the DigniCap™ System in preventing hair loss among patients. A success has been determined to be when the patient grades her hair status as Grade 0-2 (Dean Scale) 4 weeks after the last chemotherapy visit. Any Dean score of 4 during the chemotherapy visits or a score of 3 or 4 at the visit 4 weeks after the last chemotherapy will be considered a failure. To assess efficacy, the primary endpoint will be the grade of alopecia 4 weeks after the last chemotherapy treatment as assessed by the patient with photographic documentation (digital photos) compared to standardized photographs.

The product will be considered a useful device if the success rate is shown to be greater than the control group rate and also is greater than 50% 4 weeks after the last chemotherapy visit whereas if the success rate for the device is shown to not be greater than the control group rate or is shown to be less than or equal to 50% then the device will be considered ineffective. As described above, a success is defined by the patient grading her hair status as Grade 0-2 4 weeks after the last chemotherapy visit. The proportion of success in preventing hair loss among all treated patients who complete their chemotherapy treatment is the primary endpoint for evaluation of the device. We now describe our two hypotheses for primary efficacy. The first is defined as:

Null hypothesis (H₀): $P_{\text{control}}=P_{\text{treatment}}$

Alternative Hypothesis (H₁) $P_{\text{control}}\neq P_{\text{treatment}}$

A Fisher's Exact test will be used to test whether the two groups have equal proportions or not.

Since there is a high expectation that the patients in the control arm will experience a high level of failure (i.e. high amount of hair loss) there will be an early interim analysis performed to determine whether the full sample of patients in the control arm need to be included. This interim analysis will occur after 15 patients are enrolled. If 12 or more out of the first 15 control patients have a Dean score of 4 (greater than 75% hair loss at any chemotherapy treatment then the control arm will stop recruitment. However, if less than 12 out of the first 15 patients show hair loss then the remaining 15 patients (for a total of 30) will be enrolled.

Our second hypothesis for the primary efficacy is defined using only the patients in the treatment arm. It is important to distinguish between the language of the statistical hypothesis which will be used to establish a statistical test to determine efficacy and the clinical hypothesis which is linked to the threshold for efficacy that exists for the clinical realm. With this in mind the "clinical" hypothesis is that the observed success rate of the device must exceed 50% in order to be clinically effective. The "statistical" hypothesis is that in addition to the observed success rate being over 50% the lower bound of a 95% confidence interval for the observed success rate must exceed 40%. Thus, we can state this statistical hypothesis using 40% as the Null Hypothesis value since that is the success rate that we must rule out. Thus the hypotheses can be written as:

Null hypothesis (H0): $P \leq p_0$ (40%); The success rate that we wish to statistically rule out, and

Alternative Hypothesis (H1): $P > p_1$ (40%); A success rate of greater than 40% which we consider to be evidence that the device is clinically useful if the observed success rate also exceeds 50%..

A chi-square will be used to test the significance of the study results. In addition to performing this hypothesis test, a two-sided 95% confidence interval for the success rate will be calculated.

13.3 Sample Size and Power Estimation

This is a two-arm open label PMA study. For the comparison with the non-randomized control group there will be either 15 (if stopped at interim analysis) or 30 control patients and 110 treated patients. After accounting for a 10% drop out rate, we expect a total of 100 evaluable patients in the treatment arm.

Using a Fisher's exact test to compare the control arm to the treated arm, with a type 1 error rate of 5% (2-sided test) we will have 90% power to detect the difference between the Control group proportion of 20% (or less) and the treated group proportion of 66% (or greater) when the sample sizes are 15 and 100, respectively. If we do not stop the control arm after the first 15 patients then there is 93% power to detect the difference between the Control group proportion of 20% (or less) and the treated group proportion of 56% (or greater) when the sample sizes are 30 and 100, respectively.

For the comparison within the treated group only, using a one group chi-square test for proportions, with type I error of 5% (2-sided), for a sample size of 100 patients, there is 92% power to detect the difference between the null hypothesis proportion of less than 40% versus an alternative proportion of 56% (or greater). For the evaluable population (n=100), there is 90%

power to detect the difference between the null hypothesis proportion of less than 40% versus an alternative proportion of 56%. In other words, there is ample power to reject the null hypothesis that the success rate is 40% with a sample size of 110 patients (100 evaluable) if we assume that the expected proportion of patients that will be successes under the alternative hypothesis is 56% (or more). The rejection of the null hypothesis will be sufficient to rule out the possibility that the true success rate is 40% or less.

13.4 Interim Analysis and Stopping Rules

The study device has shown very promising results from large number of patients in previous trials overseas. Although we don't expect any serious adverse safety concerns in this study, a DSMB will meet every 6 months to review all safety data. If issues arise, then the DSMB can recommend changing consent/protocol or even suspending/stopping the trial. In addition, the DSMB will examine the control participant data after the first 15 patients are enrolled and if they find that 12 or more of the first 15 patients lose more than 75% of their hair then this arm will discontinue enrolment.

13.5 Handling of Missing Values/Discontinuations

Since this study is not a randomized trial, imputing "failures" into all women who drop out of the study regardless of the reason would be too conservative and likely give a biased estimate of the true failure rate of the device. Therefore, we propose the following plan for the primary analysis. All patients who drop out due to not completing the full prescribed chemotherapy cycles due to any reason such as toxicity of the chemotherapy will be excluded from the primary efficacy analysis. However, patients with missing endpoint assessment or who drop for any other reason such as toxicity or intolerability of the cap or hair loss will be considered as evaluable patients and "failures" for the primary efficacy analysis. We will recruit patients until the number of evaluable patients reaches the target (n=100) determined in the power/sample size calculation.

In addition to this primary efficacy analysis based on evaluable patients, we will perform a sensitivity analysis where we examine two different methods. The first will be an analysis where all patients that drop-out of the study (for any reason) will be considered as "failures" in the efficacy analysis. The second will be an analysis where only patients who complete the full series of measurements and adhere to the protocol are included in the efficacy analysis.

13.6 Analysis

Descriptive statistics (means, standard deviations, frequencies, etc.) will be presented for pretreatment patient characteristics and the outcome measures mentioned by treatment group. Tables, graphs, and charts will be used to illustrate the data when appropriate. Each of the outcomes mentioned above will be analyzed and reported separately. The primary outcome analysis will be performed using a Fisher's exact test to compare the treated and control groups based on the above definitions of success and failure. Next, a one-sample Chi-square test will be performed to test the treated group alone to rule out a lower bound of success of 40%. In addition, a 95% confidence interval will be constructed for the success rate in the treated group and the lower bound of this interval should exceed 40% while the observed success rate also exceeds 50%. Toxicity reports listing the incidence of all reported toxicities will be generated. All patients registered will be used for toxicity reports whether or not they are evaluable for

efficacy response. Any Grade 4 or 5 toxicities will be reported to the Institutional Review Boards/Ethics Committee responsible for oversight of the study at the investigator's institution.

The secondary endpoints will be reported with descriptive statistics (means, medians, and measures of variability, including 95% confidence intervals for continuous measures and counts and percents, with corresponding 95% confidence intervals for categorical variables):

1. Tolerability defined as the percentage of patients who complete all planned cycles of chemotherapy using the DigniCap™ System.
2. Assessment of hair loss by patient using the quantitative Dean scale.
3. Assessment of hair re-growth at the 3 and 6 month follow-up visits compared to hair status after completion of chemotherapy, by a three person independent panel. Hair re-growth is defined an improvement in the Dean scale by at least one level.
4. Assessment of hair regrowth by the patient using the Hair Regrowth Follow Up Survey.
5. Assessment of Quality of life during and after treatment with the DigniCap™ System by the patients using the EORTC-QLQ-BR23 scale and BIS.
6. Assessment of the impact of hair loss on treatment decisions in patients offered therapy with the DigniCap™ System at the follow up visit 3 months after completion of treatment.
7. Assessment of quality of treatment response in terms of quality/ quantity of hair re-growth from baseline during follow-up period 3, 6, and 12 months after completion of treatment. Patients will grade the hair in terms of texture, manageability and color variation from baseline.
8. Assessment of the scalp for the occurrence of scalp metastases at 3 and 6 months.

All toxicities experienced will be documented.

14. PUBLICATION POLICY

The investigators are free to decide about publication of the study results in oral presentations at meetings, posters or full journal articles but are expected to give Dignitana AB a minimum of two weeks to comment on drafts.

15. SPONSOR

Dignitana AB is the sponsor of the study.

16. CONFIDENTIALITY

All study data is identified via codes and patient information is confidential and not traceable without the code key.

17. REFERENCES

General References

ICH/GCP

Declaration of Helsinki, latest version.

EN ISO 14155-1:2003, Clinical investigation of medical devices for human subjects – Part 1: General requirements.

EN ISO 14155-2:2003, Clinical investigation of medical devices for human subjects – Part 2: Clinical investigation plans.

FDA 21cfr PART 812.25.

Works Cited

1. Batchelor D. Hair and cancer chemotherapy: consequences and nursing care-a literature study. *Eur J Cancer Care* 2001; 10:147-63.
2. Mulders M, Vigerhoets A, Breed W. The impact of cancer and chemotherapy: Perceptual similarities and differences between cancer patients, nurses and physicians. *Eur J Oncol Nursing* 2008; 12:97-102.
3. Prevezas, C, Matard, B, Piquier L, Reygagne, P. Irreversible and severe alopecia following docetaxel or paclitaxel cytotoxic therapy for breast cancer. *Br J Dermatol* 2009; 160:883-885.
4. Trüeb RM. Chemotherapy-Induced Alopecia. *Semin Cutan Med Surg* 2009 March; 28 (1): 11-14 *Hair and Nail Disorders*.
5. Medical Specialties of California (MSC) website. Penguin cold cap therapy, stopping chemotherapy induced alopecia. Retrieved February 14, 2012, from <http://www.msc-worldwide.com/indexusa.html>.
6. Paxman Coolers [Database on the Internet] www.paxman-coolers.co.uk.
7. Komen M.M.C, Smorenburg, C.H., van den Hurk C.J.G., en Nortier, J.W.R. (Hans). Hoofdhuidkoeling tegen alopecia door chemotherapie. *Ned Tidschr Geneeskd*. 2011; 155: 2053-7 (article in Dutch).
8. Grevelman and Breed. Prevention of chemotherapy-induced hair loss by scalp cooling. *Ann Oncol*. 2005 Mar;16(3):352-8.
9. Breed WPM, van den Hurk Corina JG, Peerbooms M. Presentation, impact and prevention of chemotherapy-induced hair loss: scalp cooling potentials and limitations. *Expert Rev Dermatol*. 2011; 6(1):109-25.
10. Hendriks M.A.E. et al. Evaluation of Cohens Cross-Section Trichometer for Measuring Hair Quantity. *Dermatol. Surg*. 2012; 1-4.

11. Poder T., Hez J., Lemieux R. Efficacité du casque réfrigéren Chimiothérapie. Bull Cancer. 2011; 98: 1119-28.
12. Lundgren-Eriksson L, Edbom G, Olofsson Y et al. Total prevention of taxoid-induced alopecia by a new model of cold cap (Dignitana). Eur J Cancer 1999; 35 (Suppl 4): 376.
13. Henriksen T, Jensen BK. Advanced computerized cold cap for preventing chemotherapy – induced alopecia. Herlev hospital, University of Copenhagen, Abstract and scientific poster ECCO 12. Sept 21-25 2003.
14. Ridderheim M, Bjurberg M, Gustavsson A. Scalp hypothermia to prevent chemotherapy induced alopecia is effective and safe: a pilot study of new digitized scalp-cooling system used in 74 patients Support Care Cancer 2003; 11:371-7.
15. Byahov M, Shevelev O. Alopecia prevention in chemotherapy patients. Method of controlled scalp cooling. Presentation at All-Russian Convention of Oncologists 2006. Published in Meditsinskaya Cartoteka, 2006.
16. Kato M , Sakuyama A., Imai R., Kobayashi TK. Evaluation of DigniCap System for the prevention of chemotherapy-induced hair loss in breast cancer patients. 12th St. Gallen International Breast Cancer Conference, 2011 (Poster Nb P330).
17. Abramov M., Semenova I. Cooling of the Scalp to prevent anticancer chemotherapy-induced alopecia. Eur J Cancer. 2011; 47 (suppl 1): S321 (abstract 4245).
18. Clinical Evaluation Report (Dignitana document) May 2012.
19. Dignitana AB Post Market Surveillance Report 2001-Aug. 2011. November 2011.
20. Breed WP. What is wrong with the 30-year-old practice of scalp cooling for the prevention of chemotherapy-induced hair loss? Support Care Cancer 2004; 12:3–5.
21. Lemieux J et al., [Incidence of scalp metastases in breast cancer: A retrospective cohort study in women who were offered scalp cooling](#). Breast Cancer Res Treat. 2009 Dec: 118(3): 547-52. Epub 2009 Feb 25.
22. Dean JC, Griffith KS, Cetas TC et al. Scalp hypothermia: a comparison of ice packs and the Kold Kap in the prevention of doxorubicin-induced alopecia. J Clin Oncol 1983; 1:33-7.
23. Rugo HS and Melin SA. Expert Statement on: Scalp Cooling with Adjuvant/ Neoadjuvant Chemotherapy for Breast Cancer and the Risk for Scalp Metastases. Feb 2012.
24. Van den Hurk C, Mols F, Vingerhoets J et al., Impact of alopecia and scalp cooling on the well-being of breast cancer patients. Psycho oncology. 2010 Jul:19(7):701-9
25. Camp-Sorrell D (1991) Scalp hypothermia devices: current status. ONS News 6:1–5
26. Bloomberg. Lisbon on Gel Cap That Prevents Hair Loss. Retrieved May 29, 2012, from <http://www.bloomberg.com/video/66131544/>.

27. Braff, D (2012, January 4). Cold caps show promise in keeping hair through chemo. Retrieved May 29, 2012, from <http://www.chicagotribune.com/health/sc-health-0104-chemo-cap-20120104,0,5128904.story>.
28. Ivanhoe Newswire (2011, December 26). Chemo Cold Cap: Cancer Patients Keep Their Hair. Retrieved May 29, 2012, from <http://www.newschannel5.com/story/16393701/chemo-cold-cap-cancer-patients-keep-their-hair>.
29. Aleccia, J (2010, December 20). Cold caps may help cancer patients keep their hair. Retrieved May 29, 2012, from <http://on.msnbc.com/hv3CdI>.
30. University of California – San Francisco (2010, December 14). UCSF physicians evaluate devices that could reduce hair loss in breast cancer patients undergoing chemotherapy. Retrieved May 29, 2012, from <http://bit.ly/fxvGvK>.
31. Dance, A (2010, December 27). Cooling caps tested to help cancer patients keep hair. Retrieved May 29, 2012, from <http://lat.ms/gESCzc>.
32. Johnson, C (2010, December 6). Cooling cap offers hope for chemo patients. Retrieved May 29, 2012, from <http://bit.ly/hJR8Ph>.
33. Zalkin, M (2010, October 28) Cold Cap Therapy May Help Women Undergoing Chemotherapy Keep Hair. Retrieved May 29, 2012, from <http://abcn.ws/cLg5Oi>.
34. Gregory, KL (2011, November 24). Cold Caps Aim to Preserve Hair for Cancer Patients. Retrieved February 21, 2012, from <http://m.vcstar.com/news/2011/nov/24/cold-caps-aim-to-preserve-hair-for-cancer/>.
35. Rapunzel Project website. The Rapunzel project. Retrieved February 14, 2012, from <http://www.rapunzelproject.org/>.
36. Weiss, S (2011, January 11). Breast cancer patient uses super-chilled headgear to try to retain her hair. Washington Post. Retrieved February 14, 2012, from http://www.washingtonpost.com/wp-dyn/content/article/2011/01/10/AR2011011006036.html?tid=wp_ipad.
37. Zalkin, M (2010, October 28). Cold Cap Therapy May Help Women Undergoing Chemotherapy Keep Hair. Retrieved February 21, 2012, from <http://abcnews.go.com/Health/OnCallPlus/cold-cap-therapy-women-chemotherapy-hair/story?id=11985624>.
38. Wills S, Ravipati A, Nguyen M, Dana Z, Jaiyesimi I, Margolis J, Decker D. Scalp Hypothermia Minimizes Alopecia in Breast Cancer Patients Receiving Non-Anthracycline Adjuvant Chemotherapy San Antonio Breast Symposium 2009; abstr 5040.
39. JC Dean, SE Salmon, and KS Griffith. Prevention of doxorubicin-induced hair loss with scalp hypothermia. N Engl J Med 1979; 301 (26):1421-1427.

Clinical Performance, Efficacy and Safety of the DigniCap™ System, a Scalp Hypothermia System, in Preventing Chemotherapy Induced Alopecia in Patients with Early Stage Breast Cancer

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SYNOPSIS

TITLE	Clinical Performance, Efficacy and Safety of the DigniCap™ System, a Scalp Hypothermia System, in Preventing Chemotherapy Induced Alopecia in Patients with Early Stage Breast Cancer
PHASE	IDE PMA Study
BACKGROUND	<p>Alopecia is a non-life threatening complication of the majority of effective adjuvant chemotherapy regimens for early stage breast cancer. It has a significant impact on quality of life and affects decisions regarding the risks and benefits of treatment.</p> <p>Scalp cooling prevents hair loss through vasoconstriction, and thus a lower concentration of chemotherapy is delivered to the scalp. Scalp cooling also decreases cellular uptake of drugs and decreases the intra-follicular metabolic rate.</p> <p>We propose to study the safety and efficacy of the DigniCap™ System in women undergoing standard adjuvant chemotherapy for early stage breast cancer at 5 centers in the United States. The study design is a two arm study with a non-randomized active arm and a concurrent non-randomized control group. We believe that scalp cooling, now commonly used around the world outside of the U.S., is an important tool that should be studied in American women.</p>
OBJECTIVES	<p>The overall objective is to assess the clinical performance, efficacy and safety of a Scalp Hypothermia System in breast cancer patients receiving specific chemotherapy treatments that, unless counteracted by simultaneous hypothermia treatment, result in hair loss.</p> <p>Primary Objective: To assess the ability of the DigniCap™ System to prevent hair loss in women receiving specific chemotherapy regimens for early stage breast cancer. Efficacy will be measured by assessment of hair loss up to 4 weeks (3-6 week window) after the completion of the last chemotherapy cycle by patient self-assessment of standardized photographs using the Dean scale by patients in the treatment and control groups</p> <p>Secondary Objectives: To assess safety of the DigniCap™ System in women receiving specific chemotherapy regimens for early stage breast cancer.</p> <p>To assess tolerability of the Digni-Cap™.</p>

	<p>To evaluate hair loss and recovery as assessed by the patient during and following chemotherapy using the alopecia self-report.</p> <p>To evaluate hair re-growth at 3 and 6 months after completion of chemotherapy compared to the greatest hair loss as assessed by the patient using the hair regrowth follow up survey.</p> <p>To assess patient quality of life and satisfaction with hair during and after treatment with the DigniCap™ System.</p> <p>To assess the impact of hair loss on treatment decisions.</p>
STUDY ENDPOINTS	<p>Primary endpoint: Success of the DigniCap™ System to prevent hair loss, defined as a maximum Dean score of ≤ 2 using standardized photographs graded by the patient up to 4 weeks after the last chemotherapy treatment, in at least 50% of patients enrolled in the treatment group with a lower bound of the 95% CI greater than 40%, and statistical superiority over a concurrent control group.</p> <p>Secondary endpoints: Safety as determined by spontaneous reporting of adverse events and as negative scalp changes determined by physical examination.</p> <p>Tolerability is defined as the percentage of patients who complete all planned cycles of chemotherapy do so using the DigniCap™ System.</p> <p>Patient assessment of hair loss by the alopecia self-report at each chemotherapy.</p> <p>Hair re-growth assessed by the patient using the hair regrowth follow up survey.</p> <p>Quality of life as measured by the EORTC-QLQ-BR23 quality of life questionnaire and a Body Image Scale.</p> <p>Assessment of the impact of hair loss on breast cancer treatment decisions at 6 months after completion of chemotherapy.</p>
PATIENT POPULATION AND SAMPLE SIZE	110 women with stage I or II breast cancer scheduled to receive at least 4 cycles of specific anthracycline or taxane based chemotherapy regimens in the adjuvant or neoadjuvant setting

	<p>will be enrolled to ensure a sample size of at least 100 patients that complete the study.</p> <p>An age- and treatment regimen-matched control group of up to 30 patients will be enrolled; hair loss will be assessed during treatment using the same procedures as the treatment group.</p>
INVESTIGATIONAL PRODUCTS:	The DigniCap™ System
PATIENT SELECTION CRITERIA Treatment Group	<p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. Female patients \geq 18 years of age 2. Documented diagnosis of stage I or II breast cancer. 3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens: <ul style="list-style-type: none"> • Doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 2 - 3 weeks • Docetaxel 75 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 3 weeks • Paclitaxel 80 mg/m² weekly IV x at least 12 weeks with or without IV trastuzumab • Paclitaxel 175 mg/m² IV every 2 weeks x 4 – 6 cycles (without an anthracycline) • Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks • Docetaxel 75 mg/m² and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks • Targeted agents such as trastuzumab or lapatinib are allowed 4. Plan to complete chemotherapy within 6 months 5. At least two years out from the last chemotherapy causing hair loss with complete recovery of hair 6. Karnofsky performance status \geq 80% 7. Willing and able to sign informed consent for protocol treatment 8. Willing to participate in study procedures including having photographs of the head before each cycle of chemotherapy and 1 month after the last chemotherapy 9. Willing to enroll in an extension protocol for follow up for 5 years following the end of chemotherapy treatment
	<p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. Patients with female pattern baldness resembling picture I-3 or higher on the Savin scale (Appendix IB)

	<ol style="list-style-type: none"> 2. Autoimmune disease affecting hair; e.g. alopecia areata, systemic lupus with associated hair loss 3. A history of whole brain radiation 4. Plans to use a chemotherapy regimen other than those specified in the inclusion criteria. Specifically, patients receiving a regimen including both an anthracycline and a taxane are not eligible for this trial (AC/T, EC/T, TAC, etc.) 5. Concurrent hormone therapy with chemotherapy. Hormone therapy should be used as indicated following completion of chemotherapy 6. Underlying clinically significant liver disease including active viral hepatitis with abnormal liver function tests >1.5 times the upper limit of normal, including alkaline phosphatase, AST, and total bilirubin. Patients with Gilbert’s disease (elevated indirect bilirubin only) will be eligible for participation. 7. Clinically significant renal dysfunction defined as serum creatinine > the upper limit of normal. 8. A serious concurrent infection or medical illness that would jeopardize the ability of the patient to complete the planned therapy and follow-up 9. A history of persistent grade 2 (or higher) alopecia induced by prior chemotherapeutic regimens 10. Participation in any other clinical investigation or exposure to other investigational agents, drugs, device or procedure that may cause hair loss 11. Intercurrent life-threatening malignancy 12. A history of cold agglutinin disease or cryoglobulinemia 13. Evidence of untreated or poorly controlled hyper- or hypothyroidism 14. A history of silicon allergy 15. American Society of Anesthesiologist Class ≥ 3 (Appendix IV.A)
<p>PATIENT SELECTION CRITERIA Control Group</p>	<p>Inclusion Criteria:</p> <ol style="list-style-type: none"> 1. Female patients ≥ 18 years of age 2. Documented diagnosis of stage I to III breast cancer. 3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens: <ul style="list-style-type: none"> • Doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 2 - 3 weeks • Docetaxel 75 mg/m² and cyclophosphamide 600 mg/m² x 4 - 6 cycles IV every 3 weeks • Paclitaxel 80 mg/m² weekly IV x at least 12 weeks with or without IV trastuzumab • Paclitaxel 175 mg/m² IV every 2 weeks x 4 – 6 cycles

	<p>(without an anthracycline)</p> <ul style="list-style-type: none"> • Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks • Docetaxel 75 mg/m² and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks • Targeted agents such as trastuzumab or lapatinib are allowed <ol style="list-style-type: none"> 4. At least two years out from the last chemotherapy causing hair loss with complete recovery of hair 5. Karnofsky performance status \geq 80% 6. Willing and able to sign informed consent for protocol treatment 7. Willing to participate in study procedures including having photographs of the head before each cycle of chemotherapy and 1 month after the last chemotherapy 8. Chooses not to use scalp cooling during chemotherapy
	<p>Exclusion Criteria:</p> <ol style="list-style-type: none"> 1. Patients with female pattern baldness resembling picture I-3 or higher on the Savin scale (Appendix IB) 2. Autoimmune disease affecting hair; e.g. alopecia areata, systemic lupus with associated hair loss 3. A history of whole brain radiation 4. Plans to use a chemotherapy regimen other than those specified in the inclusion criteria. Specifically, patients receiving a regimen including both an anthracycline and a taxane are not eligible for this trial (AC/T, EC/T, TAC, etc.) 5. Concurrent hormone therapy with chemotherapy. Hormone therapy should be used as indicated following completion of chemotherapy 6. Underlying clinically significant liver disease including active viral hepatitis with abnormal liver function tests >1.5 times the upper limit of normal, including alkaline phosphatase, AST, and total bilirubin. Patients with Gilbert's disease (elevated indirect bilirubin only) will be eligible for participation. 7. Clinically significant renal dysfunction defined as serum creatinine $>$ the upper limit of normal. 8. A serious concurrent infection or medical illness that would jeopardize the ability of the patient to complete the planned therapy and follow-up 9. A history of persistent grade 2 (or higher) alopecia induced by prior chemotherapeutic regimens 10. Intercurrent life-threatening malignancy 11. Evidence of untreated or poorly controlled hyper- or

	hypothyroidism 12. American Society of Anesthesiologist Class ≥ 3 (Appendix IV.A)
STUDY DESIGN	This is a prospective, non-randomized, concurrent age- and treatment-matched control, clinical trial. The control group will establish whether a similar group of women based on disease, age, and treatment regimen will experience an expected high percentage of hair loss. An interim analysis will be conducted and if at least 12 out of the first 15 control group women have a Dean score of 4 (lose greater than 75% of their hair) at any chemotherapy visit, enrollment of the control group will be discontinued.

1. BACKGROUND AND RATIONALE

1.1 Chemotherapy Induced Hair Loss

Chemotherapy acts on cells with a high proliferation rate, targeting not only tumor cells but also benign proliferating cells, including those comprising the hair follicles. One previously unavoidable and emotionally distressing side effect from chemotherapy is chemotherapy-induced hair loss, or alopecia.

Chemotherapy is commonly utilized as adjuvant therapy for potentially curable malignancies such as breast cancer; the majority of patients with early stage disease will receive some sort of adjuvant chemotherapy. Different chemotherapy agents as well as variations in dose and schedule of administration result in varied effects on hair follicles. However, the most effective and most commonly administered adjuvant chemotherapy regimens for breast cancers include those that cause complete alopecia, anthracyclines and/or taxanes [1]. In contrast, some agents used primarily in the metastatic setting are not associated with significant hair loss, such as capecitabine and vinorelbine. Despite improvements in supportive care, and new chemotherapy regimens with less systemic toxicity, hair loss remains universal in the early stage setting.

Although genomic assays that predict chemotherapeutic benefit are an exciting approach that already are helping to determine which patients are most likely to benefit from adjuvant chemotherapy, hair loss remains a major issue in decision making for many patients. Patients with cancer rate chemotherapy induced alopecia as one of the most distressing side effects of treatment [2]. Complete alopecia is a constant reminder for the patient and others of their disease. This side effect is mostly, but not always, reversible [3]. It takes months to a year after completion of chemotherapy for the hair to recover, and it may be different in quality, color, and thickness, and baldness is a public declaration of illness. Cranial prostheses, or wigs, are helpful but uncomfortable, and often readily identifiable.

1.2 Methods Of Preventing Chemotherapy Induced Hair Loss

Chemotherapy induced hair loss potentially can be prevented by various methods, including minoxidil, CDK2 (cell division protein kinase) inhibitors, and scalp cooling. However, the efficacy of minoxidil and CDK2 inhibitors to prevent chemotherapy induced hair loss has not been very successful [4]. The most widely used and successful method today is scalp cooling.

1.2.1 Scalp Cooling Rationale

Scalp cooling prevents hair loss through vasoconstriction, and thus a lower concentration of chemotherapy is delivered to the scalp. Scalp cooling also decreases cellular uptake of drugs and decreases the intra-follicular metabolic rate. Cooling is normally initiated 30 minutes prior to the chemotherapy infusion, then continues during the infusion and for a period of time after the infusion is completed. The post infusion cooling time depends on the chemotherapy regimen and dose that is administered, but cooling normally continues for 60-90 minutes after termination of the infusion.

1.2.2 Scalp Cooling Development

Scalp cooling was first performed using ice packs that were placed on the patient's head, but with unsatisfactory results. The ice packs were subsequently replaced with ice caps. The most

common system of this type is called the Penguin Cold Cap [5]. The caps are frozen when placed on the patient's head and then thaw over time. The caps therefore have to be replaced frequently (approximately every 20 minutes). Numerous caps are required for a chemotherapy session. Every time a cap has been used it needs a certain time (12-24h) in the freezer before it can be used again. In order for a center to support the use of these ice caps, a large freezer as well as refrigerated storage are required, and each patient needs multiple caps for a single chemotherapy session. The frequent changing of caps is labor-intensive and requires a caregiver or health care worker. In addition, the fluctuation of temperature could potentially affect efficacy. This led to the development of cooling systems that could provide continuous cooling of the scalp.

1.2.3 Continuous Scalp Cooling

The DigniCap™ System has been available since 1999. The scalp is cooled by a liquid coolant that is flowing from a refrigeration unit through tubes into the channels of the DigniCap™ and then back to the cooling system. The DigniCap™ is a silicone cap that fits uniformly to the scalp, with internal automatic temperature regulation. The cap is available in four different sizes and is specifically designed not to cover the patient's ears for comfort. Each cap contains two cooling compartments and the temperature in both compartments is monitored and automatically adjusted by a security sensor to prevent side effects from excessive cooling. Two patients can be treated at the same time using one refrigeration unit. Default time and temperature settings can easily be altered for patient comfort. In September 2009, the new generation of the DigniCap™ System was introduced: the Digni C3/DigniCap™ System. This new generation device offers a number of improvements in design, potentially improving both tolerance and efficacy.

The competing scalp cooling system on the European market is the Paxman hair loss prevention system [6]. In analogy with the DigniCap™ System, the Paxman system offers continuous scalp cooling and consists of a refrigeration unit, cooling caps and a liquid coolant. On the contrary, Paxman does not measure the temperature on the head and has only one cooling circuit.

1.3 The Efficacy Of Scalp Cooling To Prevent Chemotherapy Induced Hair Loss

1.3.1 Efficacy Determinants

The efficacy of scalp cooling depends on several factors [7-9]: chemotherapy regimen and dose, dose interval, performance status of the patient, scalp cooling temperature, post cooling time, and the scalp cooling system. The optimal scalp cooling system can maintain a constant low temperature of the scalp and comes with a snug fitted cap. 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.

1.3.2 Efficacy Measures

Hair preservation is generally evaluated by assessing hair loss. Assessments are performed either by the patient herself and/or by the clinician. Clinicians assess hair loss either directly, when meeting with the patient, or afterwards when looking at photographs. Different scales for assessing hair loss are used: the modified WHO scale, the Dean scale and the visual analogue scale (VAS) [29]. The modified WHO scale and the Dean scale are both 5-grade scales but with different cut-points for the grades. The VAS is a continuous scale used for patient assessment of, in this case, hair loss.

Another way to measure efficacy of scalp cooling is wig use. This is a subjective method that may or may not reflect efficacy but rather patient satisfaction with their hair. Another method is the Cohen's Cross Section Trichometer, a device for measuring hair quantity. This is a new promising method that has not yet been evaluated in scalp cooled patients [10]. Clearly a number of methods to measure hair loss exist, without clear superiority to one method. However, the Dean scale is a validated measure of hair quantity that can be graded based on photographs taken at 5 angles, and may be the most reproducible measure for use in multicenter studies.

1.3.3 Literature Review

In the extensive review by Breed in 2011 [9], the efficacy of scalp cooling was evaluated. 57 studies and 3 personal communications involved over 6000 patients were treated with scalp cooling were included. The author states that scalp cooling is effective, but not for all patients. In the review by Poder et al. [11] it is concluded that, "scalp cooling seems to get good performance in its aim to prevent hair loss in patients receiving chemotherapy."

The efficacy and safety of the DigniCap™ System has been evaluated in a number of studies [12-17]. These studies are described in detail in the Dignitana Clinical Evaluation Report [18]. Overall the data demonstrates the ability of the system to prevent chemotherapy induced hair loss in a number of settings. There is an ongoing evaluation of the DigniCap™ System in Japan [16]. The latest report was presented in St. Gallen in 2011, in 359 women diagnosed with early stage breast cancer. Photographs were taken and hair loss was evaluated using VAS. 70% of the patients were treated with weekly dose paclitaxel 60 mg/m² plus cyclophosphamide 400 mg/m², 8% were treated with paclitaxel plus trastuzumab, 15% were treated with epirubicin 40 mg/m² and cyclophosphamide 400 mg/m² biweekly, and 7% were treated with combinations including fluorouracil, irinotecan, vinorelbine or capecitabine. 48% of the patients did not lose any hair, 33% experienced a little hair loss, and 16% experienced mild hair loss. Only 4% experienced moderate hair loss and reported using a wig.

The clinical experience regarding efficacy and safety was reviewed in the Dignitana Post Market Surveillance Report [19]. Data was collected through phone calls and clinic visits. From 2001 until August 2011, more than 6000 patients have used the DigniCap™ System in Sweden, Norway, Denmark, Finland, England, Germany, Greece, Turkey, Russia, Japan, Singapore, Chile and Venezuela. The majority of patients in the report are breast and ovarian cancer patients. The overall success rate in terms of patient satisfaction is approximately 83%. Since most of the clinics do not log the number of patients or the results of scalp cooling, the numbers presented are conservative estimations by the treating nurse. Taken together, the DigniCap™ System has been evaluated in a variety of chemotherapy regimens, both in the adjuvant and in the palliative setting.

1.4 Safety Of Scalp Cooling

1.4.1 Short Term Side Effects

Based on published accounts of more than 2000 patients, it is concluded that scalp cooling is generally very well tolerated [20] with infrequent and mild side effects that rarely result in stopping cooling. 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 [8]. Uncomfortable cold sensations and headaches were especially pronounced in

studies where pre-cooled caps, which are usually chilled to -15°C to -25° , were used. Patients also complain about a heavy feeling of the head, and transient light-headedness following cap removal [1]. In addition, patients experienced neck pain due to heavy weight of some cooling caps [1]. Frostbite or freezing of skin has never been reported. There are only a few small, older studies in which more than 10% of the patients reported that side effects were a reason for stopping scalp cooling [8].

Side effects reported specifically from the use of the DigniCap™ System are limited. In a pilot study of 26 patients, it was reported that the side effects and the extra time required for scalp cooling was acceptable [13]. When evaluating discomfort during scalp cooling using a 10 point graded visual analogue scale (VAS) (0=none, 10=as bad as it could be), the discomfort was modest among the entire group (median value 1.5; range 0.5–8). In a larger study, only two out of 74 patients discontinued the treatment, one because of discomfort and one due to hair loss and discomfort [14]. Interestingly, side effects from chemotherapy such as uncomfortable scalp itching and distinctive scalp pain, and dermatitis (including hyperemia and skin flaking), appeared to be less frequent in the patients treated with the DigniCap™ System as compared to non-cooled patients [15].

1.4.2 Long Term Side Effects

Scalp cooling prevents hair loss through vasoconstriction, decreases cellular uptake of drugs, and decreases the intra-follicular metabolic rate. A theoretical increased risk of scalp metastases among breast cancer patients has been of concern since breast tumors may metastasize to the scalp. However, scalp metastases are rare in breast cancer, occurring in approximately 1% of all patients and almost always occurring in the presence of additional sites of disease[21]. Only a fraction of patients (0.025%), experience scalp metastasis as the first site of recurrence [22].

In the Dignitana Post Market Surveillance [19] including 6000 patients scalp cooled with the DigniCap™ system, only two patients have been reported with scalp metastases. Both patients had multiple sites of metastatic disease at the time of diagnosis with scalp involvement.

Breed et al. concluded, regarding scalp metastases, that “for breast cancer patients the theoretical risk of scalp cooling during adjuvant chemotherapy seems to be minimal” [9]. A recent extensive literature review has been conducted and the conclusion is that scalp cooling has not been shown to increase the incidence of scalp metastases in patients with both early and late stage breast cancer [23]. The author’s opinion is that scalp cooling can and should be offered to breast cancer patients who will be treated with adjuvant chemotherapy, and also to those who are offered palliative chemotherapy associated with a significant risk of alopecia. The risks involved in scalp cooling 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 [23].

1.5 Scalp Cooling In Relation To Well Being

Well-being has been evaluated in breast cancer patients treated with and without scalp cooling [24]. Patients completed questionnaires (including the EORTC QLQ-C30 and EORTC-QLQ-BR23, and BIS) before, during, and after completion of the last cycle of chemotherapy. At all three times of measurement, alopecia was considered among the most distressing problems. The

study showed a positive trend towards higher well-being in successfully scalp-cooled patients as indicated by a general better health-related quality of life and better body image.

1.6 Scalp Cooling: Available To Cancer Patients World Wide

Scalp cooling has been used for decades in Europe, and is now also under evaluation in the United States, Japan, the Middle East, Canada and South America.

Previously, scalp cooling was not available in the U.S. In 1991 the FDA stopped the approval of scalp cooling because of lack of documentation about efficacy and safety [25]. There has been increasing interest in scalp cooling in the United States, with increasing numbers of websites, TV shows and articles that discuss scalp cooling [26-37], and development of an advocacy group.

At this time, outside of a clinical trial, only Penguin Cold Caps are available to patients in the U.S. and are marketed by a group in Southern California and shipped from the U.K. directly to patients. Outside of the setting of a clinical investigation, patients generally investigate the caps through online research and chat rooms, then coordinate and pay themselves for the cap rental. Sharing of caps orchestrated by the company is quite common, allowing patients to obtain the caps with short notice. As of late 2010, BreastCancer.org had more than 1500 posts related to cold cap therapy, and seven medical centers in the U.S. currently or will soon have freezers dedicated to cooling Penguin Cold Caps on site (37).

A study on scalp cooling using the Penguin Cold Caps was presented at the San Antonio Breast Cancer Symposium, but has not yet been published [38]. The objective of the study was to determine the effectiveness of scalp hypothermia in patients with stage I-IIIc breast cancer receiving either anthracycline (n=22) or non-anthracycline based adjuvant chemotherapy (n=12). For patients who used scalp hypothermia through chemotherapy, the median incidence of alopecia was 10% for those treated with the combination of docetaxel-cyclophosphamide and docetaxel-carboplatin-trastuzumab. In patients treated with doxorubicin-cyclophosphamide, doxorubicin-cyclophosphamide followed by paclitaxel, and docetaxel-doxorubicin-cyclophosphamide combined, the median incidence of alopecia was 50%. Hair loss was thus reduced in those receiving anthracyclines and almost completely prevented in the group receiving non-anthracycline based chemotherapy. These data document existing use of scalp cooling in the U.S., and use is clearly increasing (personal communication, Frank Fronza).

1.7 Feasibility Study Of Scalp Cooling With The Dignicap™ System In The US

A pilot study was conducted in the United States at the University of California San Francisco, and Wake Forest University, evaluating the feasibility of use of the DigniCap™ System in patients with breast cancer receiving adjuvant chemotherapy known to cause significant alopecia. Eligible patients included women diagnosed with stage I breast cancer planning to receive chemotherapy in the adjuvant or neo-adjuvant setting. 20 patients were enrolled. The majority (80%) received docetaxel and cyclophosphamide (TC) every three weeks for four to six doses. Other chemotherapy regimens included 12 cycles of weekly paclitaxel with trastuzumab (10%), and docetaxel and carboplatin with trastuzumab every three weeks for six cycles (10%).

The primary endpoint of the pilot study was to determine the feasibility of use of the DigniCap™ System in this setting. Feasibility was defined as less than 50% of patients discontinuing use of

the cap due to cap-associated toxicity. Nineteen of 20 patients (95%) completed all chemotherapy using the DigniCap™ System, indicating that this system is feasible for use by women with breast cancer receiving adjuvant chemotherapy.

Secondary endpoints included prevention of hair loss, assessed by an independent panel as well as by patients. The Dean scale was used to grade extent of hair loss, with up to grade 2 ($\leq 50\%$ hair loss) considered successful prevention of hair loss. Using these criteria, the independent panel assessed that 75% of patients had no more than grade 2 alopecia at any time during their treatment and follow-up. The patient-reported hair loss using the Dean scale was also considered a success, as 55% of patients experienced grade 2 or less alopecia throughout their entire treatment and follow-up.

Overall, scalp cooling was well tolerated, with 68% and 32% of patients experiencing grade 1 and 2 toxicity respectively. With a median follow-up under two years, no scalp metastases have been observed.

The most common side effects experienced by patients using the DigniCap™ System were head pain, scalp pain, and feeling chilled. The majority of patients took over-the-counter pain medications as prophylaxis before starting the cooling process to counteract the initial headache. Head pain was experienced by 65% of patients during only one treatment (31%) or at most during three treatments (31%). More patients (50%) reported head pain during their second treatment than during any other treatment. The average level of head pain ranged from 39 (Cycle 2) to 46 (Cycle4) as assessed on a scale from 0-100.

Scalp pain was experienced by 95% of patients during at least one treatment. More patients (80%) reported scalp pain during their third treatment than during any other treatment. Most patients (65%) experienced scalp pain during 2 or 3 treatments, and this symptom was most prevalent during the third treatment, as 80% of patients reported scalp pain at this time. The average level of scalp pain ranged from 38 (Cycle 2) to 46 (Cycle1) as assessed on a scale from 0-100.

Chill was experienced by 80% of patients. Of these patients, 40% felt chilled during every treatment. The third treatment caused the most number of patients to feel chilled (80%). the average level of chill during treatment ranged from 42 (Cycle 1) to 54 (Cycle 3), as assessed on a scale from 0-100.

Overall, average patient satisfaction with hair was 85% at baseline, and 82% three months after the completion of chemotherapy. This pilot study demonstrated both feasibility and success of the DigniCap™ System in terms of preventing significant hair loss in the majority of women receiving non-anthracycline based adjuvant chemotherapy. These data support the planned pivotal trial to better evaluate the use of scalp cooling in women with early stage breast cancer receiving adjuvant chemotherapy.

1.8 The Need For A Prospective Study Of Scalp Cooling

Alopecia is a non-life threatening complication of the majority of effective adjuvant chemotherapy regimens for early stage breast cancer, but has a significant impact on quality of life and affects decisions regarding the risks and benefits of treatment. A safe and well tolerated system to prevent the majority of hair loss would be a powerful addition to our expanding

armamentarium of tools for supportive care, and would improve quality of life for women undergoing adjuvant therapy for these common malignancies.

2. OBJECTIVES

The overall objective is to assess the clinical performance, efficacy and safety of a Scalp Hypothermia System in breast cancer patients receiving specific chemotherapy treatments that, unless counteracted by simultaneous hypothermia treatment, result in hair loss.

2.1 Primary Objective

To assess the ability of the DigniCap™ System to prevent hair loss in women receiving specific chemotherapy regimens for early stage breast cancer. Efficacy will be measured by assessment of hair loss up to 4 weeks (3-6 week window) after the completion of the last chemotherapy cycle by patient self-assessment of standardized photographs using the Dean scale by patients in the treatment and control groups.

2.2 Secondary Objective

- To assess safety of the DigniCap™ System in women receiving specific chemotherapy regimens for early stage breast cancer.
- To assess tolerability of the DigniCap™ System
- To evaluate hair loss and recovery as assessed by the patient during and following chemotherapy using the alopecia self-report.
- To evaluate hair re-growth at 3 and 6 months after completion of chemotherapy compared to the greatest hair loss as assessed using the hair regrowth follow up survey.
- To assess patient quality of life and satisfaction with hair during and after treatment with the DigniCap™ System.
- To assess the impact of hair loss on treatment decisions.

3. TREATMENT ENDPOINTS

3.1 Primary Endpoint

Success of the DigniCap™ System to prevent hair loss, defined as a maximum Dean score of ≤ 2 using standardized photographs graded by the patient up to 4 weeks after the last chemotherapy treatment, in at least 50% of patients enrolled in the treatment group with a lower bound of the 95% CI greater than 40%, and statistical superiority over a concurrent control group.

3.2 Secondary Endpoints

Safety as determined by spontaneous reporting of adverse events and as negative scalp changes determined by physical examination.

Tolerability is defined as the percentage of patients who complete all planned cycles of chemotherapy do so using the DigniCap™ System.

Patient assessment of hair loss by the alopecia self-report at each chemotherapy.

Hair re-growth assessed by the patient using the hair regrowth follow up survey.

Quality of life as measured by the EORTC-QLQ-BR23 quality of life questionnaire and a Body Image Scale.

Assessment of the impact of hair loss on breast cancer treatment decisions at 6 months after completion of chemotherapy.

4. TREATMENT PLAN**4.1 Schedule Of Investigational Events for Treatment Group**

Assessments	Baseline ¹	Each Chemo-therapy cycle	1 month after last chemo-therapy infusion	Follow-up Visit (3 months)	Follow-up Visit (6 months)
Chemotherapy treatment		X			
Scalp cooling		X			
Signed Informed Consent, Appendix III	X				
Eligibility checklist, Appendix I	X				
Baseline Case Report Form, Appendix IV	X				
Case Report Form for all chemotherapy cycles, Appendix V		X			
Treatment follow-up form at 3 months after chemotherapy completion, Appendix VI				X	
Treatment follow-up form at 6 months after chemotherapy completion, Appendix VII				X	X
Photographs of hair/scalp (Section 8.1.1; Appendix XXI)	X		X		
Alopecia self-report, Appendix VIII	X	X	X	X	X
Patient symptoms survey ² , Appendix IX		X			
EORTC-QLQ-BR233, Appendix X ³	X	X ³	X	X	X
Body Image Scale (BIS) ³ , Appendix XI	X	X ³	X	X	X
Impact of hair loss on treatment decision, Appendix XII					X
Hair re-growth follow-up survey, Appendix XIII				X	X
Medwatch, Appendix XIV		X	X	X	X
Case Report Form for Device Use, Appendix XXIII		X			

Screening Log- Non Enrolled Patients, (If applicable), Appendix II	X				
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¹All baseline measurements must be done prior to treatment administration unless otherwise specified.

²This survey should be administered at the end of each chemotherapy session.

³QOL (EORTCQLQ-BR233 and BIS) to be completed at Cycle 4 only during Chemotherapy and at the last Chemotherapy Visit if the patient is discontinued early because of hair loss

4.2 Schedule Of Investigational Events for Control Group

Assessments	Baseline¹	Each Chemo-therapy cycle	1 month after last chemo-therapy infusion
Chemotherapy treatment		X	
Signed Informed Consent, Appendix III	X		
Eligibility checklist, Appendix I	X		
Baseline Case Report Form, Appendix IV	X		
Case Report Form for all chemotherapy cycles, Appendix V		X	
Photographs of hair/scalp (Section 8.1.1; Appendix XXI)	X		X
Alopecia self-report, Appendix VIII	X	X	X
EORTC-QLQ-BR233, Appendix X ³	X	X ³	X
Body Image Scale (BIS) ³ , Appendix XI	X	X ³	X
Medwatch, Appendix XIV		X	X
Screening Log- Non Enrolled Patients, (If applicable) Appendix II	X		

¹All baseline measurements must be done prior to treatment administration unless otherwise specified.

²This survey should be administered at the end of each chemotherapy session.

³QOL (EORTCQLQ-BR233 and BIS) to be completed at Cycle 4 only during Chemotherapy and at the last Chemotherapy Visit if the patient is discontinued early because of hair loss

5. PATIENT SELECTION CRITERIA

5.1 Treatment Group

5.1.1 Inclusion Criteria

In order to be eligible for the study, patients should fulfil all of the following inclusion criteria:

1. Female patients ≥ 18 years of age
2. Documented diagnosis of stage I or II breast cancer.
3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens:
 - Doxorubicin 60 mg/m^2 and cyclophosphamide $600 \text{ mg/m}^2 \times 4 - 6$ cycles IV every 2 - 3 weeks
 - Docetaxel 75 mg/m^2 and cyclophosphamide $600 \text{ mg/m}^2 \times 4 - 6$ cycles IV every 3 weeks
 - Paclitaxel 80 mg/m^2 weekly IV x at least 12 weeks with or without IV trastuzumab
 - Paclitaxel 175 mg/m^2 IV every 2 weeks x 4 – 6 cycles (without an anthracycline)
 - Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles and trastuzumab IV weekly or every 3 weeks
 - Docetaxel 75 mg/m^2 and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles and trastuzumab IV weekly or every 3 weeks
 - Targeted agents such as trastuzumab or lapatinib are allowed
4. Plan to complete chemotherapy within 6 months
5. At least two years out from the last chemotherapy causing hair loss with complete recovery of hair
6. Karnofsky performance status $\geq 80\%$
7. Willing and able to sign informed consent for protocol treatment
8. Willing to participate in study procedures including having photographs of the head before the first cycle of chemotherapy and 1 month after the last chemotherapy
9. Willing to enroll in an extension protocol for follow up for 5 years following the end of chemotherapy treatment

5.1.2 Exclusion Criteria

1. Patients with female pattern baldness resembling picture I-3 or higher on the Savin scale (Appendix IB)
2. Autoimmune disease affecting hair; e.g. alopecia areata, systemic lupus with associated hair loss
3. A history of whole brain radiation
4. Plans to use a chemotherapy regimen other than those specified in the inclusion criteria. Specifically, patients receiving a regimen including both an anthracycline and a taxane are not eligible for this trial (AC/T, EC/T, TAC, etc.)
5. Concurrent hormone therapy with chemotherapy. Hormone therapy should be used as indicated following completion of chemotherapy
6. Underlying clinically significant liver disease including active viral hepatitis with abnormal liver function tests >1.5 times the upper limit of normal, including alkaline phosphatase, AST, and total bilirubin. Patients with Gilbert's disease (elevated indirect bilirubin only) will be eligible for participation.

7. Clinically significant renal dysfunction defined as serum creatinine > upper limit of normal.
8. A serious concurrent infection or medical illness which would jeopardize the ability of the patient to complete the planned therapy and follow-up
9. A history of persistent grade 2 (or higher) alopecia induced by prior chemotherapeutic regimens
10. Participation in any other clinical investigation or exposure to other investigational agents, drugs, device or procedure that may cause hair loss
11. Intercurrent life-threatening malignancy
12. A history of cold agglutinin disease or cryoglobulinemia.
13. Evidence of untreated or poorly controlled hyper or hypothyroidism
14. A history of silicon allergy
15. American Society of Anesthesiologist Class ≥ 3 (Appendix IV.A)

5.2 Control Group

5.2.1 Inclusion Criteria

In order to be eligible for the study, patients should fulfil all of the following inclusion criteria:

1. Female patients ≥ 18 years of age
2. Documented diagnosis of stage I to III breast cancer.
3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting with curative intent including one of the following regimens:
 - Doxorubicin 60 mg/m^2 and cyclophosphamide $600 \text{ mg/m}^2 \times 4 - 6$ cycles IV every 2 - 3 weeks
 - Docetaxel 75 mg/m^2 and cyclophosphamide $600 \text{ mg/m}^2 \times 4 - 6$ cycles IV every 3 weeks
 - Paclitaxel 80 mg/m^2 weekly IV x at least 12 weeks with or without IV trastuzumab
 - Paclitaxel 175 mg/m^2 IV every 2 weeks x 4 – 6 cycles (without an anthracycline)
 - Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles and trastuzumab IV weekly or every 3 weeks
 - Docetaxel 75 mg/m^2 and carboplatin AUC 6 IV every 3 weeks x 4 - 6 cycles and trastuzumab IV weekly or every 3 weeks
 - Targeted agents such as trastuzumab or lapatinib are allowed
4. At least two years out from the last chemotherapy causing hair loss with complete recovery of hair
5. Karnofsky performance status $\geq 80\%$
6. Willing and able to sign informed consent for protocol treatment
7. Willing to participate in study procedures including having photographs of the head before the first cycle of chemotherapy and 1 month after the last chemotherapy
8. Chooses not to use scalp cooling during chemotherapy

5.2.2 Exclusion Criteria

1. Patients with female pattern baldness resembling picture I-3 or higher on the Savin scale (Appendix IB)
2. Autoimmune disease affecting hair; e.g. alopecia areata, systemic lupus with associated hair loss

3. A history of whole brain radiation
4. Plans to use a chemotherapy regimen other than those specified in the inclusion criteria. Specifically, patients receiving a regimen including both an anthracycline and a taxane are not eligible for this trial (AC/T, EC/T, TAC, etc.)
5. Concurrent hormone therapy with chemotherapy. Hormone therapy should be used as indicated following completion of chemotherapy
6. Underlying clinically significant liver disease including active viral hepatitis with abnormal liver function tests >1.5 times the upper limit of normal, including alkaline phosphatase, AST, and total bilirubin. Patients with Gilbert's disease (elevated indirect bilirubin only) will be eligible for participation.
7. Clinically significant renal dysfunction defined as serum creatinine > upper limit of normal.
8. A serious concurrent infection or medical illness which would jeopardize the ability of the patient to complete the planned therapy and follow-up
9. A history of persistent grade 2 (or higher) alopecia induced by prior chemotherapeutic regimens
10. Participation in any other clinical investigation or exposure to other investigational agents, drugs, device or procedure that may cause hair loss
11. Intercurrent life-threatening malignancy
12. Evidence of untreated or poorly controlled hyper or hypothyroidism
13. American Society of Anesthesiologist Class ≥ 3 (Appendix IV.A)

6. INVESTIGATIONAL DEVICE

6.1 The Dignicap™ System

The DigniCap™ System consists of the digitized system for controlled scalp cooling (Digni C3) in conjunction with the soft, tight-fitting silicon cap (DigniCap™), the neoprene outer cap (DigniTherm™), and the liquid coolant (DigniCool™). DIGNISTICK™ is prepared to log data from a treatment when inserted in the slot. DIGNICARD™ is a key card which has to be inserted in order to start a treatment.

The liquid coolant circulates from the cooling unit to and through the channels of the cap and back to the cooling unit again. The scalp temperature is monitored by three separate thermometers. Deviations from the pre-set temperature are immediately and automatically adjusted by the system (scalp temperature can be controlled with an accuracy of $\pm 2.0^{\circ}\text{C}$).

6.2 Dignicap™

6.2.1 Composition

The silicon cap has two separate cooling circuits, one for the front of the head and one for the back of the head (as the front of the head is warmer than the back of the head). Two sensors for controlling the cooling circuits, plus one for the safety system are attached.

6.2.2 Product Safety

Minimal risk associated with rare incidence of silicon allergy.

6.2.3 Storage Requirements

Product should be protected from non-operator handling and cleaned with alcohol swabs after each use.

6.2.4 Biocompatibility

Silicon is tested < 24h contact with intact skin without any remarks (cytotoxicity, sensitization, intracutaneous reactivity).

6.3 Dignitherm™

An outer neoprene cap that insulates and keeps the inner cap in place.

6.4 Digni C3

6.4.1 Specifications

Voltage 115 VAC 50-60 Hz.

Maximum Volt ampere 1500 VA.

Digni C3 weighs approximately 76 kg.

6.4.2 Temperature Control

The temperature in the DigniCap™ is kept at $\pm 2.0^{\circ}\text{C}$ from the set value. The safety system controls that the temperature never goes below 0°C . The unit is fully hermetically sealed and is using CFC-free R404A refrigerant.

6.5 Dignicool™

6.5.1 Product Name

Monopropylene Glycol diluted with water. DigniCool™ Hazards Information and Material Safety Data, Appendix XXV.

6.6 Labeling

Guide to Device Labeling, please see Appendix XXIV.

6.7 Investigational Device Accountability

When a device shipment is received at the site, a designee of the investigational team at each site should verify the contents, sign the packing invoice provided with the shipment, and maintain the original copy for review by the study monitor.

Each shipment of investigational supplies will contain an accountability log to allow maintaining current and accurate inventory records covering receipt, dispensing, and disposition of the investigational device. During the study, the following information must be noted in the accountability log: the identification number(s), initials of patient(s) to whom device is dispensed, the date(s) that the investigational device is dispensed, and the initials of the designee who dispensed it.

The study monitor will examine the inventory during the study. Additionally, the inventory records must be readily available and may be subject to regulatory authorities, the local regulatory agency, or an independent auditor's inspection at any time. At the completion of the study, to satisfy regulatory requirements regarding device accountability, all remaining investigational device items, used as well as unused, should be found in the inventory, reconciled and retained or destroyed according to applicable state and federal regulations.

Device Accountability Log, Appendix XXII.

6.8 Training And Experience For The Use Of The Device

Dignitana AB is responsible for installation of the DigniCap™ System and instruction and training of dedicated medical personnel.

Appropriate training on the hardware, software and fitting of the caps and communication with patients are ensured through a 3 day training program. Supplementary training can be performed in case of need. Education in handling and maintenance for dedicated medical personnel is performed at sufficient level to ensure correct experience and knowledge to carry out recommended use and maintenance.

Training of personnel will be performed according to Training Protocol, Appendix XIX, and is to be documented in the Checklist Training of Personal, Appendix XX.

7. STUDY DESIGN

This trial will be conducted in compliance with the GCP, Declaration of Helsinki and applicable regulatory requirements.

Only patients receiving chemotherapy treatment that may result in hair loss by the completion of chemotherapy will be included in the study.

Patients who choose not to undergo scalp cooling during chemotherapy are eligible to enrol in the study as part of the concurrent control group. The control group is being enrolled to determine whether the expected frequency of almost total hair loss will occur using the criteria of this study. The control patients will be matched by disease (breast cancer), age (± 5 years) and chemotherapy treatment regimen. If at least 12 out of the first 15 control patients have a Dean score of 4, or lose greater than 75% of their hair, enrolment of the control group will be discontinued. Otherwise, a total of 30 control patients will be recruited.

Patients will be informed that an extension protocol will be implemented to follow this protocol and that they will be asked to participate in the extension protocol in order to obtain long term follow up information on the risk of scalp metastases.

7.1 Study Treatment

No study specific assessments or treatments will commence prior to obtaining written signed informed consent from the patient.

Patients will receive scalp hypothermia as delivered by the DigniCap™ System. Scalp cooling will begin 30 minutes prior to administration of chemotherapy. Scalp temperature will be maintained at $+5^{\circ}\text{C}$ (41°F) throughout drug administration and for 60-90 minutes after discontinuing the infusion, depending on the chemotherapy regimen as outlined in Section 7.2.

7.2 Point Of Enrollment

Patients must be recruited and sign informed consent before initiation of treatment in order to be checked for eligibility and enrolled in the study. The Eligibility Checklist (Appendix I) should be completed prior to enrolment. If the patient meets all eligibility criteria and treatment must be started over a weekend or during a holiday, a maximum of 72 hours may elapse between the initiation of treatment and enrolment of the patient.

Eligible patients must be scheduled to receive either anthracyclines or taxanes as outlined in Section 5.1.

Patients found to be ineligible following study enrolment will be replaced in order to guarantee a 110-patient study population enrolment. Ineligible patients who have received treatment using the DigniCap™ System will be monitored for potential device-associated toxicity for 30 days following treatment. Upon determination of ineligibility, these patients will not have any more photographs taken nor will they be asked to complete any more protocol-mandated surveys.

Any patients who elect to discontinue study treatment prior to chemotherapy completion will also be monitored for potential device-associated toxicity for 30 days following treatment and will be followed for recurrence and survival. Upon study withdrawal, these patients will not have

any more photographs taken nor will they be asked to complete any more protocol mandated surveys.

7.3 Chemotherapy Regimens and Cooling Times

Chemotherapy Regimen	Dose	Post Infusion Cooling Time (minutes)
AC x 4 or 6 cycles, every 2-3 weeks	Doxorubicin: 60 mg/m ² , Cyclophosphamide 600 mg/m ²	60
TC x 4 or 6 cycles, every 3 weeks	Docetaxel 75 mg/m ² , Cyclophosphamide 600 mg/m ²	60
Paclitaxel x at least 12 cycles every week	Paclitaxel 80 mg/m ²	60
Paclitaxel and Carboplatin x 6 cycles, 3 on/ 1 off	Paclitaxel weekly and carboplatin AUC 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles with or without trastuzumab IV weekly or every 3 weeks	60
Paclitaxel x 4 – 6 cycles every 2 weeks	Paclitaxel 175 mg/m ² IV every 2 weeks (without an anthracycline)	90
TCH x 6 cycles every 3 weeks	Docetaxel 75mg/m ² , Carboplatin AUC 6, Trastuzumab weekly or every 3 weeks	60

Targeted therapeutics not associated with hair loss are allowed (including trastuzumab, lapatinib, neratinib, bevacizumab, etc.).

Dose reductions if required for patient safety or toxicity are allowed but full dose therapy should be planned at treatment start.

Patients should receive standard supportive care including myeloid growth factors as indicated.

Concomitant use of hormone therapy is not allowed. Hormone therapy should be started following completion of chemotherapy.

8. ASSESSMENTS

8.1 Photographic Documentation

Photographic documentation for all treatment and control patients will be performed before initiation of the first cycle of chemotherapy, each subsequent cycle of chemotherapy, and at a visit 4 weeks (3-6 week window) after the last cycle of chemotherapy. At each time point, 5 photographs should be taken: from the front (bangs should be held back), behind, both sides and the top with the hair divided in the midline with both hands (See Guidelines for Study Photographs, Appendix XXI). Hair loss will be assessed by comparing the photographs against standardized photographs to estimate the percentage of hair lost according to the Dean scale.

8.2 Assessments At Baseline

Eligible patients who consent to this study will have the following baseline assessments: Medical history, physical examination, vital signs, and Karnofsky Performance status. Each patient will be examined for cutaneous metastases of the scalp. The use of concomitant medication will also be assessed at baseline. Hair will be photographed before initiation of the first cycle of chemotherapy by the physician or study personnel as detailed above. Patients will be asked to assess their current hair status by comparing the photographs against standardized photographs using of the quantitative Dean scale and to assess the impact of hair loss on treatment decision. Quality of Life questionnaires including the EORTC-QLQ-BR23 scale and BIS will be filled out by the patient.

8.3 Assessments At Each Cycle Of Chemotherapy

Before infusion:

The medical history of the patients and the use of concomitant medication will be reassessed and a physical examination will be performed. Hair will be photographed by the physician or study personnel. Patients (treatment and control) will be asked to assess their current hair loss by examination of the photographs using the quantitative Dean scale compared to standardized photographs. Any patient with a Dean score of 4 at any visit will be considered to have met the study definition of “treatment failure” and will not have additional photographs. Treatment and control patients with a Dean score of 3 or lower will continue to be followed with photographic documentation until 4 weeks after the last chemotherapy visit. Use of any head cover such as wig, scarves or cap will be documented as “never”, “sometimes”, or “always”. Patients will fill out the quality of life questionnaires including the EORTC-QLQ-BR23 scale and BIS before cycle 4 of chemotherapy, or at the visit that they are considered to have failed because of hair loss.

At the end of the infusion:

Discomforts such as headache, being chilled, and scalp pain will be assessed using a visual analogue scale. Any adverse events will also be reported.

Device use parameters will be reported in the Device Use Log.

8.4 Assessment 4 Weeks (3-6 Week Window) Following The Last Cycle Of Chemotherapy

Evaluation of the last chemotherapy cycle will take place 4 (± 1 week) weeks after the last cycle of chemotherapy. The medical history of the patient and the use of concomitant medication will be reassessed, and a physical examination will be performed. Hair will be photographed by the physician or study personnel. Patients (treatment and control) will be asked to assess their current hair loss by examination of the photograph set using the quantitative Dean scale. Use of any head cover such as wig, scarves or cap will be documented as “never”, “sometimes”, or “always”. Patients will also fill out the quality of life questionnaires including the EORTC-QLQ-BR23 scale and BIS. Control group patients will end participation in the study at this visit.

8.5 Assessments At The Follow-Up Visit 3 (± 2 Weeks) Months After The Completion Of Study Treatment

Vital signs, medical history, physical examination, examination for cutaneous metastases of the scalp will be carried out in the treatment group patients. The use of concomitant medication and any adverse events will be reported. The patient will compare her hair status as compared to baseline in the Hair Re-growth Follow-Up Survey using the quantitative Dean scale. Quality of life questionnaires including EORTC-QLQ-BR23 scale and BIS will be assessed.

Use of any head cover such as wig, scarves or cap will be documented as “never”, “sometimes” or “always”. The impact of hair loss on treatment decision will be evaluated.

8.6 Assessments At The Follow-Up Visit 6 Months (± 2 Weeks) After The Completion Of Study Treatment

Assessment at 6 Months

The use of concomitant medication and any adverse events will be reported. The patient will compare her own hair status as compared to baseline in the Hair Re-growth Follow-Up Survey using the quantitative Dean scale. Quality of life questionnaires including EORTC-QLQ-BR23 scale and Body Image will be assessed.

Use of any head cover such as wig, scarves or cap will be documented as “never”, “sometimes” or “always”.

The presence of any cutaneous metastases of the scalp will be documented.

9. Adverse Events (AE)

An *Adverse Event* is any untoward medical occurrence in a patient treated with an investigational product but which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not associated to the investigational treatment.

9.1 Adverse Device Events (ADE)

An *Adverse Device Event* is any untoward and unintended response to a medical device, including any event resulting from insufficiencies or inadequacies in the instructions for use of the device, and/or any event that is a result of a user error.

All conditions that are pre-existing to treatment with the study device should be recorded on the Medical History section within the patient's Baseline Case Report Form (CRF), Appendix IV.

9.2 Recording Of Adverse Events Any Adverse Device Events

Solicited adverse events/adverse device events will be asked for and will be recorded in the CRF.

Adverse events/adverse device events already documented in the CRF, e.g. at a previous visit, and were classified as "ongoing", should be reviewed at subsequent visits. If resolved or changed severity, this should be documented in the CRF accordingly.

9.3 Assessment Of Severity

The severity of an adverse event/adverse device event will be recorded according to the following guidelines;

0	None	
1	Mild	An event, which is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
2	Moderate	An event, which is sufficiently discomforting to interfere with everyday activities.
3	Severe	An event, which prevents normal everyday activities and requires medical treatment.

9.4 Assessment Of Causality

Causal relationship, if any, to treatment with the investigational product/device should be assessed according to the following categories:

NR	Not related	The event is definitely not causally related to treatment with the investigational product/device.
UL	Unlikely	There are other, more likely causes and treatment with the investigational product/device is not suspected as a cause.
SU	Suspected (<i>reasonable possibility</i>):	A direct cause and effect relationship between the treatment with the investigational product/device and the event has not been demonstrated but there is a reasonable possibility that the event was caused by treatment with the investigational product/device.
PB	Probable	There probably is a direct cause and effect relationship between the event and treatment with the investigational product/device.

9.5 Follow-Up Of Adverse Events And Assessment Of Outcome

The investigator should follow patients with non-serious adverse events, until symptoms resolve or has stabilized and advise the monitor of the final outcome.

The duration in days, or in hours, (if applicable) of the adverse event should be assessed.

The outcome of the adverse event will be assessed as:

- 1 = Resolved
- 2 = Improved
- 3 = Unchanged
- 4 = Worse
- 5 = Fatal
- 6 = Not available

The action taken as a result of the adverse event will be assessed as:

- 1 = None
- 2 = Therapy required
- 3 = Procedure discontinued due to AE
- 4 = Hospitalization required or prolonged

9.6 Unexpected Adverse Event

An “*unexpected*” adverse event is one not identified in nature, severity, or frequency in the Investigator’s Brochure or the product package insert for the investigational product/device.

9.7 Serious Adverse Event

A “*serious*” adverse event is one that results in any of the following:

- fatal (leading to death)
- life threatening, i.e. placing the patient at immediate risk of death in the judgment of the investigator
- permanently disabling or impairing a body structure or a body function
- requiring inpatient hospitalization or prolongation of existing hospitalization
- requiring medical or surgical intervention to prevent permanent impairing a body structure or a body function
- leads to a congenital anomaly or birth defect, fetal distress or fetal death.

9.8 Relationship To Study Intervention

9.8.1 Probably Related

The event occurs within a reasonable time period following the intervention and cannot be reasonably explained by known patient characteristics (including use of concomitant medications) at the associated chemotherapy.

9.8.2 Unknown Relationship

The etiology of the event is not known and the event does not occur within a reasonable time period following the intervention and does not follow a known response pattern for chemotherapy.

9.8.3 Definitely Not Related

The event is known not to be related to the study intervention.

9.9 Foreseeable Investigational Treatment Related Adverse Events

9.9.1 Hypersensitivity Reactions

Allergic reactions or urticaria from contact with silicon are extremely rare, but have been reported in some patients receiving silicone gel breast augmentation. If severe hypersensitivity reactions thought to be due to silicon occur, remove the patient from protocol therapy.

9.9.2 Pain Or Discomfort Reactions

Transient cephalgia, scalp pain, has been reported in patients treated with the DigniCap™ System for systemic cytotoxic chemotherapy. Patients who report pain or discomfort will have all complaints documented and treated symptomatically if thought to not be severe. Treatment interruption will not be indicated unless the patient requires it due to patient reported severe symptoms.

9.9.3 Toxicity Reporting

Toxicity Criteria: Skin toxicity will be determined using the revised NCI Common Toxicity Criteria (CTC) version 4.0 for Toxicity and Adverse Event Reporting.

All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded with details regarding duration, severity of each episode and outcome. The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to investigational product or their clinical significance. The description of the AE will include the onset date, duration, date of resolution, severity, seriousness, etiology, and the likelihood of relationship of the AE to study treatment.

Information regarding AEs will be collected from the time the patient signs the informed consent form up to 30 days after the last dose of investigational product is administered.

9.10 Reporting Adverse Events

9.10.1 Immediate Reporting By Investigator To Sponsor

Any AE considered serious by the Principal Investigator or Sub-investigator or which meets the previous criteria must be entered as an SAE on the adverse event form and communicated to Dignitana AB within one business day (24 hours) from the time that the site personnel first becomes aware of the serious adverse event.

The written SAE report must consist of the Serious Adverse Event Report Form (MEDWATCH) (Appendix XIV) and data not entered in the CRF (e.g. lab reports, ECG reports, etc.). If the patient is hospitalized because of or during the course of an SAE, then a copy of the hospital discharge summary should be faxed to Dignitana AB as soon as it becomes available. Withdrawal from the study and all therapeutic measures will be at the discretion of the Principal Investigator or Sub-investigator. All reported SAEs (related or not to the investigational product) will be followed until satisfactory resolution or until the Principal Investigator or Sub-investigator deems the event to be chronic or the patient to be stable.

This will be documented on a MEDWATCH form (Appendix XIV). The form must be completed and supplied to Dignitana AB within 24 hours/one business day at the latest on the following working day. The initial report must be as complete as possible, including details of

the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational intervention.

9.10.2 Non Expedited Reporting

In the event of any other types of events not requiring expedited reporting, the investigator will notify Dignitana AB within 7 business days. If at any time that the events noted in this category changes (i.e. is upgraded), the investigator should notify Dignitana AB accordingly as noted in the section above.

9.10.3 Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA and GCP safety reporting requirements. All adverse experience reports must include the patient number, age, sex, severity of reaction (mild, moderate, severe), relationship to study intervention (probably related, unknown relationship, definitely not related), date and time of administration of intervention and all concomitant medications, and medical treatment provided. The investigator will record this information on the MEDWATCH form (Appendix XIV) and will provide reports of adverse experiences on a regular basis during the study. The investigator is responsible for evaluating all adverse events to determine whether criteria for “serious” and “unexpected” as defined above are present. The investigator is responsible for reporting adverse events to Dignitana AB as described under “Immediate reporting by investigator to sponsor” and “Non Expedited Reporting” above.

Dignitana AB’s business fax number is: 46(0)46 16 30 99 and business telephone number is 46(0)46 16 30 90.

The Address of Dignitana is:

DIGNITANA AB

Ruben Rausings Gata 9, SE-223 55 Lund

PO Box 240 22, SE-224 21 Lund Sweden

9.10.4 Sponsor Reporting Responsibilities

Dignitana AB will report to FDA without any delay.

9.10.5 Deviations From The CIP And/Or Amendments

Any deviation from the CIP and/or amendments must be reported to Dignitana and will be reviewed by Dignitana AB and principle investigators.

9.11 Data Safety Monitoring Board

The Data Safety Monitoring Board will be constituted by charter to review safety and to assess the interim analysis of the concurrent control group.

10. PATIENT EVALUATION CRITERIA

10.1 Criteria For Response Assessment

Criteria for grading of alopecia will be assessed using the Dean scale [22].

- Grade 0: no hair loss
- Grade 1: up to 25% hair loss
- Grade 2: between 25 and 50% hair loss
- Grade 3: between 50 and 75%
- Grade 4: greater than 75% hair loss

Quantitative Grade 0-2 will be considered adequate protection from alopecia. Grade 3 and 4 will be considered study treatment failure.

10.2 Endpoint Variables

10.2.1 Alopecia Report Assessment by the Patient

Hair loss will be assessed by the patient review of digital photographs taken of their hair/scalps at baseline, at each chemotherapy visit, and 4 weeks (3-6 weeks window) after the last chemotherapy treatment. The photographs will include 5 views and will be graded by the quantitative Dean scale as above (Appendix VIII). A Dean score of 4 at any evaluation will be considered essentially complete hair loss and the patient will not have additional photographs.

The patient will also complete the Alopecia Self Report, Appendix VIII.

10.2.2 Adverse Events Related to Use of the Dignicap™ System

Adverse events related to use of the DigniCap™ System are to be reported by the patient using the Symptoms Survey, Appendix IX.

The scalp of the patient will be thoroughly examined by the physician prior to each chemotherapy session, at one month after completion of chemotherapy, and at the follow-up visits at 3 and 6 months after completion of treatment using the corresponding CRFs.

10.2.3 Quality Of Life in Women Using the Dignicap™ System

Quality of Life measured by the EORTC-QLQ-BR23 scale and BIS at Baseline, Cycle 4 of chemotherapy and 4 weeks after the last cycle of chemotherapy.

10.2.4 Hair Re-Growth

Hair re-growth will be evaluated at the Month 3 and 6 visits. Information regarding quality of treatment response defined as patient reported grading of quality of hair in terms of texture, manageability, and color variation from baseline will be collected.

10.2.5 Impact of Hair Loss on Treatment Decisions

Information regarding the perceived impact of hair loss on treatment decisions will be collected at baseline and 3 months after completion of chemotherapy.

10.3 Criteria and Procedures for Withdrawal from Protocol Treatment

Patients may withdraw from this study under the following conditions:

- The patient withdraws consent to participate in the study.
- The investigator feels that it is in the best interest of the patient.
- During study treatment patient experiences severe hypersensitivity reaction due to silicon.
- During study treatment patient reports severe symptoms of cephalgia or of severe pain/discomfort.
- The patient has a serious or life-threatening adverse event.
- Disease Progression: In the event of documented disease progression, significant clinical decline resulting in discontinuation or prolonged treatment which effect alopecia the patient will be withdrawn.
- The patient develops scalp metastases during the chemotherapy treatment.

Any patients who elect to discontinue use of the cap prior to completing their prescribed chemotherapy regimen will be considered to have entered study follow-up at the time of stopping cap use. They will have hair/scalp photographs taken and will complete surveys according to the protocol-mandated follow-up schedule. If study consent is withdrawn, patients will be monitored for potential device-associated Serious Adverse Events (SAEs) for 30 days following treatment.

10.3.1 Hypersensitivity Reactions

Allergic reactions or urticaria from contact with silicon are extremely rare, but have been reported in some patients receiving silicone gel breast augmentation. If severe hypersensitivity reactions thought to be due to silicon occur, remove the patient from protocol therapy.

10.3.2 Pain or Discomfort Reactions

Transient cephalgia, scalp pain, has been reported in patients treated with the DigniCap™ system for systemic cytotoxic chemotherapy. Patients who report pain or discomfort will have all complaints documented and treated symptomatically if thought to not be severe. Treatment interruption will not be indicated unless the patient requires it due to patient reported severe symptoms.

10.4 Early Termination or Suspension of the Investigation

See section 12.4.

11. DEVICE RISK ANALYSIS AND RISK ASSESSMENT

List of hazards (see Appendix XXVI).

12. DATA quality

12.1 Original Data

Original data, also known as source data/records, are those data elements that represent the first recording of study data. Original data contain all the information that is necessary for the reconstruction and evaluation of the study. Examples of original data are 1) subject's information used in a clinical trial whether collected on paper or electronically at the time of the subject's visit, 2) certified copies of original records, 3) observations, and 4) laboratory data from clinical laboratories. Clinical investigators maintain control over source data from inception and until the end of the regulatory retention period. The Investigator must permit access to these data during sponsor monitoring visits, audits, IRB reviews and regulatory inspections.

In addition to original records maintained by the clinical site as part of their standard practices of patient care, this study will use direct data entry of clinical trial data into the Target e*CRF[®] (EDC) system, using the Target e*CTR[™] (Target e*Clinical Trial Record) process. This process enables clinical study site personnel to perform data entry of original data directly into Target e*CRF[®] at the time of the subject's office visit. This process stores the original data, along with transcribed data, in PDF format in the Target e*CTR data repository, access to which is controlled by the clinical Investigator. Authorized users can review these PDF documents using the Target e*CTR Viewer. In this data flow, the system stores all of the entered data first in the Target e*CTR repository (as PDF documents) before transmitting them to the Target e*CRF[®] database. At any point during the study or after completion of the study, each site can generate, or the system host will provide them with, an electronic file containing all of the records and audit trail, in PDF format, for all subjects at their site.

12.2 Target e*CRF[®] (Electronic Data Capture)

Personnel at the investigative site will enter all required clinical trial data into Target e*CRF[®], a validated 21 CFR Part 11 compliant Internet-based EDC system. Site personnel similarly manage all changes to the clinical trial data, through the EDC system's change management functionality that is subject to a full audit trail.

Target Health personnel will train investigator and site staff on the use of Target e*CRF[®] prior to enrollment of the first subject. Target Health maintains a list of authorized users and grants role-based access to the EDC system only after ensuring that site personnel have received system training. Target Health restricts access to the e*CRF database only to authorized personnel.

At the end of the study, the clinical investigator or authorized sub-investigator electronically signs the completed online eCRF. A certification must be obtained from all authorized persons in order to sign electronically, indicating that their electronic signature is equivalent to their hand-written signature. In order to sign electronically, the signer must log in with his or her username and password and then reenter this password on the page(s) requiring a signature(s). At the end of the trial, Target Health will provide each site with an electronic file containing all of the eCRF records for all subjects at their site.

12.3 Target e*CTR[®] Viewer (Target e*Clinical Trial Record Viewer)

Target e*CTR Viewer is a validated 21 CFR Part 11 compliant Internet-based software system. The PDF documents, representing both original and transcribed subject data, reside in a read-only environment. Authorized personnel at the investigative site control users' access to the Target e*CTR[®] Viewer. The Investigator can download a bookmarked PDF copy of records of individual subjects or all subjects at his/her site, including an audit trail of changes and electronic signatures. At the end of the study, the system host will provide each investigator with an electronic file containing all of the records and audit trail for all subjects at his/her site. Target Health personnel will train investigator and site staff on the use of Target e*CTR prior to enrollment of the first subject.

12.4 Certified Copies of Original Data

In the event that site personnel find that they are unable to perform direct data entry at the time of the study visit, they will record original data using paper records or equivalent media. Certified copies of these original data can be created, for example, by creating an exact copy of a paper record by scanning the paper or taking a photograph and storing it electronically. In order to do this, each site must have an SOP supporting this process. These scanned documents must be available to Target Health personnel during monitoring visits and during regulatory review.

12.5 Quality by Design (QbD)

12.5.1 Data Management

Target Health Data Management personnel create the data management plan (DMP) to specify data management activities for the study. The following summarizes the DMP:

Target Health hosts and manages the clinical database (i.e., Target e*CRF EDC system) during the lifetime of the study. At the conclusion of the study, Target Health provides a database extract to the sponsor for analysis and reporting to regulatory authorities. Target e*CRF will be used for online edit checks, batch edit checks and query management. Sponsor or authorized representatives capture the EDC specifications in an Application Setup Instructions (ASI) document. The ASI document contains the specific instructions for both the EDC development and data management (DM) staff.

The Data Validation Plan (DVP) provides specifications for the edit-checks. Within the DVP, there are three types of automated validation checks:

- Online edit-checks – Performed by the EDC system during data entry. Target Health personnel are responsible for programming and resolving any hits based on these checks.
- Batch edit-checks – Target Health personnel are responsible for programming and resolving any hits based on these checks.
- Manual checks – Performed by the monitor and data manager (DM). The DM is responsible for providing the listings if used by the monitors for manual checks.

Monitors manage queries within the Target e*CRF[®] application. Authorized site personnel (e.g., study coordinator) respond to and resolve queries. All changes to the database require a “Reason for Change” and are subject to an audit trail. The audit trail identifies the changed data,

reason(s) for change, who changed the data and the time and date of the change (based on the Target e*CRF[®] server's time).

EDC management reports are also available to view the data for consistency. Standard reports include:

- Overall Data Entry Status (By Site/Subject)
- Investigator Signature Status (By Site/Subject)
- Query Age Report (by Site)
- Query Report (by Site/Subject)
- Query Frequency by Site
- Query Frequency by Edit Check
- Query Frequency by Form
- Subject Visit Status Report (by Site / Subject)
- AE Report (By Site/Subject)
- Concomitant Medication Report (By Site/Subject)
- Serious AE Report (by Site/Subject)
- Subject Status Report (by Site)
- Protocol Violation Report (by Site / Subject)
- Treated (by Site / Subject)
- Subject Tracking Report (Individual)

Monitors and reviewers can request and specify changes to existing reports as well as additional management reports during the course of the study. Management of these requests fall under Change Control SOPs.

12.5.2 Centralized Monitoring

Study monitors carry out centralized (i.e., remote) monitoring of entered data daily or at an agreed-upon frequency, as defined in the Clinical Data Monitoring Plan (CDMoP). The following are samples of reports that assist in the centralized monitoring process. Study specific reports are found in Target e*CRF.

1. Time from subject visit to data entry
2. Online edit checks
3. Batch edit checks
4. Data listings

At the QbD meetings, monitoring findings are discussed. Clinical research and DM personnel meet to review and discuss data quality and data management issues, and capture relevant observations and decisions in meeting minutes. When necessary, the DMP and CDMoP are revised and corrective actions are implemented.

12.6 Record Retention

All study records will be retained for a period of time defined by the regulatory authority for the country in which the investigation is conducted. In general, this period is at least 2 years following the date on which the drug receives regulatory approval. In other situations (e.g., where the investigation is not in support of or as part of an application for a research or marketing permit), the retention period is 2 years following the date on which the entire clinical program is completed, terminated or discontinued, or the investigational application under which the investigation is being conducted is terminated or withdrawn by the regulatory authorities.

In the event the Investigator retires, relocates or for any other reason withdraws from the responsibility for maintaining records for the time period required, custody of the records may be transferred to any other person who will accept responsibility for the records. Notice of such a transfer must be given in writing to the sponsor. The Investigator must contact the sponsor prior to disposal of any records related to this study.

12.7 Confidentiality of Subject Data

The Investigator will preserve the confidentiality of the subjects' data. CRFs and other documents submitted to the sponsor will reference subjects only by an anonymized subject ID, which uniquely identifies the subject in the context of the study. The Investigator will maintain documents not meant for submission to the sponsor, e.g., the confidential subject identification code and the signed informed consent forms, in strict confidence. All data are subject to monitoring, audits and inspection.

12.8 Clinical Data Monitoring Plan (CDMoP)

The CDMoP identifies the monitoring schedule and the rationale for the frequency and type of monitoring visits. Since this study is using Direct Data Entry (DDE), in addition to agreed-upon source data verification (SDV), on-site monitoring visits will be limited to: assuring that the sites understand and are following the protocol, are adequately monitoring subject safety, and are managing the drug supply. The CDMoP also provides details with regard to the use of risk-based monitoring and source document verification. If the monitor is not allowed access to any e-source records during source document verification, certified printouts provided by sites can be used. In addition to on-site monitoring, monitors will perform central (i.e., remote) monitoring, electronically reviewing data in near real-time.

Communication	Timeframe
Site initiation visit (SIV)	All sites will have a SIV. The investigator meeting may serve as the SIV.
First on-site monitoring visit	See CDMoP.
Interim monitoring visits (IMV)	As specified in the CDMoP
Closeout visit (COV)	All sites must have a COV. Non-enrolling sites may have a COV over the telephone as permitted by the sponsor.

Communication	Timeframe
Site Update and Monitoring Calls	Monitors will contact sites as needed via email or telephone, based on review of site activity and the quality of data entry.
Teleconferences between the sites and CRO	Monitors will schedule teleconferences as appropriate to discuss the overall study status and to discuss study-wide related issues.
Initiation, Monitoring and Closeout Visit Reports	<p>Interim monitoring visits can be performed on-site or online. On-site visits are preceded by a confirmation letter sent to the site. The confirmation letter must outline the date, time and purpose of the monitoring visit</p> <p>Monitors will route all online Qualification, Monitoring and Closeout Visit Reports for signature to their supervisor(s). The supervisor will review the report and enter comments if needed.</p> <p>Following the completion of an on-site monitoring visit report, the monitor provides feedback to the site, identifying any outstanding issues from the visit.</p>
Study updates, Protocol Amendments, etc.	Will be forwarded to sites during study.
Adverse Events (AE) and Serious Adverse Events (SAE)	The primary method for reporting the event consists of entering data into the AE and Pharmacovigilance forms in Target e*CRF [®] .

12.9 Site Qualification Visit

Sites will undergo a qualification visit prior to the site initiation visit. The qualification of the site must include:

- The experience of the site personnel
- Availability of the population under investigation
- The suitability of the site facilities and equipment
- The suitability of the site for IMP storage
- Assurance that site personnel are not on the FDA debarment list

Sponsor or Target Health may waive the qualification visit if the study site has been previously qualified within a 12-month period of the site initiation visit for the same or similar indication. The Project Manager will document any such waivers in the project file (eTMF). Acceptable forms of documentation of previous qualification include previous approved site qualification reports from THI or similar documentation from the sponsor or their representatives.

12.10 Site Initiation Visit

The purpose of the study initiation visit is to train Investigators and site personnel on the specific requirements and procedures needed to satisfy the study protocol. This training may occur at the

Investigator site, during a joint Investigator Meeting, or via Internet-based training or teleconference.

The site initiation visit will include the following elements:

- Review of the protocol
- Review of the IMP handling procedures
- Training of appropriate staff on GCP regulations (including SAE reporting requirements)
- Training of the Investigator on the Investigator responsibilities listed on the FDA Form 1572
- Training of appropriate staff on maintenance of the Trial Master File in Target Document
- Training of appropriate staff on eCRF completion and expectations
- Training on eSource and access to the Target e*CTR Viewer

Task	Protocol-Specific Requirements
Prior to the site initiation visit, the following documents should be collected and uploaded into the Target Document electronic Trial Master File (TMF)	<ol style="list-style-type: none"> 1. Signed Confidentiality Agreement (CDA) 2. Mutually signed Clinical Trial Agreement (CTA) 3. Signed Statement of Investigator (Form 1572) 4. CV's of the Investigator and sub-Investigators (including current medical licenses). 5. Disclosure of Financial Interests and Financial Arrangements of staff listed on the 1572 (Form 3455). 6. IRB approval letter of protocol and Informed Consent Form
At the time of the site initiation visit, the following items will be available for the site personnel	<ol style="list-style-type: none"> 1. Personnel Signature Logs 2. Documentation of sponsor personnel participating in on-site visits 3. Training Records (GCP, protocol training)

12.11 First On-Site Monitoring Visit

During the first on-site monitoring visit, monitors will check:

- Adherence to the study protocol, with special focus on subject eligibility, IMP management and titration-related activities
- Informed consent process
- Medical histories and protocol eligibility, and verify transcription into Target e*CRF
- Drug accountability and storage
- SDV of paper source of questionnaires (if applicable) and verify transcription into Target e*CRF®
- Outstanding questions or issues with Investigator and study coordinator

12.12 Interim Monitoring

Monitoring of the clinical trial will occur both by on-site visits as well as by central (i.e., remote or in-house) review of eCRF forms, data management reports and the electronic Trial Master

File (eTMF). Monitors document the results of their monitoring assessments, both on-site and central, via online monitoring report functionality integrated into the EDC (eCRF) system.

The purpose of interim monitoring is to ensure protection of the rights and well-being of each subject, that the site understands and is following the protocol, that trial data are accurate, complete and verifiable, that the site is following ICH GCP guidelines, and that the trial site and staff remain qualified.

Interim monitoring activities typically include:

- Review of study and enrollment status (on-site or central)
- Review of consent forms, source documents and the eCRFs (on-site only)
- Review of study conduct and protocol adherence (on-site or central)
- Review of adverse events and that all Serious Adverse Events have been accurately been reported to the sponsor and IRB (on-site or central)
- Review of IRB approval and essential documents (on-site or central)
- IMP documentation and reconciliation (on-site only)
- Review of facility, personnel and delegation (on-site only)
- Personnel Signature Logs and delegation of authority (on-site only)
- Training Records (on-site only)
- Follow-up of outstanding issues (on-site or central)
- Documentation of sponsor personnel participating in on-site visits (on-site only)

When findings indicate that retraining is required, this must occur within 3 working days and if necessary the site will be informed not to enroll additional subjects until successful completion of the training.

It is the responsibility of the monitor to inform his/her supervisor of any issues that suggest the need for increased scrutiny across sites. The project manager will coordinate cross-site review and remediation, where warranted, to avoid or minimize repetition of the behaviors that led to the findings. Online management reports will support these cross-site reviews. These reports and all entered eCRF forms must be reviewed daily at the beginning of the study, defined as the first visit of the first subject, and corrective action reports generated as appropriate. It is critical that monitors document and share all findings that have an impact on the sites and study performance with the project manager and other study monitors.

Initially, the project manager will schedule Quality by Design meetings weekly, to review monitoring procedures and study progress. Based on findings from these meetings, the project manager will adjust the frequency of the meetings as appropriate. As well, the findings will drive remediation efforts as warranted. The project manager will document the results of each meeting and the decisions and the rationale for changing any of the procedures in the Quality by Design report.

The Monitor must immediately inform the Clinical Project Manager if he/she suspects fraud/misconduct at the site. The Clinical Project Manager will notify the sponsor of suspected fraud/misconduct and will propose an investigational action plan for approval by the sponsor.

12.13 Site Closeout

The purpose of the closeout visit is to bring to official completion all trial-related activities at the site.

During the visit, the monitor performs the following:

- Final resolution of outstanding data queries and verification of completeness of eCRFs.
- Final review for completeness of the eTMF.
- Reconciliation and disposition of the IMP.
- Review with the PI notification to the IRB that the study is closed. The correspondence should include the number of subjects enrolled, discontinued, and completed.
- Review with the site personnel the document retention requirements.

12.14 Audits

The Investigator will make all trial-related source data and records available at any time to a quality assurance auditor mandated by the sponsor or to domestic/foreign regulatory inspectors or representatives from IECs, who will audit/inspect the trial..

13. STATISTICAL CONSIDERATIONS

13.1 Objectives

This study is designed to assess the ability of scalp hypothermia using the DigniCap™ System to prevent chemotherapy induced alopecia. ‘Activity’ will be quantified using alopecia grading scales as described above, which will be used to define the proportion of responders among all evaluable patients. The primary goal of this study is to assess the efficacy of this system. To assess efficacy, the primary endpoint will be grade of alopecia 1 month after the last chemotherapy treatment as assessed by the patient with photographic documentation (digital photos), comparing current hair loss versus baseline.

Comparisons of the primary endpoint will be made with a concurrent non-randomized control group and also with a pre-defined level of clinical efficacy.

A secondary objective is to examine the safety of the system, in terms of adverse symptoms and adverse device effects reported by patients during use of the DigniCap™ System and during the follow-up period 3 and 6 months after completion of treatment will be examined.

The secondary endpoints also include tolerability of the DigniCap™ System, quality/quantity of hair re-growth at follow-up visits at 3 and 6 months, quality of life measures assessed using the EORTC-QLQ-BR23 scale and BIS during chemotherapy and follow-up visits, the 5-level Dean score measured on a continuous scale and the impact of hair loss on treatment decisions assessed at follow up using a 4-level ordered categorical measure. These secondary outcomes will be evaluated in all patients, whether or not they are evaluable for response.

13.2 Statistical Hypothesis and Model

The primary goal of this study is determine the success rate for the DigniCap™ System in preventing hair loss among patients. A success has been determined to be when the patient grades her hair status as Grade 0-2 (Dean Scale) 4 weeks after the last chemotherapy visit. Any Dean score of 4 during the chemotherapy visits or a score of 3 or 4 at the visit 4 weeks after the last chemotherapy will be considered a failure. To assess efficacy, the primary endpoint will be the grade of alopecia 4 weeks after the last chemotherapy treatment as assessed by the patient with photographic documentation (digital photos) compared to standardized photographs.

The product will be considered a useful device if the success rate is shown to be greater than the control group rate and also is greater than 50% 4 weeks after the last chemotherapy visit whereas if the success rate for the device is shown to not be greater than the control group rate or is shown to be less than or equal to 50% then the device will be considered ineffective. As described above, a success is defined by the patient grading her hair status as Grade 0-2 4 weeks after the last chemotherapy visit. The proportion of success in preventing hair loss among all treated patients who complete their chemotherapy treatment is the primary endpoint for evaluation of the device. We now describe our two hypotheses for primary efficacy. The first is defined as:

Null hypothesis (H₀): $P_{\text{control}}=P_{\text{treatment}}$

Alternative Hypothesis (H₁) $P_{\text{control}}\neq P_{\text{treatment}}$

A Fisher's Exact test will be used to test whether the two groups have equal proportions or not.

Since there is a high expectation that the patients in the control arm will experience a high level of failure (i.e. high amount of hair loss) there will be an early interim analysis performed to determine whether the full sample of patients in the control arm need to be included. This interim analysis will occur after 15 patients are enrolled. If 12 or more out of the first 15 control patients have a Dean score of 4 (greater than 75% hair loss at any chemotherapy treatment then the control arm will stop recruitment. However, if less than 12 out of the first 15 patients show hair loss then the remaining 15 patients (for a total of 30) will be enrolled.

Our second hypothesis for the primary efficacy is defined using only the patients in the treatment arm. It is important to distinguish between the language of the statistical hypothesis which will be used to establish a statistical test to determine efficacy and the clinical hypothesis which is linked to the threshold for efficacy that exists for the clinical realm. With this in mind the "clinical" hypothesis is that the observed success rate of the device must exceed 50% in order to be clinically effective. The "statistical" hypothesis is that in addition to the observed success rate being over 50% the lower bound of a 95% confidence interval for the observed success rate must exceed 40%. Thus, we can state this statistical hypothesis using 40% as the Null Hypothesis value since that is the success rate that we must rule out. Thus the hypotheses can be written as:

Null hypothesis (H0): $P \leq p_0$ (40%); The success rate that we wish to statistically rule out, and

Alternative Hypothesis (H1): $P > p_1$ (40%); A success rate of greater than 40% which we consider to be evidence that the device is clinically useful if the observed success rate also exceeds 50%..

A chi-square will be used to test the significance of the study results. In addition to performing this hypothesis test, a two-sided 95% confidence interval for the success rate will be calculated.

13.3 Sample Size and Power Estimation

This is a two-arm open label PMA study. For the comparison with the non-randomized control group there will be either 15 (if stopped at interim analysis) or 30 control patients and 110 treated patients. After accounting for a 10% drop out rate, we expect a total of 100 evaluable patients in the treatment arm.

Using a Fisher's exact test to compare the control arm to the treated arm, with a type 1 error rate of 5% (2-sided test) we will have 90% power to detect the difference between the Control group proportion of 20% (or less) and the treated group proportion of 66% (or greater) when the sample sizes are 15 and 100, respectively. If we do not stop the control arm after the first 15 patients then there is 93% power to detect the difference between the Control group proportion of 20% (or less) and the treated group proportion of 56% (or greater) when the sample sizes are 30 and 100, respectively.

For the comparison within the treated group only, using a one group chi-square test for proportions, with type I error of 5% (2-sided), for a sample size of 100 patients, there is 92% power to detect the difference between the null hypothesis proportion of less than 40% versus an alternative proportion of 56% (or greater). For the evaluable population (n=100), there is 90%

power to detect the difference between the null hypothesis proportion of less than 40% versus an alternative proportion of 56%. In other words, there is ample power to reject the null hypothesis that the success rate is 40% with a sample size of 110 patients (100 evaluable) if we assume that the expected proportion of patients that will be successes under the alternative hypothesis is 56% (or more). The rejection of the null hypothesis will be sufficient to rule out the possibility that the true success rate is 40% or less.

13.4 Interim Analysis and Stopping Rules

The study device has shown very promising results from large number of patients in previous trials overseas. Although we don't expect any serious adverse safety concerns in this study, a DSMB will meet every 6 months to review all safety data. If issues arise, then the DSMB can recommend changing consent/protocol or even suspending/stopping the trial. In addition, the DSMB will examine the control participant data after the first 15 patients are enrolled and if they find that 12 or more of the first 15 patients lose more than 75% of their hair then this arm will discontinue enrolment.

13.5 Handling of Missing Values/Discontinuations

Since this study is not a randomized trial, imputing "failures" into all women who drop out of the study regardless of the reason would be too conservative and likely give a biased estimate of the true failure rate of the device. Therefore, we propose the following plan for the primary analysis. All patients who drop out due to not completing the full prescribed chemotherapy cycles due to any reason such as toxicity of the chemotherapy will be excluded from the primary efficacy analysis. However, patients with missing endpoint assessment or who drop for any other reason such as toxicity or intolerability of the cap or hair loss will be considered as evaluable patients and "failures" for the primary efficacy analysis. We will recruit patients until the number of evaluable patients reaches the target (n=100) determined in the power/sample size calculation.

In addition to this primary efficacy analysis based on evaluable patients, we will perform a sensitivity analysis where we examine two different methods. The first will be an analysis where all patients that drop-out of the study (for any reason) will be considered as "failures" in the efficacy analysis. The second will be an analysis where only patients who complete the full series of measurements and adhere to the protocol are included in the efficacy analysis.

13.6 Analysis

Descriptive statistics (means, standard deviations, frequencies, etc.) will be presented for pretreatment patient characteristics and the outcome measures mentioned by treatment group. Tables, graphs, and charts will be used to illustrate the data when appropriate. Each of the outcomes mentioned above will be analyzed and reported separately. The primary outcome analysis will be performed using a Fisher's exact test to compare the treated and control groups based on the above definitions of success and failure. Next, a one-sample Chi-square test will be performed to test the treated group alone to rule out a lower bound of success of 40%. In addition, a 95% confidence interval will be constructed for the success rate in the treated group and the lower bound of this interval should exceed 40% while the observed success rate also exceeds 50%. Toxicity reports listing the incidence of all reported toxicities will be generated. All patients registered will be used for toxicity reports whether or not they are evaluable for

efficacy response. Any Grade 4 or 5 toxicities will be reported to the Institutional Review Boards/Ethics Committee responsible for oversight of the study at the investigator's institution.

The secondary endpoints will be reported with descriptive statistics (means, medians, and measures of variability, including 95% confidence intervals for continuous measures and counts and percents, with corresponding 95% confidence intervals for categorical variables):

1. Tolerability defined as the percentage of patients who complete all planned cycles of chemotherapy using the DigniCap™ System.
2. Assessment of hair loss by patient using the quantitative Dean scale.
3. Assessment of hair re-growth at the 3 and 6 month follow-up visits compared to hair status after completion of chemotherapy, by a three person independent panel. Hair re-growth is defined an improvement in the Dean scale by at least one level.
4. Assessment of hair regrowth by the patient using the Hair Regrowth Follow Up Survey.
5. Assessment of Quality of life during and after treatment with the DigniCap™ System by the patients using the EORTC-QLQ-BR23 scale and BIS.
6. Assessment of the impact of hair loss on treatment decisions in patients offered therapy with the DigniCap™ System at the follow up visit 3 months after completion of treatment.
7. Assessment of quality of treatment response in terms of quality/ quantity of hair re-growth from baseline during follow-up period 3, 6, and 12 months after completion of treatment. Patients will grade the hair in terms of texture, manageability and color variation from baseline.
8. Assessment of the scalp for the occurrence of scalp metastases at 3 and 6 months.

All toxicities experienced will be documented.

14. PUBLICATION POLICY

The investigators are free to decide about publication of the study results in oral presentations at meetings, posters or full journal articles but are expected to give Dignitana AB a minimum of two weeks to comment on drafts.

15. SPONSOR

Dignitana AB is the sponsor of the study.

16. CONFIDENTIALITY

All study data is identified via codes and patient information is confidential and not traceable without the code key.

17. REFERENCES

General References

ICH/GCP

Declaration of Helsinki, latest version.

EN ISO 14155-1:2003, Clinical investigation of medical devices for human subjects – Part 1: General requirements.

EN ISO 14155-2:2003, Clinical investigation of medical devices for human subjects – Part 2: Clinical investigation plans.

FDA 21cfr PART 812.25.

Works Cited

1. Batchelor D. Hair and cancer chemotherapy: consequences and nursing care-a literature study. *Eur J Cancer Care* 2001; 10:147-63.
2. Mulders M, Vigerhoets A, Breed W. The impact of cancer and chemotherapy: Perceptual similarities and differences between cancer patients, nurses and physicians. *Eur J Oncol Nursing* 2008; 12:97-102.
3. Prevezas, C, Matard, B, Pinguier L, Reygagne, P. Irreversible and severe alopecia following docetaxel or paclitaxel cytotoxic therapy for breast cancer. *Br J Dermatol* 2009; 160:883-885.
4. Trüeb RM. Chemotherapy-Induced Alopecia. *Semin Cutan Med Surg* 2009 March; 28 (1): 11-14 *Hair and Nail Disorders*.
5. Medical Specialties of California (MSC) website. Penguin cold cap therapy, stopping chemotherapy induced alopecia. Retrieved February 14, 2012, from <http://www.msc-worldwide.com/indexusa.html>.
6. Paxman Coolers [Database on the Internet] www.paxman-coolers.co.uk.
7. Komen M.M.C, Smorenburg, C.H., van den Hurk C.J.G., en Nortier, J.W.R. (Hans). Hoofdhuidkoeling tegen alopecia door chemotherapie. *Ned Tidschr Geneeskd*. 2011; 155: 2053-7 (article in Dutch).
8. Grevelman and Breed. Prevention of chemotherapy-induced hair loss by scalp cooling. *Ann Oncol*. 2005 Mar;16(3):352-8.
9. Breed WPM, van den Hurk Corina JG, Peerbooms M. Presentation, impact and prevention of chemotherapy-induced hair loss: scalp cooling potentials and limitations. *Expert Rev Dermatol*. 2011; 6(1):109-25.
10. Hendriks M.A.E. et al. Evaluation of Cohens Cross-Section Trichometer for Measuring Hair Quantity. *Dermatol. Surg*. 2012; 1-4.

11. Poder T., Hez J., Lemieux R. Efficacité du casque réfrigéren Chimiothérapie. Bull Cancer. 2011; 98: 1119-28.
12. Lundgren-Eriksson L, Edbom G, Olofsson Y et al. Total prevention of taxoid-induced alopecia by a new model of cold cap (Dignitana). Eur J Cancer 1999; 35 (Suppl 4): 376.
13. Henriksen T, Jensen BK. Advanced computerized cold cap for preventing chemotherapy – induced alopecia. Herlev hospital, University of Copenhagen, Abstract and scientific poster ECCO 12. Sept 21-25 2003.
14. Ridderheim M, Bjurberg M, Gustavsson A. Scalp hypothermia to prevent chemotherapy induced alopecia is effective and safe: a pilot study of new digitized scalp-cooling system used in 74 patients Support Care Cancer 2003; 11:371-7.
15. Byahov M, Shevelev O. Alopecia prevention in chemotherapy patients. Method of controlled scalp cooling. Presentation at All-Russian Convention of Oncologists 2006. Published in Meditsinskaya Cartoteka, 2006.
16. Kato M , Sakuyama A., Imai R., Kobayashi TK. Evaluation of DigniCap System for the prevention of chemotherapy-induced hair loss in breast cancer patients. 12th St. Gallen International Breast Cancer Conference, 2011 (Poster Nb P330).
17. Abramov M., Semenova I. Cooling of the Scalp to prevent anticancer chemotherapy-induced alopecia. Eur J Cancer. 2011; 47 (suppl 1): S321 (abstract 4245).
18. Clinical Evaluation Report (Dignitana document) May 2012.
19. Dignitana AB Post Market Surveillance Report 2001-Aug. 2011. November 2011.
20. Breed WP. What is wrong with the 30-year-old practice of scalp cooling for the prevention of chemotherapy-induced hair loss? Support Care Cancer 2004; 12:3–5.
21. Lemieux J et al., [Incidence of scalp metastases in breast cancer: A retrospective cohort study in women who were offered scalp cooling](#). Breast Cancer Res Treat. 2009 Dec: 118(3): 547-52. Epub 2009 Feb 25.
22. Dean JC, Griffith KS, Cetas TC et al. Scalp hypothermia: a comparison of ice packs and the Kold Kap in the prevention of doxorubicin-induced alopecia. J Clin Oncol 1983; 1:33-7.
23. Rugo HS and Melin SA. Expert Statement on: Scalp Cooling with Adjuvant/ Neoadjuvant Chemotherapy for Breast Cancer and the Risk for Scalp Metastases. Feb 2012.
24. Van den Hurk C, Mols F, Vingerhoets J et al., Impact of alopecia and scalp cooling on the well-being of breast cancer patients. Psycho oncology. 2010 Jul:19(7):701-9
25. Camp-Sorrell D (1991) Scalp hypothermia devices: current status. ONS News 6:1–5
26. Bloomberg. Lisbon on Gel Cap That Prevents Hair Loss. Retrieved May 29, 2012, from <http://www.bloomberg.com/video/66131544/>.

27. Braff, D (2012, January 4). Cold caps show promise in keeping hair through chemo. Retrieved May 29, 2012, from <http://www.chicagotribune.com/health/sc-health-0104-chemo-cap-20120104,0,5128904.story>.
28. Ivanhoe Newswire (2011, December 26). Chemo Cold Cap: Cancer Patients Keep Their Hair. Retrieved May 29, 2012, from <http://www.newschannel5.com/story/16393701/chemo-cold-cap-cancer-patients-keep-their-hair>.
29. Aleccia, J (2010, December 20). Cold caps may help cancer patients keep their hair. Retrieved May 29, 2012, from <http://on.msnbc.com/hv3CdI>.
30. University of California – San Francisco (2010, December 14). UCSF physicians evaluate devices that could reduce hair loss in breast cancer patients undergoing chemotherapy. Retrieved May 29, 2012, from <http://bit.ly/fxvGvK>.
31. Dance, A (2010, December 27). Cooling caps tested to help cancer patients keep hair. Retrieved May 29, 2012, from <http://lat.ms/gESCzc>.
32. Johnson, C (2010, December 6). Cooling cap offers hope for chemo patients. Retrieved May 29, 2012, from <http://bit.ly/hJR8Ph>.
33. Zalkin, M (2010, October 28) Cold Cap Therapy May Help Women Undergoing Chemotherapy Keep Hair. Retrieved May 29, 2012, from <http://abcn.ws/cLg5Oi>.
34. Gregory, KL (2011, November 24). Cold Caps Aim to Preserve Hair for Cancer Patients. Retrieved February 21, 2012, from <http://m.vcstar.com/news/2011/nov/24/cold-caps-aim-to-preserve-hair-for-cancer/>.
35. Rapunzel Project website. The Rapunzel project. Retrieved February 14, 2012, from <http://www.rapunzelproject.org/>.
36. Weiss, S (2011, January 11). Breast cancer patient uses super-chilled headgear to try to retain her hair. Washington Post. Retrieved February 14, 2012, from http://www.washingtonpost.com/wp-dyn/content/article/2011/01/10/AR2011011006036.html?tid=wp_ipad.
37. Zalkin, M (2010, October 28). Cold Cap Therapy May Help Women Undergoing Chemotherapy Keep Hair. Retrieved February 21, 2012, from <http://abcnews.go.com/Health/OnCallPlus/cold-cap-therapy-women-chemotherapy-hair/story?id=11985624>.
38. Wills S, Ravipati A, Nguyen M, Dana Z, Jaiyesimi I, Margolis J, Decker D. Scalp Hypothermia Minimizes Alopecia in Breast Cancer Patients Receiving Non-Anthracycline Adjuvant Chemotherapy San Antonio Breast Symposium 2009; abstr 5040.
39. JC Dean, SE Salmon, and KS Griffith. Prevention of doxorubicin-induced hair loss with scalp hypothermia. N Engl J Med 1979; 301 (26):1421-1427.