

**DE NOVO CLASSIFICATION REQUEST FOR
DIGNICAP™ SCALP COOLING SYSTEM**

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Scalp cooling system to reduce the likelihood of chemotherapy induced alopecia: A scalp cooling system is intended to reduce the frequency and severity of alopecia during chemotherapy in which alopecia-inducing chemotherapeutic agents are used.

NEW REGULATION NUMBER: 878.4360

CLASSIFICATION: II

PRODUCT CODE: PMC

BACKGROUND

DEVICE NAME: DIGNICAP™ SCALP COOLING SYSTEM

SUBMISSION NUMBER: DEN150010

DATE OF DE NOVO: MARCH 6, 2015

CONTACT: *DIGNITANA AB
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REQUESTER'S RECOMMENDED CLASSIFICATION: II

INDICATIONS FOR USE

The DigniCap™ Scalp Cooling System is indicated to reduce the likelihood of chemotherapy - induced alopecia in women with breast cancer.

LIMITATIONS

The sale, distribution, and use of DigniCap™ Scalp Cooling System are restricted to prescription use in accordance with 21 CFR 801.109.

Limitations on device use are also achieved through the following statements included in the instructions for use:

Contraindications:

“Contraindications are cold sensitivity, cold agglutinin disease, cryoglobulinemia and cryofibrinogenemia.”

“Scalp cooling is contraindicated if chemotherapy is given with a curative intent in patients with hematological malignancies.”

Precautions / Warnings:

“Long-term effects of scalp-cooling and scalp metastasis have not been fully studied”

“Use of scalp cooling with taxanes plus anthracyclines when used together or in sequence has not been shown to be successful in preventing chemotherapeutic drug induced alopecia.”

“Attention: Clinical studies have produced variable success rates in patient reduction of chemotherapy induced alopecia with scalp cooling since the outcome is dependent on several factors including chemotherapy regimen, dose, duration of drug infusion, chemotherapy drug metabolism, and concomitant comorbidities.”

“Breast cancer patients treated with taxanes plus anthracyclines, when used together or in sequence, have not been shown to respond to scalp cooling for reducing chemotherapeutic drug induced alopecia. Dignicap® Scalp Cooling System should not be used in these patients.”

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The Dignitana DigniCap™ Scalp Cooling System consists of a computer controlled system that includes a refrigerated tank containing the cooling agent that is maintained at -8 ± 1 °C. The liquid coolant circulates from the cooling unit to and through the channels of the cap and back to the cooling unit. The scalp temperature is monitored by three separate thermometers. Deviations from the pre-set temperature are automatically adjusted by the system (scalp temperature can be controlled with an accuracy of ± 2.0 °C).

The DigniCap™ Scalp Cooling System components include the following:

Digni C3 system – Is a refrigerator unit with an integral control system operated via a touch screen monitor and is capable of controlling two separate cooling caps independently of each other. Scalp cooling is performed in conjunction with a silicon inner cap (DigniCap™), an outer neoprene cap (DigniTherm™), and the liquid coolant (DigniCool™).

DigniCap™ – A soft, tight-fitting silicon cap which has two separate cooling circuits, one for the front of the head and one for the back of the head plus a third sensor for overall safety control.

DigniCool™ – The liquid coolant monopropylene glycol (MPG5).

DigniTherm™ - The outer neoprene cap that insulates and keeps the inner cap in place. To improve cooling and ensure proper fitting, this cap is covers the DigniCap™ and includes a chin strap which is used to hold the cap in place. This neoprene cover cap, called the DigniTherm™, comes in different sizes and is colored coded to match the corresponding correct silicone Cooling Cap. In addition to acting as a means of maintaining cooling cap placement, this outer cap also provides insulation which improves cooling efficiency

DIGNISTICK™ – A component used to save data from a treatment or for troubleshooting when inserted in the slot. It can also be used to update software.

DIGNICARD™ – A key card which has to be inserted in order to start a treatment.



Figure 1: DigniTherm™ and corresponding DigniCap™

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The only portion of the system that comes into patient contact is the silicon DigniCap™. The DigniCap™ is a surface device that is in contact with the skin for a limited duration (≤24h). The different color caps were subjected to cytotoxicity according to ISO 10993-5 and skin sensitization and irritation testing according to ISO 10993-10.

For cytotoxicity testing, the elution method was used with MRC-5 cells as the test article. All of the eluates from the DigniCap™ plus the negative control were found to be non-cytotoxic.

Skin sensitization was tested using the mouse lymph node assay. For skin sensitization, extracts from each cap and cap color were applied to the dorsal surface of mice according to the ISO 10993-10 and compared to vehicle and positive control. Based on the test results none of the caps or cap colors was considered a potential skin sensitization material.

Skin irritation was tested using the rabbit model. Extracts of the cap and cap color material was placed on the rabbit under occlusion using polar and non-polar extracts. Based on the test results neither the polar or non-polar extract showed irritation effects thus the DigniCap™ material was determined not to be a skin irritant.

SHELF LIFE/STERILITY

This device is provided non-sterile which is appropriate for this patient population, as the cooling caps are used for cooling the scalp in a non-sterile environment. Cap cleaning between patient use involves cleaning using soap or alcohol and details to accomplish cleaning are provided in the labeling.

The manual provides instructions to the user to conduct a visual inspection of the DigniCap™. The cap should be inspected for any wear, tear, and leaks. If the DigniCap™ is damaged, it should be replaced.

Packaging and shipping testing of the device was conducted based on the ASTM standard D 4169-08 “Standard Practice for Performance Testing of Shipping Containers and Systems”. This testing consists of placing the package into -25 °C conditions for 16 hours followed by 8 hours acclimation to room temperature and then placing the packaging into 50 °C conditions for 16 hours and then again returned to room temperature for 8 hours. Transportation testing includes simulated handling incidences such as being dropped from a forklift, damage from being moved by a crane, being dropped on a corner or dropped on a flat surface, being vibrated and receiving impacts from other items that may occur in storage facilities. This testing demonstrated that the packaging was acceptable in terms of ensuring that the device can be shipped without damage using the proposed container system.

ELECTROMAGNETIC COMPATIBILITY (EMC) AND ELECTRICAL SAFETY

EMC testing was performed per the relevant requirements of IEC 60601-1-2:2007, Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral standard: Electromagnetic compatibility – Requirements and tests. Based on successful completion of the testing, the Dignitana DigniCap™ Scalp Cooling System is deemed compliant to the relevant requirements of IEC 60601-1-2:2007.

Electrical safety testing was performed per the relevant requirements of IEC 60601-1:2005, General safety standard: safety requirements for medical electrical systems. The Dignitana DigniCap™ Scalp Cooling System device passed all relevant portions of the testing and demonstrated the electrical safety for the Dignitana DigniCap™ Cooling System. Based on compliance with this standard, the Dignitana DigniCap™ Cooling System can be considered to have established a reasonable assurance of electrical safety.

SOFTWARE

The DigniC3 system is comprised of a cooling subsystem, software, logic by electronics, and a user interface through a touch screen.

The software controls the cooling diverted to the patient by controlling the valves. This control is accomplished by sending a command on the communication BUS. An adaptation function handles the timing of the valves. The software control can be overridden by a hardware watchdog monitoring the lower bound of the temperature.

All of the elements of software information corresponding to moderate level of concern device as outlined in FDA's *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices* (issued May 11, 2005) were provided. Adequate documentation describing the software development program was provided. Verification and validation (V&V) testing was conducted to address the potential hazards with satisfactory results. In addition, the software development procedures provide the foundation that the software will operate in a manner as described in the specifications. The software documentation is in sufficient detail to provide reasonable assurance that the software performs as intended and all software-related risks have been adequately mitigated.

PERFORMANCE TESTING – BENCH

Two separate verification studies were conducted to confirm that the temperature control mechanisms and safety features of the cooling system and cooling caps plus the software programming ensured proper circulating cooling temperatures in the cap. For the first study, dummy heads were developed to replicate the size of a human head. (b) (4)

. A series of different test scenarios were conducted related to cap cooling depending on target cooling temperature. The specific temperatures tested were based on the recommended treatment settings in the User Manual, 3 °C and 5 °C. The 5 °C

temperature is described as the default temperature and was used for most subjects and the 3 °C temperature is specifically identified for use with subjects with thick hair. The following test scenarios were evaluated:

- One cap connected to the system
- Two caps connected to system with both caps cooling at the same time
- Two caps connected with one cap cooling and a delayed start of the second cap cooling for several minutes.

These tests were evaluated by collection of temperature data (b) (4) during the total time of testing. Following the initial 20 minute cooling down period, the cap temperature remained stable for the 1 hour of test time for all of the different variations in cap use tested. The temperature measurements were made on scalp locations on the dummy heads thus representing what could be considered true scalp temperature.

In addition to performing the testing of the caps in their own laboratory, the sponsor also had the caps tested by a private test company using a mock environmental set-up simulating environmental conditions of a hospital or healthcare facility. This testing included a variety of ambient room temperatures and humidity. The specific parameters tested were room (b) (4) t. The target cap temperature for these tests was 5 °C. Similar to the testing above, results from the testing show that once the temperature has dropped during the 20 minute cool down time, the cap temperature remained stable for 60 minutes or longer depending on the test duration.

As part of testing of the system to verify that all of the safety features functioned to ensure cap cooling accuracy and consistency, tests related to the cooling system safety features such as tank filling and loss of fluid and over cooling (freezing of cooling solution) were conducted. These tests were included to demonstrate that system start-up time was accurate and that cap cool down times were maintained even if these safety features were engaged during actual cap cooling. Temperature graphs confirming correct operation in terms of cap cooling and maintenance of target temperature were provided. These tests duplicate actual treatment with the cooling cap in a simulated patient using head models. The testing included the total functioning of the total cooling system including proper functioning of the valve systems between tank and cap, the individual temperature sensors in the cap, and the temperature sensors in the tank related to low fluid volume and tank temperature below the safety limit.

Testing of coolant flow rates was not performed since the flowrate itself is not a critical parameter, and does not itself represent an independent hazardous situation. The critical parameter is the temperature of the cap. In order to maintain an appropriate temperature, coolant flow rate can vary depending on the temperature set for the DigniCap™, ambient temperature, etc. Verification testing for proper and controlled cap cooling demonstrated that the system functions as designed, including the maintenance of appropriate coolant flow rates.

SUMMARY OF CLINICAL INFORMATION

Two human clinical studies using DigniCap™ demonstrated reasonably safe and effective use by verifying that the device reduces chemotherapy induced alopecia in breast cancer patients. The feasibility study conducted for this device is summarized in Table 3, and the pivotal study is summarized in Table 4, below.

Table 3: Feasibility Study

Study Title	Clinical Performance, Efficacy and Safety of the DigniCap™ Scalp Cooling System, a Scalp Hypothermia System, in Preventing Chemotherapy Induced Alopecia in Patients with Early Stage Breast Cancer
Study Objective	To assess the feasibility of use of the DigniCap™ Scalp Cooling System in patients with stage I breast cancer receiving adjuvant chemotherapy treatment that, unless counteracted by simultaneous hypothermia treatment, results in > 75% hair loss by the completion of chemotherapy.
Study Endpoints	<p>Primary endpoint: To determine the feasibility of use of the DigniCap™ Scalp Cooling System in this setting. Feasibility is defined as less than 50% of patients discontinuing use of the cap due to cap associated patient toxicity.</p> <p>Secondary endpoints:</p> <ol style="list-style-type: none"> 1. Ability to complete protocol case report forms 2. Adverse events related to use of the DigniCap™ Scalp Cooling System 3. Hair loss assessment in women receiving specified chemotherapy regimens using the DigniCap™ Scalp Cooling System with success was defined as < grade 2 hair loss using the Deans scale. Considering both: <ol style="list-style-type: none"> a. Patient assessment b. Assessment by independent panel 4. Quality of life in women using the DigniCap™ Scalp Cooling System 5. Time to and quality of hair regrowth 6. Impact of hair loss on treatment decisions
Sample Size	20 subjects, 2 sites
Inclusion/Exclusion criteria	<p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. Patient 18 years of age 2. Documented diagnosis of stage I breast cancer. 3. A planned course of chemotherapy in the adjuvant or neoadjuvant setting 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 80-90 mg/m² weekly IV x at least 12 weeks with or without trastuzumab IV
 - Paclitaxel 175 mg/m² IV every 2 weeks x 4 – 6 cycles (without an anthracycline)
 - Paclitaxel weekly and Carboplatin area under the curve (AUC) 2 weekly or AUC 6 every 3 weeks IV x 4 - 6 cycles and trastuzumab IV weekly or every 3 weeks.
 - Docetaxel 75mg/m², 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 70% (i.e. cares for self; unable to carry on normal activity or to do active work).
 7. Willing and able to sign informed consent for protocol treatment, for authorized Sponsor representatives to be given access to the patient's hospital records for purposes of Source Data Verification, for photos taken before and after treatment, and for use of non-identifying information for purposes of publication
 8. Life expectancy 12 months
 9. Willing to be contacted in follow-up for at least 12 months.

Exclusion criteria:

1. Patients must not have female pattern baldness resembling picture I-3 or higher on the Savin scale.
2. No autoimmune disease affecting hair; e.g. alopecia areata, systemic lupus with associated hair loss.
3. No history of whole brain radiation.
4. No plan to use a chemotherapy regimen other than those specified in section 7. Specifically, patients receiving a regimen including both an anthracycline and a taxane are not eligible for this trial: : Adriamycin, Cytosan/taxotere (AC/T), Epirubicin/cyclophosphamide/ taxotere (EC/T), Taxotere/Adriamycin/cyclophosphamide (TAC), etc.. Patients may not receive concurrent hormone therapy; hormone therapy should be given as indicated following completion of chemotherapy.
5. No serious concurrent infection or medical illness which would jeopardize the ability of the patient to complete the planned chemotherapy.
6. No history of persistent grade 2 alopecia induced by prior chemotherapeutic regimens.
7. No participation in any other clinical investigation or exposure to other investigational agents, drugs, device or procedure that may cause hair loss.
8. No intercurrent life-threatening malignancy.
9. No history of cold agglutinin disease, cryoglobulinemia or cryofibrinogenemia.

	<p>10. No evidence of untreated or poorly controlled hyper or hypothyroidism.</p> <p>11. No history of silicon allergy.</p> <p>12. No evidence of abnormal liver function, defined as, aspartate aminotransferase (AST) $\geq 3x$ upper limit of normal.</p> <p>13. No evidence of abnormal kidney function defined as creatinine $\geq 2X$ upper limit of normal.</p> <p>14. American Society of Anesthesiologist Class ≥ 3.</p>
Procedure	<p>Eligible patients included women diagnosed with stage1 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%).</p> <p>Patients will receive scalp hypothermia as delivered by the DigniCap™ Scalp Cooling 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</p>
Follow-up	<p>Safety and tolerability in terms of adverse symptoms and adverse device effects reported by patients during use of the DigniCap™ Scalp Cooling System and during the follow-up period 3, 6 and 12 months after completion of treatment was examined.</p>
Assessment Tools	<p>Photographic documentation was performed before initiation of the first cycle of chemotherapy, before each subsequent cycle, at a visit 3 to 4 weeks after the last cycle of chemotherapy.</p> <p>Hair loss was assessed by an independent panel consisting of a hair dresser, a patient advocate, and a dermatologist specializing in hair according to the Dean Scale by review of photographs blinded to patient and sequence.</p> <p>Patients evaluated their degree of hair loss at each visit according to the Dean Scale without the review of photographs.</p> <p>Quality of Life during and after chemotherapy was assessed by the patient using the European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer-Specific Quality of Life Questionnaire (QLQ-BR23) scale and the Body Image Scale (BIS).</p> <p>A Patient Symptom Survey was completed at each chemotherapy cycle.</p>

Results	
Patient Accountability	Evaluable patients for all follow-up visits = 19.
Results	<p>Primary endpoint:</p> <p>One patient out of the 20 evaluable patients discontinued study therapy due to cap associated patient toxicity, patient assessed hair loss and severe anxiety. This represents a 5% discontinuation rate and indicates that the scalp cooling system is feasible in this setting.</p> <p>Secondary endpoints</p> <p>1. Assessment of the ability to complete protocol case report forms Patients completed a number of questionnaires throughout the study and compliance was excellent</p> <p>2. Documentation of adverse events related to use of the DigniCap™ System</p> <p>2.1 Patient Reported Symptoms</p> <ul style="list-style-type: none"> - Head Pain - 65% (13) of patients reported head pain during at least one treatment - Chill - 80% (18) of patients experienced chill during treatment. - Scalp Pain - 95% (19) of patients reported scalp pain during at least one treatment. <p>2.2 Use of Pain Medications During Treatment immediately before their chemotherapy infusion and use of the DigniCap™ Scalp Cooling System at some point during their treatment course</p> <ul style="list-style-type: none"> - 3 patients (15%) took non-prescription pain medication - 11 patients (55%) took prescription pain medication - 7 patients (35%) reported not using pain medication of any kind the morning of their infusion with the DigniCap™ Scalp Cooling System <p>2.3 Practitioner reported specific cap-related adverse events.</p> <ul style="list-style-type: none"> - No cases of metastasis, including metastasis to the scalp. - Adverse events (other than during time of actual cap use) were not related or unlikely related to cap use. <p>3. Hair loss assessment in women receiving specified chemotherapy regimens using the DigniCap™ Scalp Cooling System including:</p> <p>3.1 Patient assessment</p> <p>3.1.1. Assessment of physical hair loss according to the Deans scale.</p> <ul style="list-style-type: none"> - Baseline mean grade on Deans scale = 0.15. - Halfway through treatment (N=20): 60% of patients reported < grade 2 alopecia. The mean grade was 2.15. - One month after completion of chemotherapy (N=19): 58% of

	<p>patients reported < grade 2 alopecia. The mean grade was 2.21.</p> <ul style="list-style-type: none"> - Three months after completion of chemotherapy (N=17): 88% of patients reported < grade 2 alopecia. - Overall 55% of patients never experienced > grade 2 alopecia throughout their entire treatment and follow-up. <p>3.1.2. Assessment of quality of treatment response & quality of life.</p> <p>3.1.3. Assessment of the impact of hair loss on treatment decisions</p> <p>3.2. Assessment by independent panel</p> <ul style="list-style-type: none"> - Halfway through treatment (N=20): 85% of patients had < grade 2 alopecia and 90% of patients had < grade 3 alopecia. - One month after completion of chemotherapy (N=19): 74% had < grade 2 alopecia and 90% had < grade 3 alopecia. - Overall 75% of patients had < grade 2 alopecia throughout their entire treatment and follow-up graded by the Independent Panel. <p>4. Quality of life in women using the DigniCap™ System:</p> <p>Overall, average patient satisfaction with hair was 85% at baseline, and 82% three months after the completion of chemotherapy. At the 1 month follow up the use of wigs was reported as “always” in 11% of patients, “sometimes” in 16% of patients and “never” in 74% of patients. The percentage of patients who strongly agreed that their hair was important to them was 80% at Baseline and 81% at 1 month follow up. The percentage of patients who thought that their hair was important to their appearance increased from 74% at Baseline to 93% at 1 month follow up.</p> <p>5. Impact of hair loss on treatment decisions</p> <ul style="list-style-type: none"> - Seventy-five percent of patients said hair loss did not affect their decision at all or it affected it a little. - Overall, 17 (85%) of the participants commented at least once that the availability of the scalp cooling system made their decision much easier: they were grateful for the scalp cooling option, and/or that the opportunity relieved some of the stress involved in the decision.
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Feasibility Study Summary:

This feasibility study consisted of 20 patients from 2 centers with stage 1 breast cancer who were to receive alopecia inducing chemotherapeutic regimens. The patients were followed for one year. The objective of this study was to demonstrate that these breast cancer patients who would normally have a greater than 75% hair loss with chemotherapy, had a reduction in the incidence and frequency of hair loss with hypothermia treatment of the scalp. The DigniCap™ Scalp Cooling System was shown to decrease hair loss by over 50% in 75% of the patients. This benefit was associated with minor risks and side effects: 65% of patients experienced headaches, 80% experienced chills, and 95% of patients reported scalp pain during at least one treatment. The side effects usually resolved with termination of scalp cooling and there were no incidence of scalp metastasis during the one year follow-up. Only one patient dropped out of the study due to anxiety

and failed hair preservation. No serious adverse events or safety issues were attributed to DigniCap™ Scalp Cooling System in this feasibility study. Patient overall satisfaction with the quality and quantity of their hair was 85% at baseline and 82% three months after the completion of chemotherapy and 74% never had to use a wig. The presence of a scalp cooling system made the decision to undergo chemotherapy much easier in 85% of the patients.

Table 4: Pivotal Study

Study Title	Clinical Performance, Efficacy and Safety of the DigniCap™ Scalp Cooling System, a Scalp Hypothermia System, in Preventing Chemotherapy Induced Alopecia in Patients with Early Stage Breast Cancer
Study Design	This study was a non-randomized, multi-center (6 sites), concurrent controlled, clinical study to evaluate the effect of scalp cooling on hair loss during treatment with alopecia inducing chemotherapeutic regimens.
Study 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:</p> <ol style="list-style-type: none"> 1. To assess the ability of the DigniCap™ Scalp Cooling 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>Secondary Objectives:</p> <ol style="list-style-type: none"> 1. To assess safety of the DigniCap™ Scalp Cooling System in women receiving specific chemotherapy regimens for early stage breast cancer. 2. To assess tolerability of the DigniCap™ Scalp Cooling System. 3. To evaluate hair loss and recovery as assessed by the patient during and following chemotherapy using the alopecia self-report. 4. 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. 5. To assess patient quality of life and satisfaction with hair during and after treatment with the DigniCap™ Scalp Cooling System. 6. To assess the impact of hair loss on treatment decisions.
Study Endpoints	<p>Primary endpoint:</p> <p>Success of the DigniCap™ Scalp Cooling 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</p>

	<p>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:</p> <ol style="list-style-type: none"> 1. Safety as determined by spontaneous reporting of adverse events and as negative scalp changes determined by physical examination. 2. Tolerability is defined as the percentage of patients who complete all planned cycles of chemotherapy do so using the DigniCap™ Scalp Cooling System. 3. Patient assessment of hair loss by the alopecia self-reports at each chemotherapy. Hair re-growth is defined an improvement in the Dean scale by at least one level. 4. Quality of life as measured by the EORTC-QLQ-BR23 quality of life questionnaire and a Body Image Scale.
Number of Patients/Sites	<p>Treatment subjects: n=110 (Presumed drop-out rate of 10% results in n=100); Control subjects: n=15 (at interim analysis) or 30</p> <p>5 sites</p>
Inclusion/Exclusion Criteria	<p>Inclusion</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 - 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 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</p> <ol style="list-style-type: none"> 1. Patients with female pattern baldness resembling picture 1-3 or higher on the Savin scale 2. Autoimmune disease affecting hair; e.g. alopecia areata, systemic lupus with associated hair loss 3. 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. 4. A history of whole brain radiation 5. Concurrent hormone therapy with chemotherapy. Hormone therapy should be used as indicated following completion of chemotherapy 6. Intercurrent life-threatening malignancy 7. Clinically significant renal dysfunction defined as serum creatinine > the upper limit of normal 8. 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. 9. A serious concurrent infection or medical illness that would jeopardize the ability of the patient to complete the planned therapy and follow-up 10. A history of persistent grade 2 (or higher) alopecia induced by prior chemotherapeutic regimens 11. A history of cold agglutinin disease or cryoglobulinemia 12. Evidence of untreated or poorly controlled hyper- or hypothyroidism 13. A history of silicon allergy 14. American Society of Anesthesiologist Class ≥ 3 <p>Control Group: The inclusion and exclusion criteria are essentially the same.</p>						
<p>Study treatment</p>	<p>A patient in the treated arm wore the DigniCap cooling cap for 30 minutes before starting the chemotherapy treatment, during the chemotherapy infusion, and for up to 120 minutes after the infusion was finished for each cycle of chemotherapy.</p> <table border="1" data-bbox="358 1476 1429 1845"> <thead> <tr> <th data-bbox="358 1476 716 1696">Chemotherapy Regimen</th> <th data-bbox="716 1476 1227 1696">Dose</th> <th data-bbox="1227 1476 1429 1696">Post Infusion Cooling Time (minutes)</th> </tr> </thead> <tbody> <tr> <td data-bbox="358 1696 716 1845">Adriamycin cytoxan (AC) x 4 or 6 cycles, every 2-3weeks</td> <td data-bbox="716 1696 1227 1845">Doxorubicin: 60 mg/m², Cyclophosphamide 600 mg/m²</td> <td data-bbox="1227 1696 1429 1845">120</td> </tr> </tbody> </table>	Chemotherapy Regimen	Dose	Post Infusion Cooling Time (minutes)	Adriamycin cytoxan (AC) x 4 or 6 cycles, every 2-3weeks	Doxorubicin: 60 mg/m ² , Cyclophosphamide 600 mg/m ²	120
Chemotherapy Regimen	Dose	Post Infusion Cooling Time (minutes)					
Adriamycin cytoxan (AC) x 4 or 6 cycles, every 2-3weeks	Doxorubicin: 60 mg/m ² , Cyclophosphamide 600 mg/m ²	120					

	Taxotere carboplatin (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
	Taxotere, carboplatin herceptin (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 every 3 weeks, Trastuzumab initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks, Docetaxel 75 mg/m ²	120
	<p>Targeted therapeutics not associated with hair loss were allowed (including trastuzumab, lapatinib, neratinib, bevacizumab, etc.). Dose reductions if required for patient safety or toxicity were done, but full dose therapy was planned at treatment start. Concomitant use of hormone therapy was not allowed and was started following completion of chemotherapy.</p>		
Evaluation Tools	<p>1. The Dean Scale for alopecia:</p> <ul style="list-style-type: none"> • 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 <p>This was done by the patient from photographs taken at each visit with the final rating occurring 1 month after completion of chemotherapy.</p> <p>Photographs were standardized and include 5 view including: front (bangs held back), behind, both sides and the top with hair divided in the midline with both hands. Patients with a Dean score of 4 were exempt from additional photos.</p>		

	<p>2. EORTC-QLQ-BR23 was used to assess at baseline, cycle 4 and 4 weeks after the last cycle of chemotherapy.</p> <p>3. Body Image Scale (BIS) was done at Baseline, Cycle 4 of chemotherapy and 4 weeks after the last cycle of chemotherapy.</p> <p>4. Hair re-growth was evaluated at Month 3 and 6 post completion of chemotherapy. For this the patient graded their hair quality in terms of texture, manageability, and color variation from baseline.</p> <p>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. Hair loss will be assessed by comparing the photographs against standardized photographs to estimate the percentage of hair lost according to the Dean scale.</p> <p>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.</p>												
Follow-up	<p>Adverse Device Events (ADE) <i>An Adverse Device Event</i> 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.</p> <p>The outcome of the adverse event will be assessed as: 1 = Resolved 2 = Improved 3= Unchanged 4= Worse 5= Fatal 6= Not available</p> <p>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</p>												
Results													
Patient Accountability	<table border="1"> <thead> <tr> <th></th> <th style="text-align: center;">Treated Group (N=106)</th> <th style="text-align: center;">Control Group (N=16)</th> </tr> </thead> <tbody> <tr> <td>Safety Population</td> <td style="text-align: center;">106</td> <td style="text-align: center;">16</td> </tr> <tr> <td>Evaluable</td> <td style="text-align: center;">101</td> <td style="text-align: center;">16</td> </tr> <tr> <td>Per Protocol</td> <td style="text-align: center;">85</td> <td style="text-align: center;">15</td> </tr> </tbody> </table>		Treated Group (N=106)	Control Group (N=16)	Safety Population	106	16	Evaluable	101	16	Per Protocol	85	15
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- Patients discontinued use of the cap due to :
- 4 patients were excluded from the evaluable population due to toxicity of chemotherapy.
 - 1 patient was excluded from the evaluable population due to eligibility violation.
 - 8 patients discontinued due to hair loss
 - 1 patient withdrew because of the length of time of the study and the coldness was unbearable
 - 2 patients refused after one cycle due to the effect of cooling during and after chemotherapy
 - 4 patients discontinued due to non-compliance
 - 1 patient was lost to follow-up

Patient Demographics

		DigniCap™ N=106	Control N=16
Age	N	106	16
	Mean	53.0	54.9
	SD	11.2	8.6
	Median	55.0	56.0
	Minimum	28.0	36.0
	Maximum	77.0	67.0
Ethnicity	N	106	16
	Hispanic or Latino	17 (16.0%)	1 (6.3%)
	Not Hispanic or Latino	88 (83.0%)	15 (93.8%)
	Missing	1 (0.9%)	0 (0.0%)
Race	N	106	16
	American Indian or Alaska Native	0 (0.0%)	0 (0.0%)
	Asian	10 (9.4%)	3 (18.8%)
	Black or African	11 (10.4%)	0 (0.0%)
	Native Hawaiian or Other Pacific	0 (0.0%)	0 (0.0%)
	White	82 (77.4%)	12 (75.0%)
	Multiracial	1 (0.9%)	1 (6.3%)
	Missing	2 (1.9%)	0 (0.0%)

Note: Two subjects have multiracial background. Subject 03-C002 is American Indian or Alaska Native, Black or African American, White. Subject 03-T023 is Native Hawaiian or Pacific Islander, White.

<p>Primary Effectiveness</p>	<p>Of the 101 evaluable patients in the DigniCap™ Scalp Cooling System treatment group, 67 (66.3%) demonstrated treatment success (Dean score ≤2) compared to 0 (0%) in the control group who did not use the DigniCap™ Scalp Cooling System (95% CI, 56.2, 75.4%; p < 0.001).</p> <p>The number of patients with a maximum Dean score at any cycle is summarized</p> <table border="1" data-bbox="386 432 1416 814"> <thead> <tr> <th>Dean Score</th> <th>The DigniCap® System</th> <th>Control</th> </tr> </thead> <tbody> <tr> <td>N</td> <td>101</td> <td>16</td> </tr> <tr> <td>Grade 0 (no hair loss)</td> <td>5 (5.0%)</td> <td>0</td> </tr> <tr> <td>Grade 1 (up to 25% hair loss)</td> <td>31 (30.7%)</td> <td>0</td> </tr> <tr> <td>Grade 2 (>25% up to 50% hair loss)</td> <td>31 (30.7%)</td> <td>0</td> </tr> <tr> <td>Grade 3 (>50% up to 75% hair loss)</td> <td>19 (18.8%)</td> <td>1 (6.3%)</td> </tr> <tr> <td>Grade 4 (>75% hair loss)</td> <td>15 (14.9%)</td> <td>15 (93.8%)</td> </tr> </tbody> </table> <p>below.</p> <p>An independent panel review of the photographs was conducted and 73 patients (72%) were rated as treatment successes.</p>	Dean Score	The DigniCap® System	Control	N	101	16	Grade 0 (no hair loss)	5 (5.0%)	0	Grade 1 (up to 25% hair loss)	31 (30.7%)	0	Grade 2 (>25% up to 50% hair loss)	31 (30.7%)	0	Grade 3 (>50% up to 75% hair loss)	19 (18.8%)	1 (6.3%)	Grade 4 (>75% hair loss)	15 (14.9%)	15 (93.8%)
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<p>Secondary Endpoints</p>	<p>Tolerability is defined as the percentage of patients who complete all planned cycles of chemotherapy do so using the DigniCap™ Scalp Cooling System</p> <p>83.0% of patients completed all planned cycles of chemotherapy using the DigniCap™ System in all cycles</p> <p>Patient Symptoms Survey: looked at tolerability of the cap with respect to headaches, scalp pain and the feeling of chilling due to the cap.</p> <ul style="list-style-type: none"> • Patient Symptoms Survey results showed that 74 patients experienced headaches during the prior month; 31.1% of the patients had 1-2 headaches, 27.0% had 3-4 headaches, 21.6% had 5-6 headaches, and 20.3% had >6 headaches. • A total of 43 patients reported that headaches were triggered or exacerbated by scalp cooling treatment and the average level of pain experienced by these patients was 39.3 on a scale of 0 to 100 (with 100 being the worst pain). On average this occurred for 1 cycle but ranged up to 10 cycles. There were over 100 instances reported. • The feeling of chilliness during the cooling down period was reported by most patients (n=102) and with overall cooling treatment (n=104). • Scalp pain associated with cooling was reported by 75 patients with an average level of any scalp pain experienced by these patients of 24.2 out of 100 (range 1.7 to 85.0). Over 250 instances of scalp pain were 																					

recorded.

- Of the 105 patients, only 35 took pain medications during the chemotherapy cycles.

Patient assessment of satisfaction with their hair by the alopecia self-reports at each chemotherapy.

- A mean score of 70.9 out of 100 for satisfaction for hair quantity in the DigniCap™ Scalp Cooling System group versus 25.6 in the control group.
- A mean score of 69.1 out of 100 for satisfaction with hair quality in the DigniCap™ Scalp Cooling System group versus 37.6% in the control group.
- A mean score of 87.5 out of 100 for satisfaction with decision to use scalp cooling.

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

On the EORTC questionnaire:

- a) There was an increase in the number of patients from baseline at the last cycle of chemotherapy and one month follow-up that had dry mouth, different than usual taste in food and drink, eyes were painful, irritated or watery, lost hair, upset at hair loss, feel ill or unwell, have hot flushes, have headaches, felt physically less attractive or less feminine due to the disease or treatment. However, hair loss was twice as likely to occur in the control arm as the treatment arm.
- b) There were less changes from baseline in the number of patients in responses to the categories of difficult to look at yourself naked, dissatisfied with body imaging, worried about health in the future, interested in sex, extent of being sexually active, sexually enjoyable, pain or swollen in the arm or shoulder, difficult in raise arm or move it sideways, if pain, swollen, oversensitive or skin problem (itchy, dry flaky) in affected breast at the last cycle of chemotherapy and one month follow-up

On the Body Image Scale questionnaire:

Greater than 90% of patients in the DigniCap™ Scalp Cooling System treatment group agreed strongly and somewhat that hair is important and is important for appearance compared to 90% in the Control Group at the end of the study period. Note that at baseline in the control group 75% felt strongly.

To look further at the question of headaches, the EORTC-QLQ-BR23 also included a question regarding the frequency of headaches compared to baseline and is presented below. Of note is that the control group and a much higher rate change in response to this question than did the treated group. So although, headache may have been associated with use of the device the effect dissipated once the device was no longer used. The number of patients having a headache in

	the treated group was nearly double the baseline at last assessment, while the control group remained the same.
Adverse Events	<ol style="list-style-type: none"> 1. Eight (8) patients experienced 9 unanticipated SAEs; two (2) patients who discontinued from the study due to an AE 2. Patients events that were suspected or probably related to DigniCap™ Scalp Cooling System treatment, included: <ul style="list-style-type: none"> • Headache (4) • Pruritus (1) • Pain of skin (1) • Head discomfort (1) • 1 instance of neck pain which is listed as mild severity <p>Summary of SAE's: (There were no deaths)</p> <ol style="list-style-type: none"> 1. There were 5 unanticipated events in 4 patients in the treatment group and 4 events in the control group. 2. None of the SAE's were related to scalp cooling. 3. All were chemotherapy related and not unexpected. They included: febrile neutropenia, anemia, thrombocytopenia and a maculo-papular rash. 4. All required hospitalization and intervention but all resolved. 5. Two (2) patients discontinued from the study due to an unrelated to device AE, one (02-T010) experienced an allergic reaction, shortness of breath and facial flushing on 18Mar2014; the infusion was interrupted, the patient required oxygen. This hypersensitivity reaction (immune system disorders) recovered/resolved in one month. One patient (03-T024) experienced peripheral neuropathy, numbness in fingertips and toes on 11Apr2014. This event (nervous system disorders) recovered/resolved in two months. <p>Device Incidents: (There were 22 device incidents during the trial)</p> <ol style="list-style-type: none"> 1. Most common was cap malfunction (n=11) 2. Problems with the temperature sensor/cooling cable not working (n=9) 3. Cap never cooling down (n=4) 4. 1 event of coolant leaking was identified

Subgroup Analyses	<u>Effectiveness by Chemotherapeutic Regimen:</u>				
		n	Success Rate (%)	95% CI (%)	p-value
	Docetaxel and carboplatin	12	83.3	51.6, 97.9	0.022
	Docetaxel and cyclophosphamide	76	60.5	48.6, 71.6	<0.001
	Paclitaxel	12	83.3%	51.6, 97.9	0.066
	Note: As all control patients were failures, they are not included in this table. Although there were multiple acceptable combinations of chemotherapy in this trial the cited 3 regimens were the most common.				
	Effectiveness by Baseline Hair Quality				
	<ul style="list-style-type: none"> - Thick hair (n=32) had a 75% success rate - Medium hair (n=50) had a 64% success rate - Thin Hair (n=17) has an 82.4% success rate 				
	Effectiveness when stratified by Age, BMI, prior history of chemotherapy				
	Demonstrated no differences				

Pivotal study Summary:

This study was a non-randomized, multi-center (6 sites), concurrent controlled, clinical study to evaluate the effect of scalp cooling on hair loss during treatment with alopecia inducing chemotherapeutic regimens in patients with early stage breast cancers. There were 101 patients in the experimental group and 16 in the control group that could be evaluated. The subject device, the DigniCap™ Scalp Cooling System, resulted in less than 50% hair loss in 66.4% of the treatment group while the entire control group had greater than 50% hair loss with 94% having greater than 75% hair loss. All planned cycles of chemotherapy using the DigniCap™ System were completed in 83% of patients. Side effects of headache, chills and scalp pain were common and limited to the duration of scalp cooling. There were no serious adverse events attributed to the DigniCap™ Scalp Cooling System and no reports of scalp metastasis in the 6 month follow-up period reported. Greater than 90% of patients in the DigniCap™ Scalp Cooling System treatment group agreed strongly and somewhat that hair is important and is important for appearance compared to 90% in the Control Group at the end of the study period. For patient satisfaction, the DigniCap™ Scalp Cooling System group had a mean score of 70.7 out of 100 for hair quantity versus 25.6 in the control group. Furthermore, the DigniCap™ Scalp Cooling System group had a mean score of 69.1 out of 100 for satisfaction for hair quality, versus 37.6 in the control group. The DigniCap™ Scalp Cooling System group had a mean score of 87.5 out of 100 for satisfaction regarding the decision to use scalp cooling.

LABELING

Labeling has been provided which includes the instructions for use and an appropriate prescription statement as required by 21 CFR 801.109.

The labeling includes the following information:

- Directions for duration of use according to chemotherapeutic agent administered
- Warnings, cautions, and limitations needs for safe use of the device and risk associated with device use include the possibility of scalp metastasis.
- Information on how the device operates and the typical course of treatment including cooling temperatures
- A detailed summary of the human clinical testing pertinent to the use of the device
- Information on the patient population and chemotherapeutic agents/regimen used in the clinical study with the device. Results and adverse event were provided in the clinical summary in the user manual and patient brochure.
- A description of the verified temperature controls and safety features included in the device.

A Patient labeling that discusses the benefits and risks associated with device treatment included the following information:

- Relevant contraindications, warnings, precautions, adverse effects/complications
- Information on how the device operates and the typical course of treatment.
- Information on the patient population for which there is clinical evidence of effectiveness
- The potential risks and benefits associated with use of the device.
- The potential risks and benefits associated with use of the device.
- Post-operative care instructions
- A statement describing the potential risk of developing scalp metastasis.

RISKS TO HEALTH

Table 5 below identifies the risks to health that may be associated with use of cooling cap and the measures necessary to mitigate these risks.

Table 5: Identified risks to Health and Mitigation Methods

Identified Risk	Mitigation Method
Thermal tissue damage	Non-clinical performance data Software verification and validation Labeling
Electromagnetic Interference / Electrical Shock	Electromagnetic Compatibility and Electrical Testing

	Labeling
Adverse Tissue Reaction	Biocompatibility
Increased risk of scalp metastases	Labeling Patient Labeling
Use Error	Labeling
Scalp pain and Headache	Labeling
Chills	Patient Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, a Scalp Cooling System to reduce the likelihood of chemotherapy induced alopecia is subject to the following special controls:

1. Non-clinical performance data must demonstrate that the device meets all design specifications and performance requirements, and that the device performs as intended under anticipated conditions of use. This information must include testing to show accuracy of the temperate control mechanism.
2. Performance data must be provided to demonstrate the electromagnetic compatibility (EMC) and electrical safety of the device.
3. Software verification, validation, and hazard analysis must be performed.
4. The patient contacting components of the device must be demonstrated to be biocompatible. Material names must be provided.
5. Labeling must include the following:
 - a) A statement describing the potential risk of developing scalp metastasis.
 - b) Information on the patient population and chemotherapeutic agents/regimen for which the device has been demonstrated to be effective.
 - c) A summary of the non-clinical and/or clinical testing pertinent to use of the device.
 - d) A summary of the device technical parameters, including temperature cooling range and duration of cooling.
 - e) A summary of the device- and procedure-related adverse events pertinent to use of the device.
 - f) Information on how the device operates and the typical course of treatment.
6. Patient labeling must be provided and must include:
 - a) Relevant contraindications, warnings, precautions, adverse effects/complications.
 - b) Information on how the device operates and the typical course of treatment.
 - c) Information on the patient population for which there is clinical evidence of effectiveness.
 - d) The potential risks and benefits associated with use of the device.

- e) Post-operative care instructions
- f) A statement describing the potential risk of developing scalp metastasis.

BENEFIT/RISK DETERMINATION

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 30-150 minutes after termination of the infusion.

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.

The risks of the device are based on nonclinical laboratory as well as data collected in a clinical studies described above. Potential for scalp metastases in the future, headaches and neck pain are included.

The probable benefits of the device are also based on nonclinical laboratory and data collected in clinical studies described above. Patients may be able to have chemotherapy without the stigma of hair loss resulting in:

- Improved sense of well-being
- Improved body image.

Additional factors to be considered in determining probable risks and benefits for the DigniCap™ Scalp Cooling System include:

Patients place a high value on avoiding hair loss. The literature suggests that 8-10% of women will refuse chemotherapy because they do not want to lose their hair. It is difficult to get objective measurements, so patient satisfaction is the most important criteria. Quotes from patients illustrating benefits (C.J.G. van den Hurk, et.al., Impact of scalp cooling on chemotherapy-induced alopecia, wig use and hair growth of patients with cancer, European Journal of Oncology Nursing: 17(2013), 536-540.) include the following:

- “On good days between chemotherapy you don’t think about the disease until you look in the mirror”
- “when you look ill you feel ill”
- “I lost my personal identity with my hair”
- “ Chemotherapy induced hair loss makes cancer visible”

In the pivotal study design, the primary success endpoint was defined as greater than 50% of patients having a Dean score of ≤ 2 at 1 month (3-6 weeks) after conclusion of chemotherapy.

All chemotherapy regimens used in the study showed success. It is known that certain chemotherapeutic agents are more likely to result in hair loss regardless of use of scalp cooling. For example taxane based chemotherapeutic agents with scalp cooling result in chemotherapy induced alopecia (CIA) 80% of the time compared to 100% without cooling. Cooling prevents alopecia with anthracyclines close to 100%, yet when combine with a taxane it is only 36% effective. Even at that reduced level of effectiveness, many patients felt they benefitted from scalp cooling. The study showed an overall success of 70% of users were successes as defined by the study and in comparison 0% of controls. The controls lost all their hair when measured 1 month (3-6 weeks) after conclusion of chemotherapy. Although it was not powered for subgroup analysis, from the responses given by patients who were considered failures, there is overwhelming evidence to suggest that patients place a high value on not losing their hair.

The duration of the effect is limited to the time the treatment regimen lasts. Once chemotherapy has been completed, all patients experience a regrowth of hair.

Since it is during treatment that patients are most vulnerable to hair loss this duration of effect is valuable. Hair regrowth began at 6 weeks to 9 months after completion of chemotherapy. There are case reports of patients receiving high dose chemotherapy with bone marrow transplant who had permanent alopecia. These patients may benefit from scalp cooling in spite of presence of hematologic disease.

Regardless of the fact that hair color, texture and ability to style was different even with the cooling cap during chemotherapy, patients still saw benefit in preventing alopecia.

A total of 43 patients reported that headaches were triggered or exacerbated by scalp cooling treatment and the average level of pain experienced by these patients was 39.3 on a scale of 0 to 100 (with 100 being the worst pain). The feeling of chilliness during the cooling down period was reported by most patients (n=102) and with overall cooling treatment (n=104). Scalp pain associated with cooling was reported by 75 patients with an average level of any scalp pain experienced by these patients of 24.2 out of 100 (range 1.7 to 85.0). 10 % reported a feeling of claustrophobia. 2 patients withdrew because of cold intolerance and the increased time commitment needed for the trial. The remaining patients withdrew because they lost their hair. Patients seemed willing to accept this risk, even with the increased time commitment of 2.5 hours on the average per each chemotherapeutic session.

The risk of compromising treatment of scalp metastasis is small. National Surgical Adjuvant Breast and Bowel Project (NSABP) incidence is .025% isolated metastasis or site of first occurrence, while other studies have shown up to a 1.2 % risk of scalp metastasis. Scalp metastasis is the least common skin metastatic site. If present such a metastasis is usually an indicator of widespread metastatic disease suggesting a very poor prognosis. In these patients prevention of chemotherapy induced alopecia may not contribute to longevity but rather to quality of life. This device makes quality of life during treatment more tolerable. Up to 8-10% of women refuse chemotherapy for breast cancer for fear of alopecia. Patient blogs already encourage women to use scalp cooling to prevent hair loss and they are doing so. In the Dignitana Post Market Surveillance including 6000 patients scalp cooled with the DigniCap™

Scalp Cooling 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.

Alternatives to scalp cooling include:

- Pharmacological agents such as folic acid and a liposomal alternative of doxorubicin, minoxidil but have inconsistent with chemotherapy patients.
- Drug specific antibodies, hair growth cycle modifiers, cell cycle proliferation modifiers (epithelial growth factor) have shown limited success in small studies.
- Tourniquets
- Electrotrichogenesis (2002) using pulsed electrostatic field and has not been repeated.

These alternatives have all had equivocal results in preventing chemotherapy induced alopecia.

Patients in this country are already using ice packs to achieve the same results, which is a far more labor intensive solution and less controlled than use of this cooling cap would be.

In conclusion, given the available information above, the data supports that DigniCap™ Scalp Cooling System is indicated to reduce the frequency and severity of alopecia in female breast cancer patients.

The probable benefits outweigh the probable risks for the DigniCap™ Scalp Cooling System. The device provides substantial benefits and the risks can be mitigated by the use of general and special controls noted above. The risk of scalp metastases is low for the patients chosen for this study. Patients are already using a cruder alternative to cool their scalp during treatment, so they have clearly decided that this is an acceptable risk. In this study the patients who were successful complained about the color, quality and styling difficulties with the hair they retained while the failures were uniformly positive about the chance to try and avoid hair loss. From a patient satisfaction viewpoint, the benefit outweighs the risk and patients are empowered to weigh the risks and benefits and to participate in the decision.

CONCLUSION

The de novo for the DigniCap™ Scalp Cooling System is granted and the device is classified under the following:

Product Code: PMC

Device Type: Scalp cooling system to reduce or prevent the likelihood of chemotherapy induced alopecia

Class: II

Regulation: 21 CFR 878.4360