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DCP Protocol #: NWU2017-09-01

Local Protocol #: NCI 2017-09-01

PHASE I TRIAL OF ENDOXIFEN GEL VERSUS PLACEBO GEL IN WOMEN UNDERGOING BREAST SURGERY

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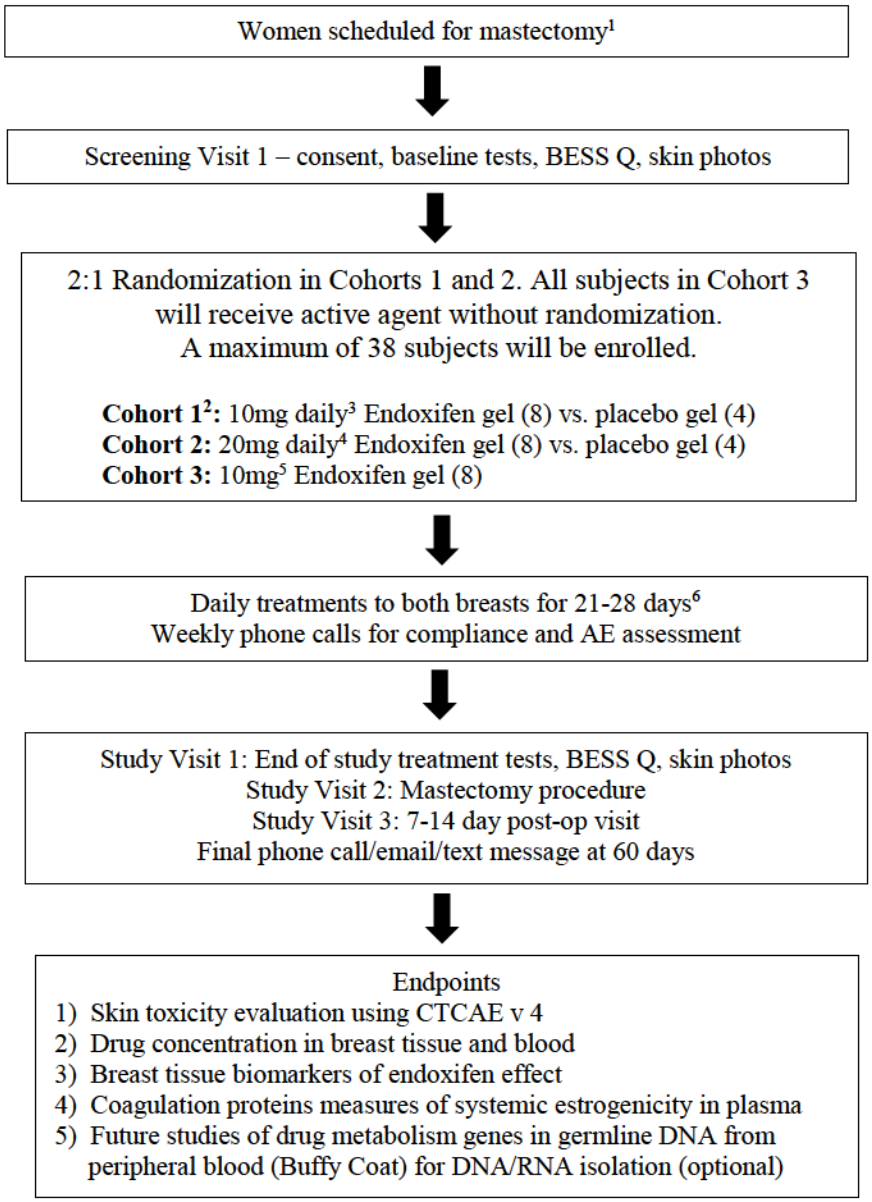
IND Sponsor: NCI/Division of Cancer Prevention
IND# [redacted]
Agent(s)/Supplier: National Cancer Institute
NCI Contract # HHSN2612201200035I
Protocol Template: Version 8.5 08/31/2016

Protocol Version Date: May 11, 2020

Protocol Revision or Amendment # Version 6.5

SCHEMA

NWU2017-09-01: Phase I trial of endoxifen gel versus placebo gel in women undergoing breast surgery



1: Mastectomy for stage 0-III breast cancer therapy or prophylaxis (BRCA mutation carriers, women with strong family history or lobular carcinoma in situ or other conditions where prophylactic mastectomy has been elected)
2: If more than one subject experiences dose-limiting toxicity in Cohort 1, the cohort will be extended to include an additional 6 subjects: 10mg daily[3] Endoxifen gel (4) vs. placebo gel (2).
3: 10 mg daily, applied 5 mg per breast
4: 20 mg daily, applied 10 mg per breast
5: Although no more than one subject experienced dose-limiting toxicity in Cohort 2, interim analysis showed more skin irritation and no permeation advantage with higher dose. Therefore, 10 mg daily dosage will be used for Cohort 3.
6: All subjects will undergo mastectomy at 21-28 days. If surgery needs to be delayed, an additional 7 days of treatment is allowed.

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1. OBJECTIVES

1.1 Primary Objective – The primary objective is to establish the dermal tolerability and safety of endoxifen (ENX) gel administered topically to both breasts at two doses: 10 mg daily (5 mg per breast) and 20 mg daily (10 mg per breast) in comparison to vehicle placebo gel, using objective assessments based on CTCAE criteria.

1.2 Secondary Objectives

1.2.1 To measure the breast tissue concentrations of (E) and (Z) isomers of N- desmethyl-4-hydroxytamoxifen (ENX) and 4-hydroxytamoxifen (4-OHT) at each dose (10 mg per day and 20 mg per day).
1.2.2 To measure the plasma concentrations of (E) and (Z) isomers ENX and 4-OHT at each dose (10 mg per day and 20 mg per day).
1.2.3 To measure plasma hormone levels for steroid hormones (estradiol, progesterone, dehydroepiandrostenedione [DHEA], androstenedione, testosterone) in comparison to vehicle placebo gel.
1.2.4 To measure serum estrogenic response to topical ENX gel therapy in comparison to vehicle placebo gel (sex hormone binding globulin and IGF pathway proteins).
1.2.5 To assess changes in coagulation parameters (Factor VIII, Factor IX, vWF, Protein S) in response to ENX gel therapy in comparison to vehicle placebo gel.
1.2.6 Using pre- and post-therapy tissue samples, to explore the potential therapeutic effects of the two doses of ENX gel in comparison to vehicle placebo gel: a) by IHC, Ki67 labelling (for cell proliferation), estrogen receptor (ER), progesterone receptor (PR) expression (for estrogen blockade); b) by expression of a panel of genes reported to change with ENX exposure (using nanostring assays).
1.2.7 Bank germline DNA for future pooled analyses of polymorphisms in tamoxifen metabolizing enzymes in comparison to vehicle placebo gel (optional).
1.2.8 To assess symptoms related to use of endoxifen gel in comparison to vehicle placebo gel, as assessed by the Breast Cancer Prevention Trial (BCPT) Eight Symptom Scale (BESS) questionnaire.

2. BACKGROUND

2.1 Need for new approaches for women with duct carcinoma in situ and those at high risk

Despite large Phase III clinical trials that have established the success of selective estrogen receptor modulators (SERMs) for breast cancer prevention[1-4] and therapy of duct carcinoma in situ (DCIS)[5, 6], the acceptance of tamoxifen (TAM) by women at high risk for breast cancer has been low [7-9]. Reasons include quality of life impairments, the possibility of serious side effects, and reluctance by healthy women to take oral medication for prevention. However, breast cancer prevention requires only that the breast be exposed to the drug; systemic exposure is both unnecessary and harmful. For example, 5 years of systemic exposure with oral TAM leads to benefits to the breast and bone, but with costs to quality of life, and health [10-12]. An alternative to oral delivery is that of transdermal delivery of drugs through the breast skin; its advantages include low systemic exposure, the avoidance of fast hepatic metabolism, and simplicity of application that will allow dissemination across the globe. Therefore, local transdermal therapy (LTT) to the breast is likely to improve the tolerability and the acceptance of pharmacological cancer prevention regimens by women.

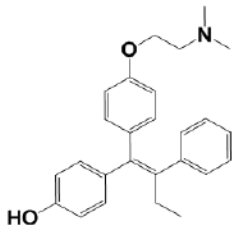
Existing data on LTT to the breast are summarized in reference 13[13], but in brief a developing body of evidence suggests that small lipophilic molecules such as 4-hydroxytamoxifen (4-

OHT), telapristone acetate (TPA), ENX and diclofenac can be locally concentrated in the breast when applied to the breast skin [14-17]. In the case of 4-OHT there is clinical data supporting good retention of drug in the breast with low systemic exposure, lack of first-pass hepatic metabolism, and biologic effect on breast cancer cells[15, 16]. For diclofenac too, we have shown retention in the breast with transdermal delivery through the breast (but not the abdominal) skin [17], and for TPA and ENX our preclinical studies demonstrate good dermal permeation with high concentrations achieved in the mammary gland where the drug was applied transdermally [17]. The sum of these clinical and preclinical studies using selective estrogen receptor modulators (SERMs) and a COX inhibitory agent lead to the proposition that LTT to the breast is a viable option for women requiring anti-tumor therapy delivered only to the breast (i.e., when there is no requirement for systemic therapy).

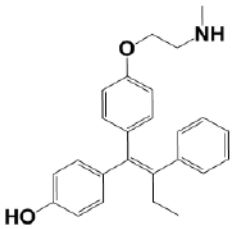
The unique features of the breast predict the success of LTT; these include the embryological origin of the breast as a skin appendage (a modified eccrine gland)[18] with a well-developed internal lymphatic circulation[19], and the presence of a subcutaneous and retro-mammary fatty envelope. Previous studies of LTT, including our recently completed pre-operative trial (NWU07-9-03) testing 4-hydroxytamoxifen (4-OHT) gel in women with ductal carcinoma in situ (DCIS), suggest that delivery is local with minimal systemic exposure, and good biological effect[15, 16, 20]. Given recent encouraging data on ENX, the other major metabolite of tamoxifen (see below), we performed preliminary testing of its dermal permeation. Our results suggested that ENX is in fact more suitable than 4-OHT for transdermal delivery[21], and led us to submit a proposal to PREVENT/DCP for the development of a transdermal formulation of ENX. Based on our preclinical data with an alcoholic gel formulation of ENX containing oleic acid 0.5% (v/v), transdermal gels of 0.5% and 1% (w/v) E/Z ENX, GMP grade, have now been formulated by investigators of the PREVENT Program, and toxicity studies are underway, with projected completion in June of 2017. The acquisition of preclinical toxicity data, as outlined below, now positions us to propose a Phase I safety and pharmacokinetic trial in women planning mastectomy. This will enable future clinical trials in women at high risk for breast cancer, and those with DCIS.

2.2 Endoxifen

ENX is particularly well suited for development as a breast LTT agent. Like 4-OHT, the binding affinities of ENX are 25-fold greater for ERα and 56-fold greater for ERβ than that of TAM [22, 23]. It has been reported that ENX and 4-OHT have similar anti-proliferative activity and selective inhibitory effects on ERα target genes when administered at equal concentrations in breast cancer cells [22, 24] and both ENX and 4-OHT induce similar changes in global gene expression patterns in MCF-7 breast cancer cells [23]. However, recent data have suggested that mechanism of ENX action may differ from 4-OHT. Wu et al. demonstrated that unlikely 4-OHT, ENX targets ERα for proteasomal degradation similar to that of the fulvestrant (ICI 182 780), ER-down regulator- [25]. Furthermore, Hawse et al., have reported that ENX-mediated recruitment of ERα to known target genes and global gene expression pattern differs from that of 4-OHT and fulvestrant in MCF cells [26]. This result contrasts to Lim's earlier finding which ENX regulates gene expression similar to 4-OHT. Both studies have used different concertation of estrogen and drug concertation in culture. Therefore a human study will be useful to investigate potential differences in mechanism of action between ENX and 4-OHT. The specific toxicity profile of ENX is under study, but results from the Mayo group suggest that, in terms of uterine weight, luminal epithelial cell height, and cell proliferation in the stroma and luminal epithelium of the uterus, ENX has similar uterotrophic effects to TAM when administered orally to rats [27]. If it shares the toxicity of the parent drug TAM and its



***(Z)*-4-hydroxytamoxifen (4-OHT)**



***(Z)*-*N*-desmethyl-4-hydroxytamoxifen (ENX)**

dermal permeation is equivalent to that of 4-OHT (or better), ENX is an excellent candidate for LTT. Additionally, the chemical structure of ENX would render it more suitable for transdermal delivery. It is smaller and more polar than 4-OHT; one methyl group at a tertiary amine is replaced with a hydrogen, resulting in a secondary amine, which is more hydrophilic than the tertiary amine of 4-OHT. With the addition of a permeation enhancer such as oleic acid (OA) which makes the stratum corneum fluidic [28, 29] and ethanol, which gives a continuous driving force [30, 31], ENX moves faster through the skin than 4-OHT [21]. The amine group of ENX may provide a favorable balance of hydrophilic and hydrophobic properties, making ENX traverse the stratum corneum more easily.

Oral ENX is well tolerated in a Phase I trial conducted by Goetz and colleagues (personal communication). The dose escalation was halted at oral doses up to 160 mg daily and the longest duration of therapy being 18 months (protocol 8821; NCT01327781) due to achieving steady-state serum concentrations of 4 μM rather than for toxicity. The major toxicity consisted of Grade 2 hot flashes. The study included dose finding groups of 3 patients at each dose and expansion cohorts of 5 patients at 40, 80, and 100 mg daily. Among these 37 Stage IV breast cancer patients treated with oral doses ranging from 20 mg to 100 mg daily, Grade 2 hot flashes occurred in 5/37 (13.5%).There were also reports of fatigue (3/37 or 8%) and anxiety (1 patient) and irritability (1 patient). A variety of other events were also observed in this pre-treated, Stage IV cancer population, which included hypertriglyceridemia (1 patient), seizure (1 patient), thromboembolism (1 patient), limb edema (1 patient), anemia and hypoalbuminemia (1 patient), sleep disturbance (2 patients), paresthesia (1 patient) and hypophosphatemia (1 patient). This agent is now being compared with oral tamoxifen in a Phase II trial in locally advanced or metastatic patients (A011203), where the ENX dose is 80 mg daily. Our previous clinical data with 4-OHT gel and transdermal diclofenac, both show low circulating drug levels with transdermal delivery. Therefore, we expect that systemic effects and tolerability will be more favorable than with the oral agent; nevertheless, we will monitor these using the BESS questionnaire, as in our previous studies.

Transdermal dose selection: Our in vitro (human skin)[21] and in vivo (rodent) data[17] demonstrates that ENX in a 60% (v/v) alcoholic gel with 0.5%(v/v) oleic acid, penetrates well and concentrates best in the mammary gland to which it is applied. (Z) ENX citrate salt (>97%) from Jina Pharmaceuticals [32, 33] was used for our in vivo animal study. Briefly, in a non-GLP (Good Laboratory Practice) study, we randomized nude rats into four groups: no treatment, oral TAM (3 mg/kg/day), 4-OHT gel (1 mg/kg/day), ENX gel (1 mg/kg/day), and treated them daily. *There were no deaths, no weight loss, and no skin irritation at the end of the experiment.* Gjerde et al. have reported dose-dependent increases in concentrations of ENX following administration of oral TAM, [34]. ENX concentration in normal breast tissue was not determined; however, it is safe to assume that these too will rise with increasing oral (and transdermal) dose. Our results from a pre-surgical phase IIb trial of transdermal 4-Hydroxytamoxifen versus oral tamoxifen in women with DCIS of the breast (NWU07-9-02) showed that women taking oral TAM 20 mg/day for at least 6 weeks achieved median ENX concentration of 8 ng/g in mammary adipose tissue [16]. Our preclinical data showed that daily oral TAM (3 mg/kg/day) for 6 weeks achieved the mammary concentration of 4-OHT and ENX of median 4~5 ng/g each in rats [17]. Plasma ENX concentration of women treated with 20 mg dose of oral TAM daily (NWU07-9-02) was 6 ng/mL (16 nM) [16]. Plasma ENX concentration of oral TAM-treated rats (3 mg/kg/day dose) was 3 ng/mL (8 nM), but 1.8 ng/mL (5 nM) in ENX-gel treated rats (1 mg/kg/day dose) [17]. ***The human equivalent dose (HED) of 3 mg/kg/day of oral TAM in rats is 0.48 mg/kg/day or 28.8 mg/day per 60 kg women and the HED of 1 mg/kg/day of 4-OHT or ENX gel in rats is 0.16 mg/kg/day or 10 mg/day per 60 kg women***. PK–PD modeling by Gong et al. shows tumor growth inhibition (TGI) in dose-ranging experiments of oral (Z) ENX in MCF7 xenograft bearing mice [35]. Therefore, our and others preclinical data suggest that our rat dose of (Z) ENX 1 mg/kg/day (***HED 0.16 mg/kg/day or 10 mg/day per 60 kg women***) is in the efficacious range, and given the expected high mammary concentrations, could potentially be lowered to reach the minimal effective dose.

Duration of exposure: the purpose of this first-in-human study of ENX gel formulated for transdermal ENX delivery in the US is to establish skin safety and to document dermal permeation. For these purposes, a duration of 21-28 days of exposure will be sufficient to show that there is no significant skin irritation caused by ENX, the carrier gel, or the oleic acid used for permeation enhancement. Studies of similar agents (4-OHT gel and telapristone gel) applied to the breast skin have shown excellent skin tolerability, and if this ENX gel formulation shows similar results, we will then plan studies with longer exposure.

ENX (E:Z=50:50) gel products - 0.5% and 1% (w/v), GMP grade: The NCI PREVENT program has developed ENX transdermal alcoholic gel products with 0.5% oleic acid as a permeation enhancer. (Z) ENX free-base in solid form is stable (data not shown) and relatively stable in ethanol with a Max solubility of ~50 mg/mL (EtOH). Long term stability testing (~6 month) was performed on the 0.5% and 1.0% (w/v) E/Z ENX mixture formulation. Overall, both formulations appear stable over time (less than 3% degradation). A total volume of each gel product is 90 mL. One pump delivers each dose in 1 mL or 0.8985 g of gel product. Each pump (1mL) contains 5 mg or 10 mg of (E/Z) ENX mixture per breast which contain 2.5 mg or 5 mg (Z) ENX per breast. Considering the application to both breasts, the final daily gel doses will contain 5 mg or 10 mg of (Z) ENX.

2.3 Rationale

2.3.1 Hypotheses

Our *primary hypothesis* is that ENX gel at 20 mg daily (10 mg per breast) will be safe and tolerable as assessed objectively using CTCAE criteria, in comparison to the placebo group.

Our *secondary hypotheses* include 1) the breast tissue concentrations of ENX at will reach the concentrations achieved in our prior study of oral tamoxifen versus 4-OHT gel (5.8 ng/g tissue) [36]. 2) The plasma concentrations of ENX at each dose (10 mg per day and 20 mg per day) will be significantly lower than those seen in women on oral tamoxifen. 3) Plasma hormones (estradiol, progesterone, DHEA, androstenedione, testosterone) will not be changed by ENX gel use. 4) Changes in serum estrogenicity (sex hormone binding globulin and IGF pathway proteins) will be minimal, if any. 5) Changes in coagulation parameters (Factor V, Factor VIII, von Willebrand factor, Protein S) will be minimal, if any. 6) Biologic endpoints such as Ki67 labeling index, ER, and PR expression, and expression of a panel of genes reported to change with ENX exposure, will be consistent with a therapeutic effect of ENX gel. 7) Polymorphisms in tamoxifen metabolizing enzymes will not affect breast tissue ENX concentration. This hypothesis will not be tested in the current study, but germline DNA will be banked for future pooled analyses of transdermally versus orally administered tamoxifen and metabolites relative to metabolic efficiency for oral tamoxifen. Banking of germline DNA for future pooled analyses will be optional for participants. 8) Symptoms reported with the use of ENX gel will be similar between treated and placebo groups.

2.3.2 The rationale for evaluating this agent in women with DCIS and those at high risk for breast cancer has been presented above in Section 2 (Background). However, the target population for the present study is women who are scheduled for mastectomy, either for risk reduction, or for breast cancer or DCIS therapy. Thus women with invasive breast cancer, who have not received neo-adjuvant treatment, will be included even though they are not the ultimate target population for transdermal ENX gel therapy. This is justified since the primary goal is to test skin safety of this agent, and transdermal permeation, both of which can be well-accomplished in a mastectomy population. Women with invasive cancer planning therapeutic mastectomy are unlikely to be harmed if they participate since the duration of intervention is short, will not delay therapeutic surgery, and poses minimal risk to the patient's eventual cancer therapy which will proceed post-operatively as clinically indicated. Literature review and

pertinent preclinical, pilot, and preliminary and/or unpublished data to support conduct of the trial is presented in Section 2 (Background).

2.3.3 We are proposing the first clinical trial of ENX gel for transdermal delivery in the US. Although a similar agent, 4-OHT, is well tolerated and safe, a Phase I study documenting safety and in vivo human skin permeation of ENX gel is needed. Components of excipients for ENX gel trial consist of oleic acid [0.5% (v/v) or 0.5% (w/w)], ethyl alcohol [60% (v/v) or 53% (w/w)], phosphate buffer at pH 7.0 [40% (v/v) or 44% (w/w), and hydroxypropyl cellulose [1.5% (w/v) or 1.67% (w/w)] (see Table 1B in Appendix G). This gel formulation is similar to the components of placebo gel used in several 4-OHT hydroalcoholic gel trials (based on 4-OHT investigator's brochure, Ascend Therapeutics Inc). Gelling material (hydroxypropyl cellulose) and dissolution method (phosphate buffer at neutral pH) are the same. Main differences are that our gel formulation contains less alcohol and uses oleic acid, 0.5%, as a skin permeation enhancer. Oleic acid (cis-9-octadecenoic acid) is a long-recognized useful permeation enhancer. Its utility is likely related to its bent *cis*-configuration, which appears to disturb the intercellular lipid packing of the stratum corneum, thereby reducing its barrier function [37, 38]. Oleic acid (OA) as a dietary substance is Generally Recognized as Safe (GRAS), and is present at concentrations of up to 70% in olive oil and peanut oil. It is used in six FDA-approved topical and transdermal formulations (generic testosterone gel, imiquimod cream and others). Information of inactive ingredients for approved drugs is publicly available at the Food and Drug Administration (FDA) website links (see Tables 2-5 in Appendix G). The FDA) allows a maximum amount of OA in unit dose up to 25% (w/w) as an inactive ingredient in topical formulations. For the transdermal patch, OA dose should not exceed 22 mg per day. Our formulation contains OA, 0.5% (w/w) which it is clearly at the low end of the range of approved products. Secondly, the FDA allows ethyl alcohol < 70% (w/w) for transdermal/topical route. Our formulation contains ethyl alcohol, 53% (w/w) which is less than an over-the-counter healthcare antiseptic, 61% (w/w) ethyl alcohol (Avagard, 3M Inc.) (see Table 3 and Figure 1 in Appendix G). Finally, hydroxypropyl cellulose and phosphate buffer have been widely used to topical/transdermal drugs already approved by the FDA (see Tables 4 and 5 in Appendix G). Based on this FDA safety information, we strongly believe that placebo gel will not have risk potential to patients if it is applied as directed.

2.3.4 Rationale for tobacco and alcohol use questionnaires: increasing evidence suggests that tobacco and alcohol use are risk factors in the development of intraepithelial neoplasia and cancer. In addition, tobacco and alcohol use may adversely affect agent intervention, for example by altering the safety profile or metabolism of a drug. Standardized assessments of tobacco and alcohol use during clinical trials will aid in understanding the potential relationship between the use of these products and clinical endpoints or cancer prevention biomarkers. Therefore, NCI, DCP is including assessment of tobacco and alcohol use at baseline and at study Visit 1, to determine the potential impact of tobacco and alcohol use on 1) treatment toxicity and symptom burden, and 2) the efficacy of treatment intervention.

3. SUMMARY OF STUDY PLAN

3.1 In this double-blind, randomized Phase I trial, a maximum of 38 participants who are planning mastectomy (unilateral or bilateral, for therapy or risk-reduction) will be accrued into each of three cohorts. The study agent is transdermal ENX gel versus placebo gel applied to the breast skin, starting with 10 mg ENX gel daily and proceeding to 20 mg daily (5 mg and 10 mg to each breast at each dose level). The ENX gel and placebo gels contain 60% (v/v) or 47.4% (w/v) alcoholic solution with 0.5% (v/v) or 0.45% (w/v) oleic acid. The trial will be conducted in the pre-surgical window setting, enrolling women who need unilateral or bilateral mastectomy, with a treatment period consisting of a 28 days ± 7 days, leading up to the day of mastectomy. Accrual will occur at NWU, MSKCC, and at Cedars Sinai Los Angeles (CS-LA).

3.2.1 We planned a 2:1 (ENX:placebo) randomization in cohort 1 and cohort 2, while all cohort 3 subjects would receive active gel at the final dose, but would cease therapy 3 days prior to surgery. Of the twelve Cohort 1 subjects, eight received ENX gel 10 mg daily (5 mg per breast) and four received placebo. Since no subject experienced dose-limiting toxicity (DLT) in Cohort 1, we proceeded to Cohort 2, where 12 subjects again were randomized 2:1. Eight received ENX gel 20 mg daily (10 mg per breast), and four received placebo gel. We initially planned that if no more than one subject experiences DLT, we would proceed to Cohort 3, where eight subjects would receive ENX gel at 20 mg daily (10 mg per breast), but stop gel application 3 days prior to surgery. An interim analysis was conducted after completion of Cohort 2 and discussed on April 13, 2020. Although only one subject in Cohort 2 experienced DLT, we observed more skin irritation in Cohort 2 participants. There was no permeation advantage with the higher dosage. Therefore, we decided to use a 10 mg daily dose for Cohort 3. Since drug concentration in the breasts was variable in the interim analysis, all Cohort 3 subjects will continue daily application of study drug until the day prior to surgery, in order to better assess the drug distribution in the breast. We expect a total of 8 subjects will complete Cohort 3, therefore a total of 32 subjects will complete the study.

3.2.2 Definition of Dose-Limiting Toxicity (DLT): for the purposes of this agent, and the anticipated need for long-term tolerability, we have used Grade 2 or greater skin toxicity as the DLT, using CTCAE criteria for the parameters shown in Table 1. The Grade 2 or greater reaction should *occur at the application site* for 48 hours or longer and be definitely, probably, or possibly related to the study drug to be a cause for participant withdrawal. After consultation with the NCI DCP medical monitor, a participant will be unblinded in the event of a DLT.

3.3 Participants will be given 1 canister of study agent, each containing 90 mL of active gel or placebo, at the baseline visit. Participants will take study agent for 21-28 days. The study will be terminated when 1) more than 2 subjects experience Grade 2 or greater toxicity (at application site for 48 hours or longer, and definitely, probably, or possibly related to study drug) in Cohort 1 and its expansion; or 2) eight subjects complete participation in Cohort 3.

3.4 No run-in period is planned.

3.5 Time points for performing study assessments for primary endpoint

3.5.1 Weekly phone calls to assess drug tolerability, with special emphasis on skin reactions if any. If skin reactions are reported by subjects between study visits, the participant will be asked to take a photograph (a single frontal view of both breasts, in good light). The participant will be provided a personalized link via email, where they can upload the photographs to a secure REDCap site. Dr. Choi will have access to this site and will evaluate the photos, and grade them using CTCAE criteria using the parameters outlined in Table 1. If she feels, or the participant requests, a consultation, this will be arranged to occur within the next 48 hours (or 72 hours if this happens to occur over a weekend). The NU dermatologist is Dr. Jennifer Nam Choi; at MSKCC Dr. Mario Lacouture; at Cedars Dr. Susan Rabizadeh. Prior to scheduling a consultation, Dr. Lacouture and Dr. Rabizadeh may also be granted access to photos from participants at their institutions through REDCap.

3.5.2 Baseline and end-of-intervention photos and skin toxicity assessment using CTCAE criteria. The photographs will be taken by the coordinator as a standardized single frontal view of both breasts (the view will include from the bottom of the neck to below the breasts, and from the lateral side of one breast to the lateral side of the other breast), and side views of each breast. They will be uploaded to NOTIS and viewed by Dr. Choi for scoring.

3.6 *Measurements taken to meet secondary study objectives*

Screening Visit 1: At entry for consent, review of eligibility, instructions on how to apply study agent, baseline symptom assessment, concomitant medication review, blood draw for clinical and research labs, urine or serum pregnancy test in women of child bearing potential, last menstrual period, BESS questionnaire, breast skin photos, CTCAE criteria assessment, and dispensing study agent.

Study Visit 1: Day before surgery. Symptom and adverse event assessment, concomitant medication review, last menstrual period, BESS questionnaire, breast skin photos, CTCAE criteria assessment, and study agent compliance.

Study Visit 2: Day of surgery. Blood draw for clinical and research labs, urine or serum pregnancy test in women of child bearing potential, physical exam, medical history, and tissue for research. Study visit 1 and 2 may be combined on day of surgery.

Study Visit 3: Post-operative visit. Symptom and adverse event assessment, concomitant medication review, last menstrual period, breast skin photos, and CTCAE criteria assessment.

3.7 Clinical procedures, lab tests and other measurements taken to monitor effects and safety of study agent.

- Skin evaluation through history, physical examination (documented by skin photographs and CTCAE criteria). This will be performed at study entry and at the end of intervention.
- Clinical blood tests pre and post intervention to establish good hematologic, renal, and liver function.
- Research blood tests pre and post intervention to evaluate effects on coagulation pathway proteins and markers of systemic estrogenicity.
- Urine pregnancy test in women with childbearing potential (pre and post intervention)
- Breast size and body mass index (BMI) pre intervention.
- Examination of breast tissue and plasma samples for drug concentration (at the end of intervention) and antiestrogenic effects of ENX gel (comparing samples obtained prior to and following intervention).

3.8 Duration of study: up to 7 days between consent and start of intervention, 21-28 days of intervention, 7-14 days after end of intervention. For participants who need to delay surgery, an additional 7 days of therapy will be allowed. Thus the minimum period on-study will be four weeks and the maximum will be seven weeks.

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

4.1.1 Women scheduled for unilateral or bilateral mastectomy for breast cancer therapy, pathology confirmed stage 0-III (including ductal carcinoma in situ), or prophylaxis (*BRCA1/2* mutation carriers, women with strong family history or lobular carcinoma in situ or other conditions where prophylactic mastectomy has been elected).

4.1.2 Age ≥18 years (since breast cancer is not a pediatric disease and no safety data are available for ENX use in children).

4.1.3 ECOG performance status ≤1 (Karnofsky ≥70%; see Appendix A).

4.1.4 Participants must have adequate hepatic and renal function tests, as defined below. Upper limits of normal (ULN) refer to those existing at each accruing institution.

Total bilirubin ……< 1.5 XULN
(in women with prior documented bilirubin elevations consistent with Gilbert's syndrome, total bilirubin up to 3X ULN will be allowed).
AST (SGOT) ……< 2.5 X ULN
ALT (SGPT) ……< 2.5 X ULN
Creatinine……< 2 X ULN
Alkaline phosphatase …… < 2.5 X ULN
Blood Urea Nitrogen……< 2 X ULN

4.1.5 Ability to understand and the willingness to sign a written informed consent document which includes a requirement to apply study agent to sensitive body parts daily.

4.1.6 Willingness and ability to schedule mastectomy 21-28 days following start of study agent. Women with breast implants may participate.

4.1.7 Willingness to avoid exposing breast skin to natural or artificial sunlight (i.e. tanning beds) for the duration of study agent dosing.

4.1.8 Negative urine or serum pregnancy test result, for participants of child bearing potential. Female of child-bearing potential is any woman (regardless of sexual orientation, whether she has undergone a tubal ligation, or remains celibate by choice) who meets the following criteria: has not undergone a hysterectomy or bilateral oophorectomy; AND has had a menstrual period at any time in the preceding 12 consecutive months).

4.1.9 The effects of topical ENX gel on the developing human fetus are unknown. For this reason, women of child-bearing potential and their male partners must agree to use effective forms of birth control (abstinence is not an allowed method) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately.

4.2 Exclusion Criteria

4.2.1 The presence of gross skin invasion/ulceration by the breast cancer, or inflammatory changes with skin edema AND erythema. Note: Paget's disease is permitted.

4.2.2 Women receiving a "nipple delay" procedure prior to mastectomy.

4.2.3 Women with skin diseases (psoriasis, eczema).

4.2.4 A history of thromboembolic disorder.

4.2.5 Endometrial intraepithelial neoplasia (also known as atypical hyperplasia) or a high risk of uterine cancer, defined here as known carriers of Lynch syndrome mutations (MLH1, MSH2, MSH6, PMS2).

4.2.6 Participants may not have received any other investigational agents in the previous 3 months.

4.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to tamoxifen.

4.2.8 Taken tamoxifen or other selective estrogen/progesterone receptor modulators (SERMs/SPRMs) within two years prior to entering study or been required to discontinue SERM therapy due to thromboembolic or uterine toxicity.

4.2.9 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

4.2.10 History of prior breast cancer-specific therapy within the previous 2 years (chemotherapy, radiation, anti-HER2 agents, endocrine agents, everolimus, CDK4-6 inhibitors). Previous unilateral radiation of the contralateral side in women scheduled for mastectomy is allowed. Study gel will be applied to both breasts.

4.2.11 History of prior mastectomy.

4.2.12 Pregnant or breastfeeding.

4.2.13 Patients receiving neoadjuvant chemotherapy with curative intent.

4.2.14 Men are excluded from this study since breast cancer is men is rare and there are no data regarding skin penetration of topical breast cancer prevention agents through male chest wall skin (which is thicker and harrier than female chest wall skin).

4.2.15 Current users of other topical medications on the breast skin must be willing and able to discontinue use for the duration of participation. Body lotion and other non-medicinal topical compounds may be applied >4 hours after study gel application.

4.3 Inclusion of Women and Minorities

Female members of all races and ethnic groups are eligible for this trial. Men are not eligible, since breast cancer is men is rare, there are no data regarding success of breast cancer prevention medications in men, and men are not included in breast cancer prevention agent guidelines. Additionally, there are no data regarding skin penetration of topical breast cancer prevention agents through male chest wall skin (which is thicker and hairier than female chest wall skin).

4.4 Recruitment and Retention Plan

Participants will be recruited at the Lynn Sage Breast Center of Northwestern University (NU), the Breast Service of Memorial Sloan Kettering Cancer Center (MSKCC), and the Saul and Joyce Brandman Breast Center of Cedars-Sinai Medical Center (CSMC); all women undergoing mastectomy for any reason will be approached. The PI at each site and/or designated staff will discuss the trial with gynecologists, primary care physicians, and oncologists of all disciplines at each center. Also, patients will be pre-screened through clinic visit lists. NU has requested a waiver of consent from the CIRB to support screening of clinic schedules of medical oncologists (or surgical oncologists etc.) and review of medical records/registry data to identify potentially eligible participants to contact about study participation. Once enrolled, patients will be under the supervision of the Principal Investigator at each site (Dr. Seema Khan at NU, Dr. Melissa Pilewskie at MSKCC, and Dr. Scott Karlan at CSMC). Dr. Khan will be responsible for the overall conduct of the study. Individuals completing the study will be reimbursed for incidental

expenses associated with these studies. Subjects will be reimbursed $100 after completion of Screening Visit 1, $100 after completion of Study Visit 1 (which may be combined with Study Visit 2 day of surgery), and $100 after completion of Study Visit 3. Subjects who are required to return to the office for a pregnancy test visit will receive an additional $100. Payments will be made at the conclusion of the participation. The day-to-day management of patients will be under the direction of Clinical Research Office at each of the Cancer Centers where the study is to be conducted (NU, MSKCC, and CSMC).

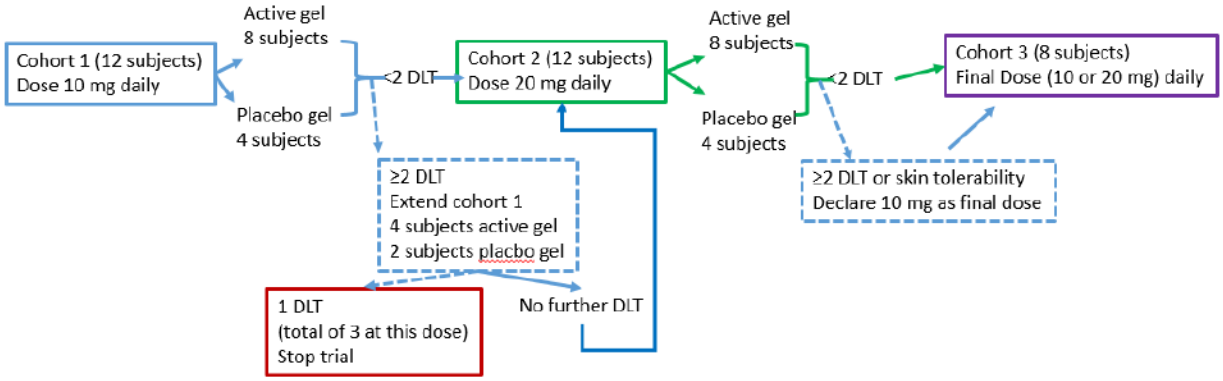
A number of contingency options can be considered if recruitment is below projections,

1) The study could be amended to include women planning breast-conserving surgery. This will still allow the assessment of skin safety, and an assessment of drug permeation, albeit more limited.
2) Protocol modification could be considered to invite women undergoing surgical resection of atypical/high risk lesions to participate. This will be a target population for eventual deployment of this agent, and therefore would be a relevant group to include if the protocol is expanded to procedures less than mastectomy.
3) Previous studies of 4-OHT gel have demonstrated steady state with 2 weeks of therapy, and therefore the treatment period could be shortened to 2-4 weeks.

5. AGENT ADMINISTRATION

Intervention will be administered on an *outpatient* basis. Reported AEs and potential risks are described in Section 6.2.

5.1 Dose Regimen and Dose Groups



This is a Phase 1 trial with a 2:1 randomization to active or placebo ENX gel applied to the breast skin, bilaterally. The study agent and placebo will be supplied by National Cancer Institute, Division of Cancer Prevention (NCI-DCP) and will be dispensed in metered canisters that deliver 1 ml of gel per pump (see more detail in 2.2 study agent). Briefly, ENX gel products with study agent were manufactured to deliver 5 mg or 10 mg of ENX mixture (E/Z=50:50) in 1mL (= 0.8985 g) of gel per pump. Therefore, one pump will deliver each dose 5 mg or 10 mg of (E/Z) ENX per breast. Considering the application to both breasts, the final daily gel doses will be 10 mg or 20 mg of ENX gel. In Cohort 1, active gel subjects will apply 10 mg ENX gel daily (5 mg gel in 1 pump to each breast) and in Cohort 2 active gel subjects will apply 20 mg ENX gel daily (10 mg in 1 pump to each breast). The last day of study agent administration will be the day before surgery. In Cohort 3, there is no randomization, all 8 subjects will apply10 mg ENX gel daily (5 mg gel in 1 pump to each breast) until the day before surgery. Skin health of the breasts will be established at baseline, and skin toxicity will be monitored weekly through phone calls, and at the

end of intervention through physical examination, and documented by photographs. Subjects with active skin disease on the breast (psoriasis or eczema) are excluded, as are those with ulcerated cancers. Subjects will be advised to not expose breast skin to direct sun or tanning beds, to not shower/bathe for at least 4 hours following gel application, and to avoid contact of breast skin with other individuals for at least 4 hours after application. After 4 hours, if contact is likely, the breast may be cleansed with a washcloth, or by bathing/showering.
The duration of intervention is 21-28 days. If required, because of a delay in surgery, up to extra 7 days of treatment will be allowed.

5.2 Study Agent Administration

5.2.1 All participants will receive either active gel or placebo gel each day and will be blinded to their randomization status. The study gel will be self-administered. All subjects in Cohort 3 will receive active drug.

5.2.2 One 90 ml canister of gel products containing placebo or study agent will be distributed to each participant at the baseline visit. Each participant will apply the gel daily to both breasts for 21-28 days. One pump (1 mL) of placebo or active gel products will be applied to both breasts once a day. The last day of gel application will be the day prior to the day of surgery.

5.2.3 The gel (ENX/placebo) should be applied in the morning after daily shower (in order to minimize potential transfer to the partner at night). Participants will be instructed on application of the drug to the breasts during the initial study visit, and will apply it each morning after a shower, allow it to dry for one minute and dress as usual. If they forget to apply the gel in the morning, administration later in the day is acceptable, as long as the skin has been washed since the last application. If a dose is missed and applied late, 12 hours should elapse before application of the next dose. Participants will be instructed not to bathe, swim, or shower for at least 4 hours after gel application. Contact of other individuals with the treated breasts is unlikely to be associated with significant transfer of drug; contact is permitted after the treated area has been washed with soap and water and washing is allowable after a minimum of 4 hours post-application.

5.2.4 The day of surgery, participants should refrain from applying any study agent, and be sure to bathe, shower, or wash their breasts before coming to surgery, to avoid the possibility of recently applied gel contaminating the samples taken for drug assays.

5.3 Run-in Procedures

No run-in procedures are planned.

5.4 Contraindications

Precautions regarding sun/tanning-bed exposure, bathing, and contact with others are described in Section 5.1.

5.5 Concomitant Medications

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant will be documented on the concomitant medication CRF and will include: 1) start and stop date, dose and route of administration, and indication. Medications taken for a procedure (*e.g.*, biopsy) should not be included.

5.6 Dose Modification

No dose modifications are planned, other than those outlined in the study schema. However, study agent will be discontinued if the participant experiences a dose-limiting toxicity.

5.7 Adherence/Compliance

5.7.1 Compliance is defined as application of 80% of doses during the intervention period (e.g. over 28 days, 22 doses must be applied, or over 21 days, 17 doses must be applied). Additionally during the last three days of planned treatment, no doses should be missed.

5.7.2 Compliance will be monitored by weighing the gel canister when dispensed, and when returned at the end of the intervention. Participants will either maintain a paper study diary or use a web-app that can be accessed by either smart-phone or computer/tablet. Compliance will also be checked during weekly phone calls.

5.7.3 Participants who do not utilize the phone website/application will receive reminders for study medication intake via email or text messages, sent by the study staff during the first week of study and further if needed. The study staff will send emails or text message on cellular phone; participants will be encouraged to respond to these messages indicating if dose has been taken. These responses will be used to assess compliance and will be reviewed at weekly phone contact. For participants who miss more than one dose in a week, the email/text reminders will continue further into dosing period.

Participant who do utilize the phone website/application will be contacted by the study coordinator if the participant misses two or more days of entry. These responses will be used to assess compliance and will be reviewed at weekly phone contact.

6. PHARMACEUTICAL INFORMATION

6.1 Study Agent (IND [redacted], NCI, Division of Cancer Prevention)

ENX Gel
(E/Z)-ENX ([E/Z]-4-hydroxy-N-desmethyltamoxifen hydrochloride), a 1:1 racemic mixture, is provided as a 0.5% (w/v, 5 mg/mL) and a 1.0% (w/v, 10 mg/mL) hydroalcoholic gel. Gel excipients include 60% ethanol, 1.5% (w/v) hydroxypropyl cellulose (Klucel HF), and 0.5% oleic acid in phosphate buffer at pH 7.0. The gel is provided in a pump with each pump action expelling 1 mL of gel containing 5 or 10 mg of ENX from the 0.5% and 1.0% mixtures, respectively.

Placebo Gel
Matching placebo gel contains the same excipients and is provided in the same pump format.

6.2 Reported Adverse Events and Potential Risks

(E/Z)-ENX gel, a 1:1 racemic mixture, is being provided in a topical hydroalcoholic gel for transdermal administration to the breasts for localized treatment. (Z) ENX is a highly active metabolite of tamoxifen, ~100 times more active, and thus this and another closely-related metabolite (Z) 4-hydroxytamoxifen (4 OHT) are thought to provide the bulk of tamoxifen's pharmacological activity. Consequently, tamoxifen is now viewed as a prodrug. ENX is formed in two steps from tamoxifen, by cytochrome P450 (CYP) 3A4 and CYP2D6, and then conjugated by phase II enzymes in the liver to inactive forms by sulfation or

glucuronidation [39]. Interconversion of (Z) - to (E)-ENX isoforms occurs spontaneously and bidirectionally in an aqueous environment, including media and biological fluids, though oxidative conditions and elevated temperatures increase isomerization [40]. (E) isomers of 4-OHT and ENX have much lower binding affinities for the estrogen receptor (ER) compared with their (Z) isomer versions, ~200 times lower affinity; thus, even in the presence of equal amounts of (E)-ENX, (Z)-ENX antagonism dominates ER pharmacological activity[41].

This protocol will be the first to treat women with topical doses of ENX gel in the US. However, women have previously been exposed to systemic ENX from oral tamoxifen dosing as a secondary consequence of its metabolism and from oral (Z)-ENX, an investigational breast cancer agent under evaluation by NCI, Division of Cancer Treatment and Diagnosis (DCTD). For the latter, in NCI-sponsored studies (NCT01327781, NCT01273168, and NCT02311933) women with ER-positive breast cancer are being treated with oral (Z)-ENX capsules, to avoid the metabolic requirement of CYP2D6 for tamoxifen since some women have CYP2D6 mutant alleles and thus are genotypically unable to properly or efficiently metabolize tamoxifen to its more active metabolites [42]. The human safety profile of oral (Z)-ENX capsules from the DCTD IND is summarized below, though topical dosing of ENX gel is anticipated to result in much lower systemic ENX so adverse events (AEs) may be significantly fewer and of lower grade. To support topical human dosing of ENX gel, animal toxicology studies have been completed and are described below. Finally, topical dosing of the closely-related molecule 4-OHT in a hydroalcoholic gel has been conducted in women for various different indications such as breast cancer [15, 36]and mastalgia (breast pain) [43]. These studies revealed that topical 4 OHT gel was well-tolerated though some transient and mild skin AEs occurred such as erythema and pruritis; topical ENX gel may exhibit a similar safety profile.

Oral (Z)-ENX - Human Safety Profile

Under the DCTD IND, which is cross-referenced by NCI, DCP's IND, women with metastatic breast cancer have been treated with capsules of oral (Z)-ENX. The dose escalation study did not identify a maximum tolerated dose (MTD) due to low toxicity of the agent and instead dose escalation was stopped at 160 mg/day since this dose achieved the target plasma steady-state concentration (Css) of >4 μM (Z)-pENX. Anti-tumor activity has been observed (data cut-off date 09/30/2014), with six partial responses in 55 evaluable patients. Common AEs in order of frequency have been (data cut-off date 09/30/2014): hot flashes (43%), lymphocyte count decreased (20%), anemia (19%), fatigue (17%), nausea (14%), platelet count decreased (13%), alanine aminotransferase increased (ALT, 12%), aspartate aminotransferase increased (AST, 12%), irritability (12%), white blood cell count decreased (12%), edema limb (10%), hypertriglyceridemia (10%), anorexia (9%), and high cholesterol (9%). Severe AEs were: ALT (grade 3), hypertriglyceridemia (grade 4), and thromboembolic events (one each grade 3 and 4).

Topical (E/Z)-ENX - Nonclinical Safety Profile <<Final results pending ongoing studies>>

ENX has undergone preclinical animal testing sponsored by NCI, DCP and DCTD to support human clinical studies. These studies include multiple routes of administration to fully understand the systemic and local toxicity profiles. 28-Day toxicology studies of oral ENX or single-isomer (Z)-ENX have been completed in rats and dogs. A 28-day dermal toxicity study of ENX applied to mammary glands is underway in minipigs (results pending). ENX is not phototoxic based on a negative in vitro neutral red study. Finally, an immunotoxicity study, dermal delayed hypersensitivity, is underway in guinea pigs (results pending).

Oral (Z)-ENX doses ≤200 mg/kg/day were well-tolerated when administered for four days to female rats. Oral (Z)-ENX administered daily to rats for 28 days resulted in lethality at doses ≥80 mg/kg/day (≥480 mg/m2/day). The MTD was 20 mg/kg/day (120 mg/m2/day). Clinical signs of toxicity (abdominal

distention, dyspnea, hunched posture, and discharge from the nose/mouth) occurred mainly in rats administered ≥80 mg/kg/day. Changes in clinical pathology parameters were noted in alkaline phosphatase (ALP), albumin, ALT, AST, calcium, and total protein; decreased uterine weight also occurred. Liver, lung, heart, kidney, gastrointestinal (GI), skeletal muscle, and reproductive tract toxicity were dose-limiting. With the exception of ovarian cysts and histiocytic infiltration of the lung, oral (Z)-ENX toxicity appeared to be reversible after a 28-day recovery period.

Oral 28-day dosing of rats with the racemic (E/Z)-ENX mixture at lower doses, 1, 20, or 40 mg/kg/day vs. single isomer (Z)-ENX at 40 mg/kg/day resulted in reduced body weight gain and/or body weight loss in males and females at all levels of treatment, though no definitive, dose-related alterations in clinical pathology parameters or clinical observations were noted. No definitive macro- or microscopic pathology observations occurred in male rats at any dose level, while the ovary was identified as a target organ in females following doses of 20 and 40 mg/kg/day (E/Z)-ENX and of 40 mg/kg/day (Z)-ENX. Microscopic pathology findings indicated that ovarian toxicity had not reversed 15 days following cessation of dosing.

Oral (Z)-ENX at 30 mg/kg/day resulted in dose-limiting emesis in female dogs after 4 consecutive days during a 28-day cycle. Reproductive tract toxicity was observed in females (vaginal epithelium hyperplasia) and males (atrophy of the prostate and testes, depletion of spermatozoa in the epididymides) and thymic atrophy in both sexes. Reproductive tract lesions were not reversible after a 28-day recovery period. A no observed adverse effect level (NOAEL) was not established. The MTD was >30 mg/kg/day (>600 mg/m2/day). With respect to body surface area, the MTD in dogs (>600 mg/m2/day) was at least five-fold greater than the rat MTD (120 mg/m2/day).

ENX dose-dependently inhibited human potassium channels in a patch-clamp study with a 50% inhibitory concentration (IC50) of 1.6 □M which was similar to the IC50 value of 1.2 μM for tamoxifen which is known cause adverse cardiovascular effects such as QT prolongation and torsades de pointes [44].

Topical (E/Z)-4-Hydroxytamoxifen - Human Safety Profile

Due to its similarity to ENX gel, the human safety profile of topical 4-OHT gel may be a guide for AEs. Topical 4-OHT in alcohol solution or gel has been administered to >450 pre- and postmenopausal women. In phase 1 safety and PK studies, topical 4-OHT was provided to women at doses ranging from 0.25–1 mg/breast/day for three weeks up to three months. Topical 4-OHT was well tolerated with only drug-related mild pruritus being observed in a few patients. Topical 4 OHT resulted in substantial breast tissue uptake with minimal metabolism and very low systemic plasma concentrations.

Phase 2 studies of topical 4-OHT up to 4 mg/day for up to six months was well-tolerated, absorbed, and pharmacologically active in breasts for reducing breast pain (mastalgia), breast density (a breast cancer risk factor), and breast cancer cell proliferation in women with ductal carcinoma in situ (DCIS) and locally advanced breast cancer. In a placebo-controlled, six-month phase 2 study of 4-OHT topical gel in premenopausal women with cyclical breast pain, the most common AEs seen in 4-OHT- vs. placebo-treated women (4 mg/day) were: headache (20% vs. 10%), nasopharyngitis (11% vs. 12%), application site reaction (4% vs. 0%), and pharyngitis (4% vs. 0% [36]. These events were all mild to moderate and some headaches and application site reactions (application site burning, itching) were deemed drug-related. Additional drug-related AEs seen in 4-OHT-treated women were decreased appetite, exfoliative dermatitis, and hypotension. No significant changes in hematologic parameters, liver function, renal function, electrolytes, or serum glucose were observed.

In a NCI, DCP-sponsored presurgical study of women with DCIS, 6–10 weeks of topical 4-OHT gel at 4 mg/day (2 mg to each breast) or oral tamoxifen at 20 mg/day resulted in similar 4-OHT breast levels and similar reductions in breast tumor cell proliferation [36]. Systemic levels of 4 OHT were markedly lower

(five-fold) with topical 4-OHT gel compared with oral tamoxifen. 4-OHT topical gel was well-tolerated and the most common AEs that were either similar or less frequent in 4-OHT- vs. tamoxifen-treated women were: hot flush (50% vs. 50%), breast pain (42% vs. 64%), fatigue (33% vs. 29%), and hyperhidrosis (25% vs. 43%). Only three AEs were elevated in 4-OHT-treated women compared with tamoxifen-treated women: pruritis (17% vs. 0%), vulvovaginal dryness (17% vs. 0%), and weight increased (17% vs. 0%).

6.3 Availability

Topical (*E/Z*)-ENX gel, 0.5% and 1.0%, an investigational agent, and matching placebo gel are supplied to investigators by NCI, DCP.

6.4 Agent Distribution

Agents will only be released by NCI, DCP after documentation of IRB approval of the DCP-approved protocol and consent is provided to DCP and the collection of all Essential Documents is complete (see DCP website for description of Essential Documents).

NCI, DCP-supplied agents may be requested by the Investigator (or their authorized designees) at each Organization. DCP guidelines require that the agent be shipped directly to the institution or site where the agent will be prepared and administered. DCP does not permit the transfer of agents between institutions (unless prior approval from DCP is obtained). DCP does not automatically ship agents; the site must make a request. Agents are requested by completing the DCP Clinical Drug Request form (NIH-986) (to include complete shipping contact information) and faxing or mailing the form to the DCP agent repository contractor:

John Cookinham
MRIGlobal
DCP Repository
1222 Ozark Street
North Kansas City, MO 64116
Phone: (816) 360-3805
FAX: (816) 753-5359
Emergency Telephone: (816) 360-3800

6.5 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from DCP using the NCI Drug Accountability Record Form (DARF). The Investigator is required to maintain adequate records of receipt, dispensing and final disposition of study agent. This responsibility has been delegated to each accrual site's pharmacy. Include on receipt record from whom the agent was received and to whom study agent was shipped, date, quantity and batch or lot number. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant.

6.6 Packaging and Labeling

Topical (*E/Z*)-ENX gel, 0.5% and 1.0%, and matching placebo gel will be packaged by NCI, DCP.

6.7 Storage

In each institutional research pharmacy, the gel must be stored in a locked and secure area at room temperature, 59-86 ° F (15-30 ° C) and protect from light and moisture. Participants will be instructed to store their study agent in a location not accessible by children, at room temperature, and protected from light and moisture.

6.8 Registration/Randomization

1. A study coordinator must upload into the Northwestern Clinical Trials Management System, a signed and complete informed consent along with HIPAA authorization and a completed eligibility form for each participant identified as eligible to be entered into the study.
2. All participants must be registered in the Northwestern University Robert H. Lurie Comprehensive Cancer Center Clinical Trials Management System (CTMS). Participants must not start protocol treatment prior to registration in the Lurie Cancer Center CTMS.
3. After registration in the CTMS, participants will be assigned a participant identification number and a randomization number when applicable.
4. An NCPC Quality Assurance Monitor will submit the following into the REDCap Randomization Information Form: (1) Study Number, (2) Site, (3) Pharmacist Email(s), (4) Participant ID [PID], (5) Participant Initials, and (6) Randomization Date.
5. An Automatic Treatment Assignment Notification email will be sent to the research pharmacist(s) containing: (1) Study Number, (2) Site, (3) Participant ID [PID], (4) Participant Initials, (5) Randomization Date, and (6) Treatment Assignment.
6. The clinical research coordinator(s) will receive a Confirmation of Registration containing the PID via email.
7. The following people will have a copy of the un-blinded randomization log: the study statistician at NU, the Quality Assurance Team at NU, and the Investigational Pharmacists at each site. The following people will have access to the REDCap study project containing randomization information: the study statistician at NU and the Quality Assurance Team at NU. The study statistician will set up randomization blocks.

When possible, the study coordinator will notify an NCPC Quality Assurance Monitor and/or send an email to ncpc@northwestern.edu prior to registering a participant. Prior notification is required for participant randomizations outside the normal business hours of Monday-Friday 9:00am-5:00pm CT.

6.9 Blinding and Unblinding Methods

Study participants will receive a prescription, blinded, from the investigational pharmacy. The blind will be maintained through the effort of the pharmacodynamics analyst and the pharmacy. Unblinding will occur when it is deemed medically necessary or in the event of a DLT and will only take place after consultation with the NCI, DCP Medical Monitor:

Name:	Marjorie Perloff, MD
Address:	Division of Cancer Prevention National Cancer Institute 9609 Medical Center Drive, 5E544 Rockville, MD 20850
Tel:	(240) 276-7097 (during normal business hours)
Cell:	(240) 731-1772
Fax:	(240) 267-7828
Email:	perloffm@mail.nih.gov

After hours consultation will be provided by Dr. Seema Khan, at telephone 312-503-4236 or cell phone 312-307-3646.

6.10 Agent Destruction/Disposal

DCP-supplied agents: at the completion of investigation, all unused study agent will be returned to NCI, DCP Repository according to the DCP "Guidelines for AGENT RETURNS" and using the DCP form "Return Drug List".

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

SCHEDULE OF EVENTS

Procedure	**Screening Visit 1[1]**	**Day 8±3, 15±3, 22±3 (1st day of study drug =day 1)**	**Study Visit 1 (day before surgery)[6]**	**Study Visit 2 Day 22 to 29 (day of surgery)[8]**	**Study Visit 3 Day 29-50 (7-14 days after surgery)**	**Phone, email, or text Follow-Up Day 60 ±7**
Assess Eligibility	X					
Informed Consent	X					
Registration	X					
Randomization	X					
Medical History	X			X[7]		
ECOG Performance Status	X					
Last Menstrual Period	X		X		X	X
Physical Exam	X			X[7]		
Vital Signs/ Height and Weight	X			X	X	
Body Mass Index	X					
Breast cup size	X					
Breast skin photos	X		X[9]		X[10]	
BESS Questionnaire	X		X			
Tobacco and Alcohol Use Questionnaires	X		X			
CTCAE skin toxicity	X	X	X		X	
Clinical Labs (LFTs and Renal function tests)	X			X		
Urine or Serum Pregnancy Test	X[2]			X[5]		
Research blood specimen collection	X			X		
Tissue procurement for research purposes[3]	X			X		
Concomitant Medications	X	X	X		X	
Dispense Study Agent and diary[4]	X					
Collect Study Agent			X			

Procedure	Screening Visit 1[1]	Day 8±3, 15±3, 22±3 (1st day of study drug =day 1)	Study Visit 1 (day before surgery)[6]	Study Visit 2 Day 22 to 29 (day of surgery)[8]	Study Visit 3 Day 29-50 (7-14 days after surgery)	Phone, email, or text Follow-Up Day 60 ±7
Review Agent Diary/Record			X			
Adverse Events assessment		X	X		X	
Telephone/Email Contact		X				X

[1]Screen 1 will occur within 6 weeks prior to registration.
[2]Required within 5 days prior to starting study treatment for females of child-bearing potential. Women of child-bearing potential whose Screening Visit 1 occurs >5 days prior to starting study agent, will have a separate office visit to conduct a second pregnancy test within 5 days of starting study agent.
[3]Tissue will be obtained from the diagnostic core needle biopsy (DCNB) as well as the surgical resection specimen for study end points. Though there is no physical collection of tissue at Screening Visit 1, release for acquisition of DCNB tissue will be completed at this visit.
[4]Participants who are unable to pick up the study medication will receive it via mail or courier delivery requiring signature to confirm receipt.
[5]Urine or serum pregnancy test is routinely performed for females of child-bearing potential prior to the surgery.
[6]Study Visits 1 and 2 may be combined on the same day if feasible and convenient (i.e. surgery start time allows completion of Study Visit 1 tasks prior to surgery start time). If this is not possible, Study Visit 1 will occur on the day prior to surgery.
[7]Source document will be anesthesiologist or surgeon pre-op history and physical. May have been performed on day of surgery or within 28 days prior.
[8]Participants who require a delay in surgery will be allowed to continue treatment for up to 7 additional days.
[9] Study Visit 1 skin photos will be taken only in participant experiencing skin toxicity, and will focus on the area showing the skin toxicity.
[10] Study Visit 3 skin photos will be taken only in participants who had documented skin toxicity at Study Visit 1, and will focus on the area showing the skin toxicity.

7.2 Baseline Testing/Pre-study Evaluation

7.2.1 Screening Visit 1

The following will be collected:

1. Informed Consent
2. Medical History per treating physician
3. ECOG performance status
4. Prior and concomitant medication review
5. Vital signs assessment
6. Physical Exam per treating physician within 6 weeks of registration
7. Clinical labs for renal and hepatic function including total bilirubin, AST, ALT, alkaline phosphatase, blood urea nitrogen, and creatinine to be collected within 6 weeks prior to registration
8. Blood collection for research purposes:
    a. Two 3 mL Blue Top tube (citrate) for coagulation panel.
    b. Two 10mL Lavender top tubes (K_2EDTA) to obtain plasma for hormone level measurement (estradiol, progesterone, and androgens [DHEA (dehydroepiandrosterone),

androstenedione, and testosterone]) and measurement of IGF-1, IGFBP-3, and SHBG. Buffy coat (white blood cells (WBC)) will be saved for DNA/RNA isolation for future pooled analyses if the subject consents to this optional study.

9. Skin symptoms per CTCAE criteria (Table 1)
10. Review of conformance with Inclusion / Exclusion criteria
11. BESS questionnaire (Appendix D)
12. Tobacco and Alcohol Use Questionnaires
13. Breast skin photos
14. Breast cup size
15. Body Mass Index (BMI)
16. Collection of last menstrual period date for premenopausal participants
17. Urine or serum pregnancy test for women with child-bearing potential
18. Registration and randomization
19. Dispensing study medication (for participants who are not able to pick it up, the study medication will be delivered via mail or courier requiring signature for confirmation of receipt). Participants of child-bearing potential will begin dosing within 5 days of a negative pregnancy test.
20. Participant diary (Appendix B and C) will be reviewed and dispensed along with the study medication.
21. Tissue will be obtained from the DCNB as well as the surgical resection specimen for study end points. Though there is no physical collection of tissue at Screening Visit 1, release for acquisition of DCNB tissue will be completed at this visit.

The amount of study agent that will be distributed to the participant at the screening visit will be 1 canister of active or placebo gel. They will return it at Study Visit 1 (the evening before or the morning of surgery).

7.3 Evaluation During Study Intervention

7.3.1 Weekly phone calls for monitoring of toxicity and compliance. (Days 8±3, 15±3, 22±3)
All participants will be followed during intervention via weekly telephone calls by the clinical research staff to assess compliance and adverse events. The study staff will call on days 8, 15, 22 from the first day of study medication (± 3 days). If these days are non-business days, the calls will be made on the next closest business day. Emails may be substituted for the weekly phone calls. Please refer to Appendix E for suggested statements for participant communications.

At these phone calls, the following with be collected:

1. Concomitant medication review
2. Adverse events – To assess adverse events participants will be asked non-leading questions, followed by the questions in Appendix E as needed, to document if they have experienced any of the following symptoms:
   a. Skin symptoms based on Table 1, explained to participants using plain language
   b. Hot flashes
   c. Vaginal discharge
   d. Uterine spotting/ Uterine bleeding
3. Additionally, any other symptom experienced by participants will be recorded to assess adverse events.

7.3.2 Study staff will also call participants four days prior to surgery to remind participants to continue study agent for the last three days prior to surgery. If a reminder call falls on a non-business day, the call will be made on the next closest business day. Reminder calls may be substituted for emails and may be combined with weekly phone calls for monitoring toxicity and compliance.

7.4 Evaluation at Completion of Study Intervention

Study Visits 1 and 2 may be combined on the same day if feasible and convenient (i.e. surgery start time allows completion of Study Visit 1 tasks prior to surgery start time. If this is not possible, Study Visit 1 will occur on the day prior to surgery. Participants will fast from midnight on the evening prior to surgery.

7.4.1 Study Visit 1 (Day before surgery, can occur on the day of surgery if feasible for participant to arrive early)

1. BESS questionnaire (Appendix D)
2. Tobacco and Alcohol Use Questionnaires
3. Skin symptoms per CTCAE criteria (Table 1).
4. Breast skin photos, taken only in participants experiencing skin toxicity, and will focus on the area showing the skin toxicity.
5. Collection of last menstrual period date for premenopausal participants
6. Concomitant medications and adverse events assessment
7. Compliance assessment (weighing gel dispensers) and collection of study agent
8. Collection of study diary.

7.4.2 Study Visit 2 (Day of surgery, day 22-29)
On arrival the following procedures/evaluations will be performed:

1. Urine or serum pregnancy test (for subjects of child bearing potential) - per standard of care prior to the surgery.
2. Medical history per treating physician
3. Physical exam. The source document for this may be anesthesia or surgery H&P, completed within 28 days prior to surgery.
4. Vital signs assessment per anesthesia assessment or pre-operative nursing evaluation
5. Clinical labs for renal and hepatic function including total bilirubin, AST, ALT, alkaline phosphatase, blood urea nitrogen and creatinine
6. Blood collection for research purposes:
    a. Two 3 mL Blue Top tube (citrate) for coagulation panel.
    b. Two 10mL Lavender top tubes (K_2EDTA) to obtain plasma for hormone level measurement (estradiol, progesterone, and androgens [DHEA (dehydroepiandrosterone), androstenedione, and testosterone]) and measurement of IGF-1, IGFBP-3, and SHBG. Buffy coat will be saved for DNA/RNA isolation for future pooled analyses if the subject consents to this optional study.
7. Blood collection should occur prior to completion of the mastectomy (i.e. if blood is not drawn prior to the patient entering the operating room, it can be drawn in the OR).
8. Tissue will be obtained from the DCNB as well as the surgical resection specimen for study end points.

7.5 Post-intervention Follow-up Period

7.5.1 Study Visit 3 (Post-op visit in the breast surgery clinic, day 29-50) (The intent is to have this visit 7-14 days after study visit 2):

1. Vital signs assessment
2. Concomitant medication follow-up assessment for those taken prior to surgery. No new concomitant medications will be recorded unless they pertain to adverse events that occurred prior to surgery.

3. Adverse event follow-up assessment for those occurring prior to surgery. No new adverse events after surgery will be recorded.
4. Collection of last menstrual period date for premenopausal participants
5. Evaluation of skin for CTCAE criteria; if ambiguity as to post-surgical change versus skin toxicity, treating surgeon and dermatologist will together assign causation to surgical or drug relationship.
6. Skin photos, taken only in participants who had documented skin toxicity at Study Visit 1, and will focus on the area showing the skin toxicity.

7.5.2 One month follow-up phone call for premenopausal subjects (day 60 ± 7)

1. Collection of last menstrual period for premenopausal participants.

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

8.1 Primary Endpoint

The primary endpoint is the dermal tolerability and safety of ENX gel at two doses: 10 mg daily and 20 mg daily, using objective assessments as defined in the CTCAE criteria (Table 1), and skin photos before and after treatment.

Table 1 Modified CTCAE for assessing skin toxicity of endoxifen gel applied to the breast skin. These assessments will be made on the breast skin (application site).

	Grade 1	Grade 2	Grade 3
Dry Skin	No erythema or pruritus	With erythema or pruritus	With erythema and pruritus
Pain of Skin	Mild pain	Moderate pain	Severe pain
Photosensitivity	Painless erythema	Mild to moderate pain with erythema	Erythema with blistering
Pruritus	Mild, requiring topical intervention	Intense, with changes from scratching, oral intervention needed	Intense, constant, limiting ADL or sleep, oral steroids needed.
Rash maculopapular	Macules or papules <25% of treated area, with or without symptoms (pruritus, burning, tightness)	Macules or papules >25% of treated area, with or without symptoms (pruritus, burning, tightness), limiting instrumental ADL	Macules or papules > 25% of treated area, with or without symptoms (pruritus, burning, tightness), limiting self-care ADL
Urticaria	Asymptomatic or mild symptoms, not requiring therapy	Moderate; limited local therapy needed, limiting instrumental ADL	Urticarial lesions covering >30% of application area; oral or IV intervention needed

8.2 Secondary Endpoints

1. Demonstrate dermal permeation of ENX gel is similar to ENX levels achieved with oral delivery (mean values of 5-6 ng/G breast tissue). The mastectomy will be bread-sliced as per usual pathology protocol. Drug concentration in non-tumor tissues will be measured at 5 different sites within each breast. The central slice (in line with the nipple, will be sampled as shown in **Figure 2** Two additional slices will be sampled, half-way between the center and the periphery of the breast, medially and laterally. The mastectomy specimen will be collected at surgery; the PCF will be called by the OR nurse as soon as the specimen is removed; details are described in section 10.2.2. If skin is resected (i.e. if the procedure is not a nipple-sparing mastectomy), a skin sample will also be collected for dermatological pathology assessment. The drug assays will be performed by LC/MS-MS as in our previous study [36] .

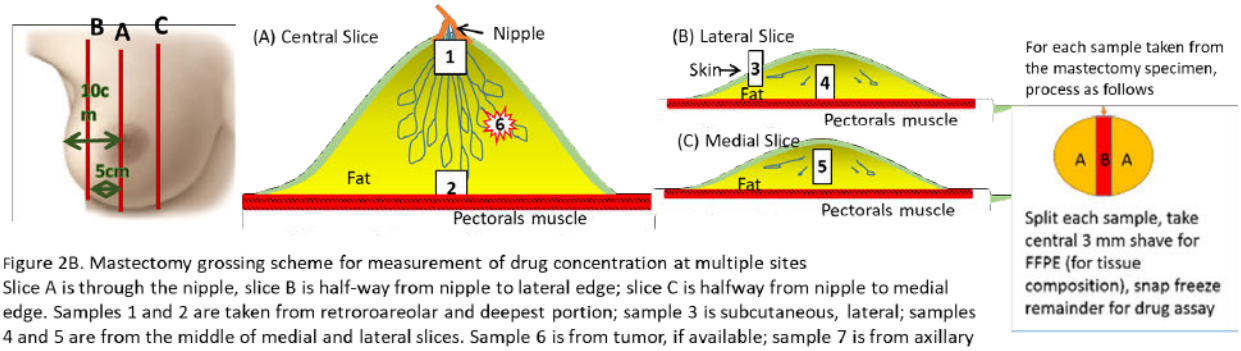


Figure 2B. Mastectomy grossing scheme for measurement of drug concentration at multiple sites
Slice A is through the nipple, slice B is half-way from nipple to lateral edge; slice C is halfway from nipple to medial edge. Samples 1 and 2 are taken from retroroareolar and deepest portion; sample 3 is subcutaneous, lateral; samples 4 and 5 are from the middle of medial and lateral slices. Sample 6 is from tumor, if available; sample 7 is from axillary lymph node, if available.

2. Plasma concentration of drug: (E) and (Z) isomers of N- desmethyl-4-hydroxytamoxifen (ENX) and 4-hydroxytamoxifen (4-OHT) to be performed by Dr. Miguel Muzzio using LC/MS/MS as published by us previously[16, 17]. Blood will be collected with anticoagulant K2-EDTA.
3. Plasma hormone levels for steroid hormones: estradiol, progesterone, dehydroepiandrosterone (DHEA), androstenedione and testosterone to be measured by LC/MS/MS using methods developed for prior studies by our group[45]. Blood will be collected with anticoagulant K2-EDTA.
4. *Plasma concentrations of IGF-1/IGFBP-3 and SHBG:* IGF-1 and its binding proteins IGFBP-3, and SHBG[16, 46] to be measured by ELISA assays at Northwestern University, Comprehensive Metabolic Core. Blood will be collected with anticoagulant K2-EDTA.
5. *Plasma levels of coagulation cascade proteins*: four blood coagulation protein assays [factor VIII, factor IX, von Willebrand factor (vWF), and Protein S] using plasma samples to be performed at Hemostasis Laboratory, Northwestern Memorial Hospital. Blood will be collected with anticoagulant citrate.

Table 2. Priority list of Biomarker analysis (FFPE tissue block , 15 sections, 4 micron each)	
1	1 H&E section for histology review (leading)
2	2 sections for Ki67 IHC assay (including an extra for repeats)
3	1 section for Progesterone Receptor IHC assay
4	1 section for Estrogen Receptor IHC assay
4	9 sections for macro-dissection and RNA extraction
5	1 H&E section for histology review (trailing)

6. *ENX-response endpoints in breast tissue samples*: Ki67 labeling index, PR and ER expression, and expression of a panel of genes reported to change with ENX exposure, will be measured in breast tissue samples obtained at diagnostic core needle biopsy (CNB) performed prior to study entry, and compared to the measurements in post-therapy surgical samples. Both Ki67 reduction and increase in PR expression are associated with tamoxifen response [47]. In addition, we will measure expression of genes selected from those modulated by 4-OHT [48] and those affected by ENX [26] in MCF7 breast cancer cells. Hawse et al., have reported that ENX treatment opposed the expression of 28 genes modulated by estradiol alone in MCF7 cell culture [26]. Of these, 12 genes were regulated by both 4-OHT and ENX but not by fulvestrant, and 6 genes were uniquely modulated by ENX but not by 4-OHT or fulvestrant. On the other hand, they also reported that ENX modulates 177 genes that are independent from its effect in opposing estrogen signaling, suggesting that the molecular mechanism of ENX actions differ from those of 4-OHT and fulvestrant [26]. Our recently opened 4-OHT gel study will provide an opportunity to compare gene expression profiles in response to ENX and 4-OHT in tumor samples. At the end of the intervention period, the mastectomy specimen will be sampled to obtain tissue for these measurements. We will use NanoString nCounter® assays (NanoString Inc., Seattle, CA) as a research platform to evaluate differential expression of 100 genes. We will include the 50 genes of the Prosigna Breast Cancer Prognostic Gene Signature Assay (formerly called the PAM50 test): 1) to define tumor subtypes (luminal A/B, Basal, etc.) of core biopsy

specimen (baseline), 2) to evaluate differential expression of proliferation genes (CENPF, ANLN, CDC20, CCNB1, CEP55, MYBL2, MKI67) by intervention. Additional 50 genes will be selected from genes commonly responding to both 4-OHT and ENX treatments as well as genes uniquely modulated by ENX not by 4-OHT in MCF7 cells as Howse et al. reported [26]. The Pathologist will mark the tumor area on the H&E slides for macro-dissection. Khan laboratory will perform macro-dissection and total RNA extraction RNA rom FFPE sections of diagnostic core biopsy block and therapeutic surgical block with purification kit (Qiagen or Roche kit). Total RNA quality and quantity will be measured by Qubit and Bioanalyzer analysis (NU genomics core). RNA samples will be stored at -80°C. The RNA samples (minimum 120 ng RNA aliquot per sample) will be shipped to NanoString headquarter (Seattle, CA) as one batch with dry ice. The mRNA gene expression profiling using 100 ng will be performed with NanoString nCounter® assays NanoString nCounter assay by NanoString company staff at NanoString headquarters.

7. Polymorphisms in tamoxifen metabolizing enzymes will not be assessed in the current study, but germline DNA will be banked for future pooled analyses of transdermally versus orally administered tamoxifen and metabolites relative to metabolic efficiency for oral tamoxifen. Subjects will be given the option to consent to this future study.

8.3 Off-Agent Criteria

Participants may stop taking study agent for the following reasons: completed the protocol-prescribed intervention, adverse event or serious adverse event, inadequate agent supply, noncompliance, concomitant medications, or medical contraindication. Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events.

All participants included in the study who received agent may be assessed for response to intervention, Participants who complete less than 80% of the planned dose or did not take the last 3 required doses will be considered non-compliant and will not be evaluable for secondary endpoints; Participants that receive agent but withdraw without initiating treatment will be replaced and will not be followed or evaluable for DLTs.

8.4 Off-Study Criteria

Participants may go ‘off-study’ for the following reasons: the protocol intervention and any protocol-required follow-up period is completed, AE/SAE, lost to follow-up, non-compliance, concomitant medication, medical contraindication, withdraw consent, death, determination of ineligibility (including screen failure), pregnancy, participant withdrawal, or physician decision.

8.5 Study Termination

NCI, DCP as the study sponsor has the right to discontinue the study at any time.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Rationale for Methodology Selection

The techniques for endpoint assessment, measurement of drugs, metabolites and drug effects have been established in prior studies[17, 36].The current study will contribute to the current knowledge base by providing critical dermal safety, pharmacokinetic and pharmacodynamic data on a potentially more effective tamoxifen metabolite than the previously tested 4-OHT; and by providing preliminary data on the anti-tumor and anti-tumorigenic efficacy of ENX.

Breast Tissue and Plasma drug concentration: The following factors should be used to assess assay performance in human plasma and breast tissue matrices: selectivity, linearity, precision, accuracy, recovery and stability, following the FDA's Guidance for Industry: Bioanalytical Method Validation [U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), May 2001.] Assays of (E) and (Z) isomers of N- desmethyl-4-hydroxytamoxifen (ENX) and 4-hydroxytamoxifen (4-OHT) will be performed by Dr. Miguel Muzzio using LC/MS/MS as published by us previously[16] [17].

IHC for Ki67, estrogen receptor (ER), and progesterone receptor (PR) analysis: other methods for measurement of proliferation are available but Ki67 labeling index (KI67-LI) is the most validated and widely used method of measuring proliferation in short-term intervention studies, and also most suited to the small tissue samples that will be available for baseline assessment (i.e. core needle biopsies). IHC is also a well-established and reproducible technique for measurement of hormone receptors. Tamoxifen and ENX have demonstrated growth suppression of established ER+ mammary DCIS and invasive carcinoma in by reduction in Ki67 [36, 49] and high PR expression correlated to the effectiveness of adjuvant tamoxifen in premenopausal ER+ breast cancer patients[50, 51]. We have also considered whether or not to perform laser capture microdissection of tumor and benign breast tissue in order to exclude stroma, but decided against this since changes in stroma may also be pertinent and LCM greatly increases the cost and complexity of the studies.

Plasma hormone levels for steroid hormones: estradiol, progesterone, dehydroepiandrosterone (DHEA), androstenedione and testosterone to be measured by LC/MS/MS using methods developed for prior studies by our group [45]. These are detailed in the PK/Biomarker Supplement.

Plasma concentrations of IGF-1/IGFBP-3 and SHBG: IGF-1 and its binding proteins IGFBP-3, and SHBG [16, 46] to be measured by enzyme-linked immunosorbent assay (ELISA) assays at Northwestern University, Comprehensive Metabolic Core. ELISA kits will be purchased from R&D systems Inc. and performed using the manufacturer's protocols. These are detailed in the PK/Biomarker Supplement.

Plasma levels of coagulation cascade proteins: four blood coagulation protein assays [factor VIII, factor IX, von Willebrand factor (vWF), and Protein S] using plasma samples to be performed at Hemostasis Laboratory, Northwestern Memorial Hospital. These are detailed in the PK/Biomarker Supplement.

RNA expression assay*:* In addition, we will measure mRNA expression of a panel to be derived from existing data on gene expression changes induced by ENX and 4-OHT [26, 48], and modified according to the best data available at the time that the final set of tissues become available. We will use NanoString nCounter analysis (Nanostring Technologies, Seattle, WA); this is a well-established and reproducible technique for determination of differential mRNA expression. These are detailed in the PK/Biomarker Supplement.

Genotyping assay for drug metabolism enzyme polymorphism analysis: Genotyping assay is a well-established, robust and reproducible technique for determination of polymorphism of genes. Khan lab has successfully done genotyping assays for study of single nucleotide polymorphisms (SNP) of enzymes involved in steroid hormone biosynthesis (NCI06B1 NAF hormone study project). We have used TaqMan® SNP genotyping assay kits from the Life Technologies Inc. With 4.5 million SNP assays available, including 3.5 million HapMap SNPs, 70,000 cSNPs and 160,000 validated assays, TaqMan® SNP genotyping assays make it easy to perform human and mouse SNP genotyping studies with the precision of TaqMan® reagent-based chemistry.[52]

9.2 Comparable Methods

Proposed methods represent standard technology for drug and hormone concentration measurement in plasma and tissue; for IHC, and for blood coagulation protein profiling as well as IGF-1/IGFBP-3 and SHBG proteins in plasma samples. Gene expression will be examined using Nanostring, which is a relatively new but now fairly standard method for measuring gene expression in paraffin embedded samples.

10. SPECIMEN MANAGEMENT

10.1 Laboratories

10.1.1 Clinical Laboratories attached to Northwestern University, Memorial Sloan Kettering Cancer Center, and Cedars-Sinai Medical Center will be responsible for performing blood laboratory analysis for participant screening eligibility.

Addresses of Clinical Laboratories:

Northwestern University Main Lab
251 E Huron
Chicago, IL 60611

Memorial Sloan Kettering Department of Laboratory Medicine, Main
1275 York Ave
New York NY 10065

Cedars-Sinai Medical Center
Department of Pathology and Laboratory Medicine
8700 Beverly BLVD, Room 3719
Los Angeles, CA 90048

10.1.2 Research Assay Laboratories are as follows

The Pathology Core Facility (PCF) at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University will receive serum, plasma and breast tissue samples from all participating study sites (except for serum pregnancy tests, which will be processed by the clinical laboratories at each accrual site). The distribution of samples to appropriate central labs for assays as listed below will be performed by the Pathology Core Facility, as directed by Dr. Khan's laboratory personnel. Details of shipping are provided in section 10.3.

Drug concentration assays of tissue and plasma samples and plasma steroid hormone assays will be performed by the laboratory of Dr. Miguel Muzzio at the Illinois Institute of Research (IITRI), using LC/MS/MS protocols established for our prior studies[16, 17][45].

Cell proliferation and progesterone receptor IHC at baseline and after treatment will be performed in the Pathology Core Facility of the Robert H. Lurie Comprehensive Cancer Center.

Plasma hormone levels for steroid hormones: estradiol, progesterone, dehydroepiandrosterone (DHEA), androstenedione and testosterone to be measured by LC/MS/MS in the laboratory of Dr. Miguel Muzzio at the Illinois Institute of Research (IITRI).

Plasma concentrations of IGF-1/IGFBP-3 and SHBG: IGF-1 and its binding proteins IGFBP-3, and SHBG [16, 46] to be measured by ELISA assays at Northwestern University, Comprehensive Metabolic Core.

Plasma levels of coagulation cascade proteins: four blood coagulation protein assays [Factor VIII, factor IX, von Willebrand factor (vWF), and Protein S] using plasma samples to be performed at Hemostasis Laboratory, Northwestern Memorial Hospital.

10.2 Collection and Handling Procedures

All participating sites will receive specific instructions for collection, processing and shipment of samples and specimen to the PCF at NU.

Refer to Specimen Manual.

10.3 Shipping Instructions

All samples will be shipped in compliance with the International Air Transport Association (IATA) Dangerous Goods Regulations.

Refer to Specimen Manual.

10.4 Tissue Banking

Biologic specimens collected during the conduct of each clinical trial that are not used during the course of the study will be considered deliverables under the contract and thus the property of the NCI. At study completion, NCI reserves the option to either retain or relinquish ownership of the unused biologic specimens. If NCI retains ownership of specimens, the Contractor shall collect, verify and transfer the requested biologic specimens from the site to a NCI-specified repository or laboratory at NCI's expense.

11. REPORTING ADVERSE EVENTS

DEFINITION: AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign), symptom, or disease temporally associated with participation in a study, whether or not related to that participation. This includes all deaths that occur while a participant is on a study.

Please note that all abnormal clinical laboratory values that are determined to be of clinical significance based on a physician's assessment are to be reported as AEs. Those labs determined to be of no clinical significance or of unknown clinical significance (per the physician's assessment) should not be reported as AEs. Any lab value of unknown clinical significance should continue to be investigated/followed-up further for a final determination, if possible.

A list of AEs that have occurred or might occur can be found in §6.2 Reported Adverse Events and Potential Risks, as well as the Investigator Brochure or package insert.

11.1 Adverse Events

11.1.1 Reportable AEs

All AEs that occur after the informed consent is signed and baseline assessments are completed must be recorded on the AE CRF (paper and/or electronic) whether or not related to study agent.

Table 1. A modified CTCAE for assessing skin application AEs.

Table 1 Modified CTCAE for assessing skin toxicity of endoxifen gel applied to the breast skin. These assessments will be made on the breast skin (application site).

	Grade 1	Grade 2	Grade 3
Dry Skin	No erythema or pruritus	With erythema or pruritus	With erythema and pruritus
Pain of Skin	Mild pain	Moderate pain	Severe pain
Photosensitivity	Painless erythema	Mild to moderate pain with erythema	Erythema with blistering
Pruritus	Mild, requiring topical intervention	Intense, with changes from scratching, oral intervention needed	Intense, constant, limiting ADL or sleep, oral steroids needed.
Rash maculopapular	Macules or papules <25% of treated area, with or without symptoms (pruritus, burning, tightness)	Macules or papules >25% of treated area, with or without symptoms (pruritus, burning, tightness), limiting instrumental ADL	Macules or papules > 25% of treated area, with or without symptoms (pruritus, burning, tightness), limiting self-care ADL
Urticaria	Asymptomatic or mild symptoms, not requiring therapy	Moderate; limited local therapy needed, limiting instrumental ADL	Urticarial lesions covering >30% of application area; oral or IV intervention needed

11.1.2 AE Data Elements:

The following data elements are required for AE reporting.

- AE verbatim term (AEs which occur on the breast should include "application site" in the verbatim term).
- NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) AE term (MedDRA lowest level term)
- CTCAE (MedDRA) System Organ Class (SOC)
- Event onset date and event ended date
- Treatment assignment code (TAC) at time of AE onset
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a SAE
- Whether or not the subject dropped due to the event
- Outcome of the event

11.1.3 Severity of AEs

11.1.3.1 Identify the AE using the CTCAE version 4.0. The CTCAE provides descriptive terminology (MedDRA lowest level term) and a grading scale for each AE listed. A copy of the CTCAE can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs will be assessed according to the grade associated with the CTCAE term. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4.0. as stated below.

CTCAE v4.0 general severity guidelines:

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

ADL

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

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

11.1.4 Assessment of relationship of AE to treatment

The possibility that the AE is related to study agent will be classified as one of the following: not related, unlikely, possible, probable, and definite.

11.1.5 Follow-up of AEs

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such.

11.2 Serious Adverse Events

11.2.1 DEFINITION: Regulations at 21 CFR §312.32 (revised April 1, 2014) defines an SAE as any untoward medical occurrence that at any dose has one or more of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to perform normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization should also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the other outcomes.

The planned mastectomy procedure will not be considered to be an SAE.

11.2.2 Reporting SAEs to DCP

11.2.2.1 The Lead Organization and all Participating Organizations will report SAEs on the DCP SAE Report Form found at http://prevention.cancer.gov/clinical-trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools/2012-consortia.

11.2.2.2 Contact the DCP Medical Monitor by phone within 24 hours of knowledge of the event.

Name: Marjorie Perloff, MD
Address: Division of Cancer Prevention
National Cancer Institute
9609 Medical Center Drive, 5E544
Rockville, MD 20850
Tel: (240) 276-7097 (during normal business hours)
Cell: (240) 731-1772
Email: perloffm@mail.nih.gov

Include the following information when calling the Medical Monitor:

- Date and time of the SAE
- Date and time of the SAE report
- Name of reporter
- Call back phone number
- Affiliation/Institution conducting the study
- DCP protocol number
- Title of protocol
- Description of the SAE, including attribution to drug

11.2.2.3 The Lead Organization and all Participating Organizations will email written SAE reports to the following people within 48 hours of learning of the event using the fillable PDF SAE Report Form:

- The NCI/DCP Medical Monitor
- DCP's Regulatory Contractor CCS Associates, Inc. (CCSA; phone: 650-691-4400) at safety@ccsainc.com
- Northwestern Cancer Prevention Consortium (NCPC, phone: 312-503-7820) at ncpc@northestern.edu

11.2.2.4 The DCP Medical Monitor and CCSA regulatory and safety staff will determine which SAEs require FDA submission as IND safety reports.

11.2.2.5 The Lead Organization and all Participating Organizations will comply with applicable regulatory requirements related to reporting SAEs to the IRB/IEC.

11.2.3 Follow-up of SAE

Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the DCP SAE Report Form in the appropriate format. Follow-up information should be sent to DCP, CCSA, and NCPC as soon as available. Subjects who experience an SAE will be followed for 30 days or until resolution.

12. STUDY MONITORING

12.1 Data Management

Data will be managed by the study statistician, Dr.Kocherginsky, according to standard operating procedures, which meet the guidelines of DCP Requirements for Data Management and which follow the Data Management Plan that Northwestern University has on file with the Division of Cancer Prevention, NCI. Source data verification will be performed by the Department of Clinical Research Services. The Consortia 2012 Data Management Plan, submitted as part of a contract agreement with the NCI (HHSN261201200035I), was approved.

12.2 Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRFs) developed from the standard set of DCP Chemoprevention CRF Templates and utilizing NCI-approved Common Data Elements (CDEs). The approved CRFs will be used by Northwestern University to create the electronic CRFs (e-CRFs) screens in the Robert H. Lurie Comprehensive Cancer Center Clinical Trials Management System (CTMS). Site staff will enter data into the e-CRFs for transmission to DCP according to DCP standards and procedures.

12.3 Source Documents

All source documents will be collected and stored in the Clinical Research Office of the site where the participant was accrued. Any data recorded directly on CRFs that constitute no prior written or electronic record of data, will be specifically identified as source data. BESS questionnaire completed in person may be completed directly on the electronic CRF and need not be transcribed from separate source documentation.

12.4 Data and Safety Monitoring Plan

A comprehensive Data Safety and Monitoring Plan has been submitted by Northwestern University, approved by the DCP, and is on file there. Any future changes will be forwarded for review.

12.5 Sponsor or FDA Monitoring

The NCI, DCP (or their designee), pharmaceutical collaborator (or their designee), or FDA may monitor/audit various aspects of the study. These monitors will be given access to facilities, databases, supplies and records to review and verify data pertinent to the study.

12.6 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, *etc*.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidances, and NCI/DCP requirements, unless the standard at the site is more stringent. The records for all studies performed under an IND will be maintained, at a minimum, for two years after the approval of a New Drug Application (NDA). For NCI/DCP, records will be retained for at least three years after the completion of the research. NCI will be notified prior to the planned destruction of any materials. The records should be accessible for inspection and copying by authorized persons of the Food and Drug Administration. If the study is done outside of the United States, applicable regulatory requirements for the specific country participating in the study also apply.

12.7 Clinical Supply Agreement

The agents, ENX gel and placebo gel, are supplied by DCP, NCI, where they were developed by investigators in the PREVENT Program. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator contained within the terms of award, apply to the use of Agent(s) in this study:

12.7.1 Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a patient participating on the study or participant's family member requests a copy of this protocol, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from the DCP website.

12.7.2 For a clinical protocol where there is an Investigational Agent used in combination with (an) other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-party Data").

12.7.3 NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

12.7.4 Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval, or commercialize its own investigational agent.

12.7.5 Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational agent.

12.7.6 Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate. All data made available will comply with HIPAA regulations.

12.7.7 When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators of Collaborator's wish to contact them.

12.7.8 Any manuscripts reporting the results of this clinical trial must be provided to DCP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days (or as specified in the CSA) from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to DCP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to DCP prior to release. Copies of any

manuscript, abstract, and/or press release/ media presentation should be sent to the Protocol Information Office at NCI_DCP_PIO@mail.nih.gov.

The Protocol Information Office will forward manuscripts to the DCP Project Officer for distribution to the Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Description

We plan a randomized, double-blind, Phase I trial with a control arm and a treatment arm, with dose escalation from 10 mg ENX gel daily (5 mg per breast) to 20 mg daily (10 mg per breast). Dose-limiting toxicity is defined as the occurrence of Grade 2 or greater skin response for any of the CTCAE parameters listed in Table 1.

Cohorts 1 and 2 will be randomized 2:1 (ENX gel and placebo). Cohort 3 will consist only of actively treated subjects. We planned that the sample size may range up to 38, depending on the frequency of DLT, and how early in each cohort DLT was observed. After completion of Cohort 2 (with accrual of 12 subjects each in Cohort 1 and 2), we will now accrue 8 subjects in Cohort 3, with a final accrual of 32 subjects. All subjects who receive any study drug will be evaluable for the primary endpoint of dermal toxicity.

We choose a 2:1 randomized design with a placebo arm with each dose in ***order to establish variability of measurements when no treatment is applied,*** and yet to provide treatment to as many subjects as possible. Randomization is double blinded, and the gel used in the treatment and control groups has similar appearance, consistency, and chemical composition, except for the presence of ENX in the active gel. The study will employ intent to treat principles. Although formal statistical comparison will be limited by the small sample size (as can be the case for Phase I trials), the placebo group will be used to interpret subjective symptoms such as skin irritation or pruritis. Combining placebo groups will yield a total of n=8, thus providing standard error of the estimate of SD/sqrt(8) and 0.5/sqrt/(8).

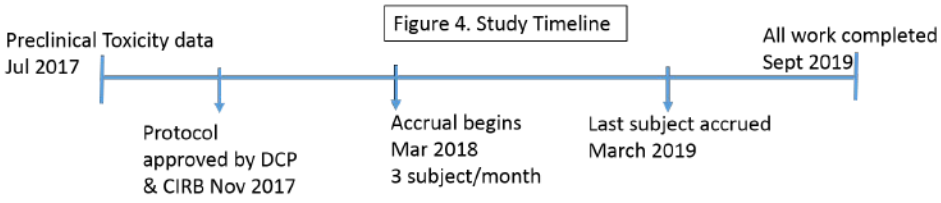
13.2 Randomization/Stratification

Randomization list will be provided by study statistician and made available to the accrual-site pharmacists. Neither stratification nor blocking will be used for demographic factors. Interim analysis for toxicity is built into the design of this escalation study (see the schema). Efficacy determination will be done for each of two doses and placebo groups with purpose of gaining all the information available.

13.3 Accrual and Feasibility

Assuming 38 women for all cohorts, we anticipate recruiting 14 at NU, and 12 each at MSKCC and CS-LA. Women of all races and ethnicities will be recruited. The duration of accrual is expected to be 12-14 months at a rate of 3 subjects per month (one subject per site per month). The anticipated timeline is shown below.

Figure 4. Study Timeline



13.4 Primary Objective, Endpoint(s), Analysis Plan

Data Analyses Plans The primary plan is to estimate and provide confidence intervals (CIs) for the incidence of skin irritation in patients treated at each dose level, as well as in the placebo, using CTCAE criteria listed in Table 1. It is expected a wealth of information on parameters of interest will be acquired from placebo group, short of formal testing.

13.5 Secondary Objectives, Endpoints, Analysis Plans

Secondary objectives:
1) Comparison of breast tissue concentrations of ENX at each dose will be done using visualization, graphics and by providing appropriate confidence interval (CI).
2) Plasma concentrations of ENX at each dose (10 mg per day and 20 mg per day), will be reported as observed concentrations with appropriate CIs.
3-5) Relate to comparison of the plasma levels for steroid hormones, plasma estrogenic response proteins, and plasma coagulation parameters. To assess treatment-related changes, the 95%CI of the mean difference post-pre and a test of the central parameter = 0 will be provided as in the previous objective.
6) To assess tissue biologic response to ENX gel treatment. These will be compared as pre- and post-therapy values, to explore the potential therapeutic effects of the two doses of ENX: a) by IHC for Ki67, ER, and PR expression; b) by nanostring assays, using a panel of genes reported to change with ENX exposure. For both IHC and gene expression, values for "pre" and for "post" measurements will be subtracted from each other and CIs for the mean difference will be provided. A nonparametric test of the central parameter being zero will be performed.
7) To bank germline DNA for future pooled analyses of polymorphisms in tamoxifen metabolizing enzymes, statistical analysis will be used as needed (optional).
8) Analysis of symptoms as reported in the BESS questionnaire: This uses scores where the lowest describes "no symptom" and the highest reflects "extremely" or "always". The high scores are adverse. When subtracting post-pre measures, negative values suggest improvement over time, while positive suggest worsening. We will provide graphical displays of these differences as histograms with x-axis values -5, -4, …0, … 4, 5 and empirical mass function on the top. To compare the dose groups (low, high) and singular dose versus placebo, if appropriate, we will use the nonparametric two sample Wilcoxon-Mann-Whitney test, with corrections for ties. The study was not specifically powered for such analysis, and resulting one and two sided p-values will be considered descriptive statistics useful for future analyses. Average, median and range of scores for each noted group will be provided as descriptive measures of location and variance. We will use multiple imputation via non-parametric probability integral transformation[53] to impute missing data as appropriate.

All tests will be two-sided. We will use multiple imputation via non-parametric probability integral transformation (Helenowski, PhD Dissertation, 2011) to impute missing data as appropriate.

13.6 Reporting and Exclusions

Compliance is defined as consumption of 80% of the prescribed dose over the whole study period, *and* of all of the last 3 required doses. Where information is available, data on non-compliant patients will be considered for dose-response analysis. Missing data will be treated via multiple imputations as described in previous sections.

13.7 Evaluation of Toxicity

All participants will be evaluated for toxicity as described in the protocol. Dose-Limiting Toxicity (DLT) is defined as Grade 2 or greater skin toxicity, using CTCAE criteria for the parameters shown in Table 1. The Grade 2 or greater reaction should occur at the application site for 48 hours or longer and be definitely, probably, or possibly related to the study drug.

13.8 Evaluation of Response

All participants included in the study who received agent will be assessed for response to intervention, even if there are major protocol deviations.

All of the participants who met the eligibility criteria (with the exception of those who did not receive study agent) will be included in the main analysis. All conclusions regarding efficacy will be based on all eligible participants.

Sub-analyses may be performed on the subsets of participants, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of intervention, major protocol violations, etc.). However, sub-analyses will not serve as the basis for drawing conclusions concerning efficacy, and the reasons for excluding participants from the analysis should be clearly reported. For all measurements of response, the 95% confidence intervals will be provided.

13.9 Interim Analysis

Interim analyses and stopping rules are those inherent in toxicity evaluation and dose escalation / de-escalation. Early termination may occur if the lowest dose is found toxic.

13.10 Ancillary Studies

Ancillary studies will be performed as needed and as possible. Power analyses have not been performed for the present time lack of knowledge of parameters and effect sizes involved. Bonferroni correction for multiple comparisons will be applied as possible in given context.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Form FDA 1572

Prior to initiating this study, the Protocol Lead Investigator at the Lead or Participating Organization(s) will provide a signed Form FDA 1572 stating that the study will be conducted in compliance with regulations for clinical investigations and listing the investigators, at each site that will participate in the protocol. All personnel directly involved in the performance of procedures required by the protocol and the collection of data should be listed on Form FDA 1572.

14.2 Other Required Documents

14.2.1 Current (within two years) CV or biosketch for all study personnel listed on the Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations. CVs or biosketches do not need to be updated for participating study staff after drug shipment authorization (DSA).

14.2.2 Current medical licenses (where applicable) for all study personnel listed on Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.3 Lab certification (*e.g.*, CLIA, CAP) and lab normal ranges for all labs listed on Form FDA 1572 for the Lead Organization and all Participating Organizations.

14.2.4 Documentation of Good Clinical Practice training for all study personnel listed on the FDA Form 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.5 Documentation of Federalwide Assurance (FWA) number for the Lead Organization and all Participating Organizations.

14.2.6 Signed Investigator's Brochure/Package Insert acknowledgement form

14.2.7 Delegation of Tasks form for the Lead Organization and all Participating Organizations signed by the Principal Investigator for each site and initialed by all study personnel listed on the form

14.2.8 Signed and dated NCI, DCP Financial Disclosure Form for all study personnel listed on Form FDA 1572 for the Lead Organization and all Participating Organizations

14.3 Institutional Review Board Approval

Prior to initiating the study and receiving agent, the Investigators at the Lead Organization and the Participating Organization(s) must obtain written approval to conduct the study from the appropriate IRB. Should changes to the study become necessary, protocol amendments will be submitted to the DCP PIO according to DCP Amendment Guidelines. The DCP-approved amended protocol must be approved by the IRB prior to implementation

14.4 Informed Consent

All potential study participants will be given a copy of the IRB-approved Informed Consent to review. The investigator will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the Informed Consent document. The study agent(s) will not be released to a participant who has not signed the Informed Consent document. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

Participants must be provided the option to allow the use of blood samples, other body fluids, and tissues obtained during testing, operative procedures, or other standard medical practices for further research purposes. If applicable, statement of this option may be included within the informed consent document or may be provided as an addendum to the consent. A Model Consent Form for Use of Tissue for Research is available through a link in the DCP website.

Prior to study initiation, the informed consent document must be reviewed and approved by NCI, DCP, the Consortium Lead Organization, and the IRB at each Organization at which the protocol will be

implemented. Any subsequent changes to the informed consent must be approved by NCI, DCP, the Consortium Lead Organization's IRB, and then submitted to each organization's IRB for approval prior to initiation.

14.5 Submission of Regulatory Documents

All regulatory documents are collected by the Consortia Lead Organization and reviewed for completeness and accuracy. Once the Consortia Lead Organization has received complete and accurate documents from a participating organization, the Consortium Lead Organization will forward the regulatory documents to DCP's Regulatory Contractor:

Paper Document/CD-ROM Submissions:
Regulatory Affairs Department
CCS Associates, Inc.
2001 Gateway Pl, Suite 350 W
San Jose, CA 95110
Phone: 650-691-4400
Fax: 650-691-4410

E-mail Submissions:
regulatory@ccsainc.com

Regulatory documents that do not require an original signature may be sent electronically to the Consortium Lead Organization for review, which will then be electronically forwarded to DCP's Regulatory Contractor.

14.6 Other

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

15. FINANCING, EXPENSES, AND/OR INSURANCE

The protocol should describe any expenses incurred by the study participant and/or their insurance carrier. This includes any injuries the participant may have related to their participation in the study.

To cover expenses related to travel, child-care, loss of work time and other similar issues, participants will receive $100 after completion of Screening Visit 1, $100 after completion of Study Visit 1 (which may be combined with Study Visit 2 day of surgery), and $100 after completion of Study Visit 3. Participants who are required to return to the office for an additional pregnancy test will receive an additional $100. It is possible that injury may result from participating in this study. Any expenses incurred as a result of research related injury will be the responsibility of the study participant and/or their insurance carrier.

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CONSENT FORM

Study Title for Study Participants:

A study testing if endoxifen, an active form of tamoxifen, can be delivered to the breast through the breast skin.

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:

NWU2017-09-01 Phase I trial of endoxifen gel versus placebo gel in women undergoing breast surgery.
Protocol v6.5 (05/11/2020)

Introduction

This is a clinical trial, a type of research study. Clinical trials include only people who choose to take part in the research. Please take your time to make your decision about volunteering. You may discuss your decision with your friends and family. You can also discuss this study with your health care team. If you have any questions, you can ask your study doctor for more of an explanation. You should only agree to participate in this study when you are comfortable enough with the information so that you can make an informed decision about joining.

What is the usual approach to my breast cancer or high risk condition for breast cancer?

You are being asked to participate because you are planning to undergo surgery to remove one or both breasts because of a cancer diagnosis or to prevent breast cancer. Your surgical and medical treatment, will be decided by you and your doctors. The medication being tested in this trial is not meant to treat your condition, and it will not interfere with your usual treatment either. The study treatment will take place prior to your scheduled surgery.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have surgery without any medical treatment before surgery.
- you may choose to take part in a different study, if one is available,
- or you may choose to do nothing.

Why is this study being done?

The purpose of this study is to test the safety of a medicated gel containing endoxifen (an active form of tamoxifen) applied to the skin of the breast at different doses to find out what effects, if any, it has on people and their risk of breast cancer. There will be up to 32 women taking part in this study. By developing methods to treat the breast with a gel applied to the skin, we hope to greatly reduce the drug dose to the rest of the body, and therefore decrease side-effects of drugs taken for prevention of breast cancer. In this study, we will test if endoxifen gel can be applied to the breast skin without causing skin irritation, compared to a placebo gel (that contains no endoxifen). The endoxifen gel will be tested at two doses in this study (10 mg endoxifen daily or 20 mg daily). We will also compare the amount of the drug that reaches the breast at each of these doses.

The use of endoxifen (the study drug) in this study is investigational, meaning that it is not approved by the Food and Drug Administration (FDA). Endoxifen given by mouth (orally) is currently being examined in clinical trials for breast cancer, where it is anticipated to be as good as or better than tamoxifen, since it is the active form of tamoxifen. This will be the first study in the US of topical endoxifen gel. All women who participate in this study will receive endoxifen gel or placebo gel for about 28 days prior to surgery. The researchers in this study would like to compare how participants will tolerate endoxifen gel applied to the breast skin at the 10 mg or the 20 mg dose, how much gets into the breast at each dose level, and how much gets into the blood.

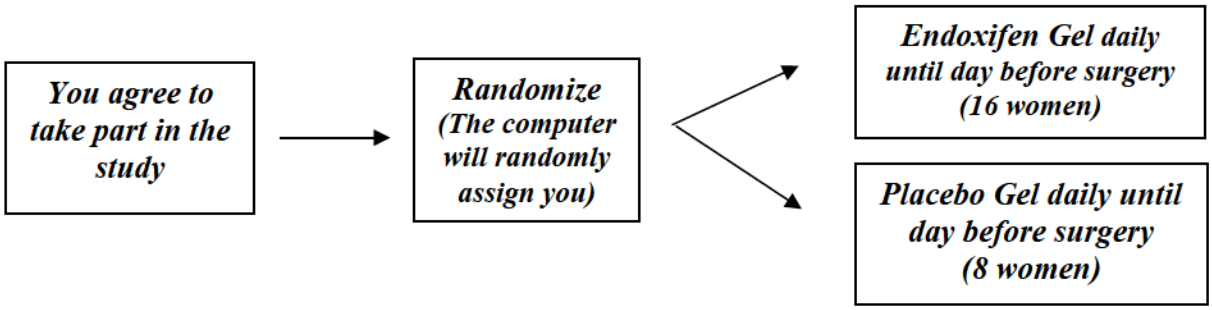
The study investigators hope to enroll up to 32 women at Northwestern University, Memorial Sloan Kettering Cancer Center, and Cedars-Sinai Medical Center.

What are the study groups?

This study is a Phase I study, which means that the goal is to study if endoxifen gel applied to the breast skin is well tolerated. The study has three groups. Different doses of endoxifen gel or placebo gel (gel with no medicine in it) will be given to several study participants. What you receive will depend on when you enroll on the study and what group you are put into. Once you are put into a group you cannot switch to another group.

The first two groups (dose escalation part):
If you are in one of the first two groups, a computer will randomly assign you to receive endoxifen gel or placebo gel. This is done because no one knows if endoxifen gel will be tolerated better or worse than the placebo gel. If you are in one of the first two groups, you have twice the likelihood to receive endoxifen gel compared to placebo gel. Neither you nor your doctor will know if you are receiving endoxifen gel or placebo gel. Your doctor cannot choose which gel you receive. A pharmacist will always know exactly what gel each participant is receiving and will be able to tell your medical team if needed for your care.

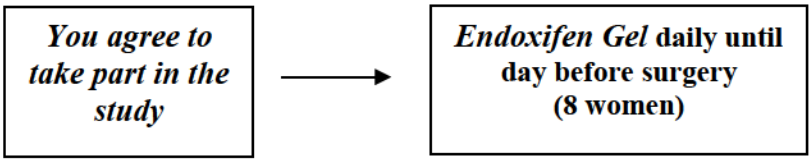
If you are in one of the first two groups….



In the first group, several study participants will receive endoxifen gel at a low dose. If the gel does not cause bothersome side effects, it will be given to the second group of study participants at a higher dose. If the low dose causes bothersome side effects in two or more women in the first group, it will be given to additional study participants at the same dose to get a better idea of how often the gel is bothersome. In this way, we hope to determine the safest/best tolerated dose of endoxifen. Once this dose of endoxifen is found, then the next part of the study will begin with the third group.

The third group (dose expansion part):
If you are in the third group, you will receive endoxifen gel. In this group, eight participants will receive the safest/best tolerated dose of the active study drug. There will be no placebo in the third group.

If you are in the third group….



How long will I be in this study?

You will receive the study drugs for 3-4 weeks (21-28 days) before your breast surgery. Even if you do not finish the study, your doctor will continue to watch you for side effects and follow your condition for one or two weeks after surgery.

What extra tests and procedures will I have if I take part in this study?

If you agree to participate, you will be required to sign this consent before you have any tests or procedures that are done only for this study. You will be asked to come to the_____ *(site specific address)*. There are 3 main parts to this study: Screening, Treatment, and Follow-Up.

Before you begin the study: Screening
Screening is a period during which tests and exams will be done to determine if you are eligible to participate in the treatment part of the study. Some of the tests and exams may have been recently done by one of your doctors and might not need to be repeated. These tests and assessments may be done on one day or two days. Some blood tests will be done for research purposes only and will not change the way your disease is treated. Your study doctor will discuss this with you.

The following tests will be required to find out if you can be in the study:

1. Review of your medical history and a physical exam
2. Urine or serum pregnancy test (for women who are able to become pregnant)
3. Assessment of your ability to complete your daily activities
4. Blood tests (about 2 teaspoons or 10 mL will be collected) to see how your liver and kidneys are functioning
5. De-identified pictures of your breasts will be taken as a baseline before study gel is applied. The photo will only be of your neck to abdomen with no facial identification.

If the exams and tests show that you can continue to take part in the study, and you choose to, then you will need the following extra procedures. These are not part of the usual approach for your condition.

- Completion of a questionnaire to determine what symptoms you are already experiencing
- Collection of blood for research purposes (a total of about 2 tablespoons or 26mL)

Your initial study visit for screening will last approximately 60 to 90 minutes. If you are found to be eligible, you will receive the study drug, which may be given to you that same day if you are able to pick it up approximately 5-6 hours later or the next day. If you are unable to wait, or to return the next day, the drug will be mailed to you.

If you are able to become pregnant, it is important that you are not pregnant when entering the study or while taking this study drug. For this reason, you will need to have a negative pregnancy test within 5 days prior to starting the study drug. If your Screening Visit does not occur within five days of starting the study drug, you will need to return to the office for another pregnancy test.

Reminders to take your study drug: You will have the option of receiving email or text messages from research staff to remind you about the study medication during the first week of study treatment period. We encourage you to respond to indicate if the dose has been taken. If you are having trouble remembering, these reminders can be extended beyond the first week. Reminder messages to use the study gel medication will also be sent during the last week of study treatment as it is very important that you not miss any dose during this week so that we are able to fully use all data collected.

Treatment

During the treatment portion of this study, instructions to apply the study medication will be reviewed with you by the study staff. Once you receive the medication, you will need to store them in your home in a place protected from light, heat and moisture.

Depending upon the group to which you are randomized you will receive one of the following treatments:

1. Endoxifen gel or placebo gel 10 mg daily (5 mg per breast)
2. Endoxifen gel or placebo gel 20 mg daily (10 mg per breast)
3. Endoxifen gel with no possibility of placebo (5 mg per breast)

You will be given a study diary to fill out and document each dose of study medication that you take. You will have the option of using a phone application/website or using a paper study diary. We will show you how to use the phone application/website and it will not contain any of your personal information. You should mark any missed or skipped doses in this diary, as well as any side effects that you are experiencing.

You will use the gel for 3 to 4 weeks (21 to 28 days) prior to your surgery. The last day that you will take your study drug will be the morning of the day before your surgery if you are in groups 1 or 2. If you are in Group 3, the last day that you will take your study drug will be the morning of the third day prior to your surgery. For example, if your surgery is on Monday, your last dose will be on the prior Friday morning. You will need to shower, bathe, or wash your breasts the morning of surgery, before you leave for the hospital.

If you choose to use the paper diary instead of the phone application/website, the study personnel will send email reminders to you every day during the first week and last week of the study. If you choose to use the phone application/website, the study personnel will contact you if you miss to enter your information for 2 days. Regardless of whether you use the paper diary or the phone app, study personnel will contact you every week by phone to check on your progress and answer any questions regarding the intake/application of study medication. You will also be asked questions about potential side effects of the study medication. These phone calls will last approximately 10 minutes. If you prefer, the study coordinator may email you instead of calling you weekly. Please let your study coordinator know how you prefer to be contacted.

You will have a study visit on the day before surgery, when your study treatment will end. If you can arrive earlier than your scheduled time on the day of surgery, it may be possible to do this visit on the same day of your surgery. During this visit, you will have a quality of life survey. The study diary will be reviewed and collected and all unused study medication will be collected at this visit.

On the day of your surgery, the baseline tests will be repeated. These tests include a medical history and physical exam, blood tests (about 2 teaspoons or 10 mL will be collected) for liver and kidney function and

blood draw for research purposes (about 2 tablespoons or 26 mL will be collected). You will fast starting at midnight before this visit. Please take your usual medicines (if any) with a sip of water on the morning of the surgery. This visit will last approximately 60 to 90 minutes. You will then proceed to have your surgery, as you would if you were not participating in the study; your surgical treatment will not be changed in any way. Once the breast is removed, it will be delivered to the pathologist who will examine your tissue and identify what is needed for diagnosis to guide treatment. In addition, samples of the surgical specimen not needed for your diagnosis will be removed to measure study drug concentrations and breast cancer markers.

In addition, tissue from the pre-surgical biopsy will be tested and the results compared with tissues removed at surgery to see the effects of endoxifen gel treatment.

As part of this study you will also be asked to answer questions about your tobacco and alcohol use, both before you begin the study and again at Study Visit 1. Researchers want to see if tobacco and alcohol use affects the side effects people might get while on this study, or if tobacco and alcohol use modifies the effects of the study agents. For the tobacco and alcohol use questions, you can decide to not answer some or all of the questions. Your decision will not affect whether you can participate in the study, and it will not affect your relationship with your doctor or the study staff.

Follow up
The follow up visit for the study will be at your post-op visit in the clinic to review your progress. This visit will be 1-2 weeks after the surgery and at this time, information about any side effects, medications, and the last menstrual period (if you are having periods), will be collected. If you are still having periods, a final phone call one month after your surgery will be made to record the date of your last menstrual period.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that you may:

- Lose time at work or home and spend more time in the hospital or doctor's office than usual (there are two study visits that may not coincide with your clinical care visits, but we will try as much as possible to minimize extra visits).
- Be asked sensitive or private questions which you normally do not discuss, for example about your tobacco and alcohol use.
- There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.
- There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during a study.

The endoxifen gel used in this study is highly unlikely to affect how different parts of your body work, such as your liver, and blood. The chances of this happening are extremely low, given what we know about tamoxifen and its active forms, through many years of clinical trials and clinical experience. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects.
Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.

The tables below show the most common side effects that we know about, based on experience with these closely related drugs: oral endoxifen, oral tamoxifen and topical 4-hydroxytamoxifen gel, some of which may be serious. Women in the US have not been treated with topical endoxifen gel before. There might be other side effects that we do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible side effects of endoxifen gel

COMMON, SOME MAY BE SERIOUS In 100 people, more than 20 may have:
• Hot flashes, hot flush • Tiredness • Nighttime sweating • Headache

OCCASIONAL, SOME MAY BE SERIOUS In 100 people, from 4 to 20 may have:
• Nausea • Irritability • Sleep disturbance • Pruritus • Vaginal discharge • Vaginal dryness • Weight gain

RARE, SOME MAY BE SERIOUS In 100 people 3 or fewer may have:
• Skin reaction following application of topical drug (i.e., feeling cold/icy in the skin followed by temporary warming)

Reproductive risks: You should not get pregnant or breastfeed while in this study. The endoxifen gel used in this study could be damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

Risks of the blood tests: Bruising, soreness, or rarely, infection may occur as a result of the needle sticks to obtain blood from you.

What possible benefits can I expect from taking part in this study?

Participating in this study is unlikely to help your condition. This study may help us learn things that could help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

For the tobacco and alcohol use questions, you can decide to not answer some or all of the questions. Your decision will not affect whether you can participate in the study, and it will not affect your relationship with your doctor or the study staff.

The study doctor will tell you about any new information or changes in the study that could affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes.
- If the study is no longer in your best interest.
- If new information becomes available.
- If you do not follow the study rules.
- If the study is stopped early for any reason by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the National Cancer Institute Central Institutional Review Board at 888-657-3711.

What are the costs of taking part in this study?

The study gel (endoxifen gel or placebo) will be supplied at no charge while you take part in this study. The cost of study-specific biopsies and exams, tests, and any other procedures will be paid for by the study.

Some costs associated with your care may be considered standard of care, and will be billed to you or your insurance company. You will have to pay for any costs (including deductibles and co-payments) not covered by your health insurer if these are required for treatment of your breast condition.

Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

To cover your expenses related to travel, child-care, loss of work time and other similar issues, you will receive $100 after your initial screening visit 1, $100 after Study Visit 1 (which may be combined with Study Visit 2 day of surgery), and $100 after completion of Study Visit 3 after your surgery. If you need to return to the office on a separate visit for a pregnancy test, you will receive an additional $100.

What happens if I am injured or hurt because I took part in this study?

If you feel you have been injured or hurt as a result of taking part in the study, it is important that you tell the study doctor immediately. You will get medical treatment if you are injured or hurt as a result of taking part in this study.

The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may

not be willing to pay for study-related injury. If you have no insurance coverage, you would be responsible for any costs. Even though you are in a study, you keep all of your legal rights to receive payment for injury caused by medical errors.

Who will see my medical information?

Your privacy is very important to us and we will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, we will do our best to make sure that any information that is released will not be able to identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private. Some of these organizations are:

- The study sponsor (National Cancer Institute).
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the US.
- The National Cancer Institute will obtain information for this clinical trial under data collection authority Title 42 U.S.C. 285.

Where can I get more information?

The National Cancer Institute will obtain information from this clinical trial under data collection authority Title 42 U.S.C. 285.

You may visit the NCI website at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

This section is about optional studies you can choose to take part in.

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records, and you or your study doctor may not know the results. You will not be billed for these optional studies.

You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

Optional Sample Collections for Laboratory Studies and/or Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your biopsies, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part, a sample of blood, and tissue from your breast will be collected. The researchers ask your permission to store and use your samples and health information for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by the Division of Cancer Prevention and supported by the National Cancer Institute.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) A sample from the tissue that was collected at the time of your surgery will be sent to the Biobank.

2) Your samples and some related information may be stored in the Biobank, along with samples and information from other people who take part. The samples will be stored at Northwestern University until the end of the study, when they may be transferred to the National Institutes of Health.

3) Qualified researchers can submit a request to use the materials stored in the Biobank. A research committee will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.

4) Neither you nor your study doctor will be notified if/when research is conducted using your samples and will not be given any results of this research.

5) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) There is a risk that someone could get access to the personal information in your medical records or other information we have stored about you.
2) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

A new Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to

discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.

- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment. All health insurance companies and group health plans must follow this law by May 21, 2010. All employers with 15 or more employees must follow this law as of November 21, 2009.

Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

3) There are laws against the misuse of genetic information, but they may not give full protection. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name or social security number) will be sent. Samples will be identified by a unique study code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and *(_____insert name of clinical trials organization)* staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom *(_____insert name of clinical trials organization)* sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part. Your samples may be helpful to research whether you do or do not have cancer. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part; however, you may receive some funds to defray some of the cost of participating (*e.g.*, parking, child care). If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option.

SAMPLES AND INFORMATION FOR FUTURE RESEARCH STUDIES:

My samples and related information may be kept in a Biobank for use in future health research.

YES NO

My samples for DNA may be kept in a Biobank for use in future health research.

YES NO

The information from my tobacco and alcohol use questionnaires may be used in future health research.

YES NO

I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

YES NO

I agree that my study doctor, or their representative, may contact me or my doctor to see if I wish to learn about the results from this study.

YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Subject's Name (printed) and Signature	Date
Name (printed) and Signature of Person Obtaining Consent	Date

APPENDIX A
Performance Status Criteria

ECOG Performance Status Scale

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Karnofsky Performance Scale

Percent	Description
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 signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

APPENDIX B

Study Diary

Protocol Number
Subject ID Name
Site Start date End Date

Day __ of Study	Date		Time	
Did you have any hot flashes in the past 24 hours?	yes	no		
If yes, how many	1-5		6-10	11-15
Did you have night sweats in the past 24 hours?	yes	no		
Did you apply your study gel as directed, a total of 2 complete pumps (1 complete pump per breast)?	yes	no		
Did you discard any doses of gel?	yes	no		
Did you experience any skin irritation?	yes	no		

Signature/Date

Day __ of Study	Date		Time	
Did you have any hot flashes in the past 24 hours?	yes	no		
If yes, how many	1-5		6-10	11-15
Did you have night sweats in the past 24 hours?	yes	no		
Did you apply your study gel as directed, a total of 2 complete pumps (1 complete pump per breast)	yes	no		
Did you discard any doses of gel?	yes	no		
Did you experience any skin irritation?	yes	no		

Signature/Date

To be repeated, for each day, until end of intervention

APPENDIX C

GEL APPLICATION INSTRUCTIONS:

1. Flammable: do not apply near fire, flame or heat, or while smoking

2. Apply the gel to your own breasts after bathing, preferably in the morning and at approximately the same time each day.

3. To apply, remove the cap from the canister. When you use a canister for the first time, you must prime it by pressing the pump fully several times until gel is dispensed (point the spout toward a sink or wastebasket and do not use the first dose, which may be incorrect).

4. Once the canister is primed, place it on a hard surface and place the palm of one hand under the pump to catch the gel. Be sure to press down completely on the pump and release it completely to dispense one dose of gel.

5. Apply a total of two complete pumps per day, **one dose of gel (one complete pump) to each breast per day** (dosage is indicated on the canister label). Do not apply more or less than one dose to each breast. Be sure to release the pump completely between both actuations.

6. If you accidentally pump twice for one breast, please discard this dose and try again to get one pump. If you press down on the pump and the gel does not fully land in your hand, please discard this dose and try again. If you do discard pumped doses, please record this on your study diary. There are extra doses in the pump to allow for priming and errors.

7. Spread the gel evenly over the entire surface of your breast, without rubbing.

8. Wash your hands immediately after applying the gel.

9. Allow the gel on your breasts to air dry for 2 minutes and then immediately cover with clothing (the gel is colorless and will not stain your clothing). Once dry, the gel is no longer flammable. Do not expose your bare breasts to sunlight at any time.

10. Do not apply any other cream, lotion or moisturizer to your breasts at any time during the study.

11. Do not wash your breasts or immerse in water (bath, swim) for at least 4 hours following application of the gel. If this is not possible, delay application of the gel that day until after immersion, and be sure to follow all the above instructions. If you regularly swim in the morning, it is better to apply the gel afterwards, after your shower.

12. After use, replace the cap on the canister.

RECOMMENDATIONS:

1. Be sure to apply **after bathing or showering, each day** during the study and preferably in the morning.

2. If you forget to apply a dose, do not double the dose to "catch up". If your next dose is scheduled within the next 12 hours, it is best just to wait; if it is more than 12 hours until your next dose, apply the dose you missed and resume your normal dosing after that.

3. For the duration of the study, avoid contact between the application area and the skin of other individuals (i.e. your child, your sexual partner, or other persons). If necessary, skin contact is allowable after the breasts have been washed. As noted above, you must wait at least 4 hours following application before washing the application area, otherwise, delay application until after washing and contact.

4. Do not ingest or swallow the gel. For external use only.

5. If the pump doesn't come back up correctly or if there's no gel delivered when you press down on the pump, do not use this canister and notify your doctor immediately.

6. After the end of study treatment, be sure to take back to your doctor **all** the gel canisters you have been given (even if empty or not used). **This is very important for the success of the study**.

STORAGE INSTRUCTIONS:

1. Keep your gel canisters at room temperature.

2. Keep the gel canisters out of the reach of children.

SPECIAL INSTRUCTIONS FOR THE DAY BEFORE SURGERY

1. **The day BEFORE surgery**, you should take your usual morning dose of the gel application. This will be your last dose of the study drug. Be sure to follow all washing instructions above.

2. **The day of surgery, do not apply the gel.** Be sure to take a shower, bathe, or wash your breasts the morning of surgery before you get to the hospital.

DELIVERY INSTRUCTIONS

Note: your institution may or may not allow for FedEx/UPS/courier delivery of gel dispensers. If you are having the dispensers delivered via FedEx, UPS, or another courier, you MUST be present to sign for the package **the first day** it arrives. If you are unable to sign for the package during the day, you have the option of requesting that the package be held for pickup.

For more information (FedEx), see: http://www.fedex.com/us/services/hold_at_location_find_locations.html.
For more information (UPS), see https://www.ups.com/content/us/en/register/reasons/myups.html.

APPENDIX D

PID: _____ Visit Date: _____

BESS Questionnaire

We are interested in knowing whether you have had any of the following problems during the **PAST TWO WEEKS**. Please mark the number which best describes how much each problem bothered you.

	PROBLEM	Not at all	Slightly	Moderately	Quite a bit	Extremely
C1	Difficulty concentrating	0	1	2	3	4
C2	Easily distracted	0	1	2	3	4
C3	Forgetfulness	0	1	2	3	4
M1	Joint pain	0	1	2	3	4
M2	Muscle stiffness	0	1	2	3	4
M3	General aches and pains	0	1	2	3	4
V1	Night sweats	0	1	2	3	4
V2	Hot flashes	0	1	2	3	4
V3	Cold sweats	0	1	2	3	4
Ga1	Vomiting	0	1	2	3	4
Ga2	Nausea	0	1	2	3	4
Ga3	Diarrhea	0	1	2	3	4
D1	Vaginal dryness	0	1	2	3	4
D2	Pain with intercourse	0	1	2	3	4
W1	Weight gain	0	1	2	3	4
W2	Unhappy with the appearance of my body	0	1	2	3	4
Gy1	Vaginal discharge	0	1	2	3	4
Gy2	Genital itching/irritation	0	1	2	3	4
Gy3	Vaginal bleeding or spotting	0	1	2	3	4
B1	Difficulty with bladder control (when laughing or crying)	0	1	2	3	4

BESS Questionnaire - continued

	PROBLEM	Not at all	Slightly	Moderately	Quite a bit	Extremely
B2	Difficulty with bladder control (at other times)	0	1	2	3	4
P1	Headaches	0	1	2	3	4
P2	Blind spots, fuzzy vision	0	1	2	3	4
P3	Constipation	0	1	2	3	4
P4	Cramps	0	1	2	3	4
P5	Breast sensitivity/tenderness	0	1	2	3	4
P6	Ringing in ears	0	1	2	3	4
P7	Chest pains	0	1	2	3	4
P8	Swelling of hands or feet	0	1	2	3	4
P9	Difficulty breathing	0	1	2	3	4
P10	Dry mouth	0	1	2	3	4
P11	Weight loss	0	1	2	3	4
P12	Decreased appetite	0	1	2	3	4
P13	Feeling of suffocation	0	1	2	3	4
P14	Excitability	0	1	2	3	4
P15	Short temper	0	1	2	3	4
P16	Tendency to take naps; stay in bed	0	1	2	3	4
P17	Tendency toward accidents	0	1	2	3	4
P18	Avoidance of social affairs	0	1	2	3	4
P19	Dizziness, faintness	0	1	2	3	4
P20	Numbness, tingling	0	1	2	3	4

BESS Questionnaire - continued

P21	Early awakening	0	1	2	3	4
P22	Abdominal pain	0	1	2	3	4
P23	Pain or cramps in the legs or feet	0	1	2	3	4
P24	Back pain or problems	0	1	2	3	4
P25	Low energy	0	1	2	3	4
P26	Blurred vision	0	1	2	3	4
P27	Any other problems?	Please Specify:				

Study Coordinator's Signature: _____ Date: _____

APPENDIX E

Please use the following suggested statements for participant communications.

For Email, Phone or Text Reminders during the first week (and subsequently if needed) please use the suggested statement:

"Hello my name is [insert name] from [site name/department], regarding NWU2017-09-01 TopEND research study. Please remember to apply your study gel and complete your participant diary. If you have any questions please call **[insert name]**, Research Coordinator at (xxx) xxx-xxx."

For Phone Calls to assess compliance, toxicity, and changes in medication please use the suggested statements:

"Hello my name is **[insert name]**, Research Coordinator at (xxx) xxx-xxx from [site name/department]. I wanted to check in with you briefly about the NWU2017-09-01 TopEND study. Is this a good time to talk?"

If no: "When would be a better time for me to call you?"

If yes: "As part of your study follow up, I am calling you to briefly assess your study compliance and symptoms. Since we last spoke on <<date>>, have you missed your study medication on any days?"

If yes: "How many days did you miss your study medication? On what dates did you miss your study medication?"

"Since we last spoke, have there been any changes to your current medications? For example, a change in dose, stopping a medication, or starting a new medication."
If yes: "Please tell me what has changed."

"Since we last spoke on <<date>>, have you noted any changes in the skin of your breast?"
If the participant reports yes, If the participant reports yes, then utilize the plain language guide below to ask more probing questions as needed.

Plain Language Guide for assessing skin application AEs

1. Is your breast skin dry from gel application? If yes, is it red or itchy?
2. Do you have pain on your breast skin? If yes, how severe?
3. Is your skin itchy from gel application? If yes, how severe? Are you taking any medicine for it?
4. Do you have rash on your breast skin? If yes, how big is the affected area? Are you taking any medicine for it? Can you please send us a picture of your rash?
5. Do you have hives on the breast skin where you have applied the gel? If yes, how big is the affected area? Are you taking any medicine for it?

"Since we last spoke on <<date>>, have you experienced any other symptoms?

"Please remember to apply your study gel and fill out the study diary. Thank you for your time."

For Reminder Phone Calls four days prior to surgery, please use the following suggested statement.

"Hello my name is [insert name] from [site name/department], regarding NWU2017-09-01 TopEND research study. This message is for [insert name]. Please remember to continue applying your study agent for the last 3 days prior to surgery and complete your participant diary. Your last gel application should be on the day before your surgery. If you have any questions please call **[insert name]**, Research Coordinator at (xxx) xxx-xxx."

For the Last Phone Call to premenopausal women, please use the following suggested statement:

"Hello my name is [insert name] from [site name/department], regarding NWU2017-09-01 TopEND research study. Is this a good time to talk?"

If no: "When would be a better time for me to call you?"

If yes: "Have you had a period since we last met? If so, what was the start date?"

"Thank you for your time and for participating in this study."

APPENDIX F

Alcohol and Tobacco Use Assessment
ALCOHOL ASSESSMENT – BASELINE

Instructions:

For the following questions about drinking alcoholic beverages, a drink means a 12 oz. beer, a 5 oz. glass of wine, or one and a half ounces of liquor.

1. In your entire life, have you had at least 12 drinks of any kind of alcoholic beverage?
   - ☐ Yes
   - ☐ No **(End)**
   - ☐ Refused **(End)**
   - ☐ Don't know/Not sure

2. In the past 12 months, on average, how often did you drink any type of alcoholic beverage?
   _____ (Enter the number of days you drank based on the timeframe checked below. Enter 0 if you never drank and skip to Question 6.)
   - ☐ Week
   - ☐ Month
   - ☐ Year
   - ☐ Refused
   - ☐ Don't know/Not sure

3. In the past 12 months, on those days that you drank alcoholic beverages, on average, how many drinks did you have per day?
   _____ (Enter the average number of drinks per day)
   - ☐ Refused
   - ☐ Don't know/Not sure

4. In the past 12 months, on how many days did you have 5 or more drinks of any alcoholic beverage?
   _____ (Enter the number of days you had 5 or more drinks, or enter 0 if none.)
   - ☐ Refused
   - ☐ Don't know/Not sure

5. Was there ever a time or times in your life when you drank 5 or more drinks of any kind of alcoholic beverage almost every day?
   - ☐ Yes
   - ☐ No
   - ☐ Refused
   - ☐ Don't know/Not sure

6. If you do not currently drink alcoholic beverages, but did in the past, how long has it been since you last drank regularly?
   - ☐ Within the past month (0 to 1 month ago)
   - ☐ Between 1 and 3 months (1 to 3 months ago)
   - ☐ Between 3 and 6 months (3 to 6 months ago)

- ☐ Between 6 and 12 months (6 to 12 months ago)
- ☐ Between 1 and 5 years (1 to 5 years ago)
- ☐ Between 5 and 15 years (5 to 15 years ago)
- ☐ More than 15 years ago
- ☐ Don't know/Not sure
- ☐ Never drank regularly

7. At the heaviest point, either now or in the past, on the days when you drank, about how many drinks did you drink a day on the average?
   _____ (Enter the number of drinks a day)

   ☐ Refused
   ☐ Don't know/Not sure

8. How many years have you been drinking (or did drink) regularly?
   _____ years

   ☐ Refused
   ☐ Don't know/Not sure

9. At what age did you begin drinking regularly?
   _____ years of age

   ☐ Refused
   ☐ Don't know/Not sure

10. What type(s) of alcohol do you drink? (Mark ALL that apply)
    - ☐ Wine
    - ☐ Liquor
    - ☐ Beer
    - ☐ Wine cooler

Coordinator Signature _____ Date __ __ / __ __ / __ __ __ __
(MM/DD/YYYY)

APPENDIX F

Alcohol and Tobacco Use Assessment
TOBACCO ASSESSMENT – BASELINE

Section A. Basic Cigarette Use Information

1. Have you smoked at least 100 cigarettes (5 packs = 100 cigarettes) in your entire life?
   - ☐ Yes
   - ☐ No → **Skip to Section B**
   - ☐ Don't know/Not sure → **Skip to Section B**

2. How old were you when you first smoked a cigarette (even one or two puffs)?
   _____ Years old

3. How old were you when you first began smoking cigarettes regularly?
   _____ Years old
   - ☐ Check here if you have never smoked cigarettes regularly.

4. How many total years have you smoked (or did you smoke) cigarettes? Do not count any time you may have stayed off cigarettes.
   _____ Years (If you smoked less than one year, write "1.")

5. On average when you have smoked, about how many cigarettes do you (or did you) smoke a day? (A pack usually has 20 cigarettes in it).
   _____ Number of cigarettes per day

6. Do you NOW smoke cigarettes?
   - ☐ Everyday
   - ☐ Some days
   - ☐ Not at all → **Skip to question 8**

7. How soon after you wake up do you smoke your first cigarette?
   - ☐ Within 30 minutes
   - ☐ After 30 minutes

8. How long has it been since you last smoked a cigarette (even one or two puffs)?
   First check which one of the following choices applies to you. Then, if applicable, write a number on the line for how many days, weeks, months, or years it has been since your last cigarette.
   - ☐ I smoked a cigarette today (at least one puff)
   - ☐ 1-7 days → Number of days since last cigarette _____
   - ☐ Less than 1 month → Number of weeks since last cigarette _____
   - ☐ Less than 1 year → Number of months since last cigarette _____
   - ☐ More than 1 year → Number of years since last cigarette _____
   - ☐ Don't know/Don't remember

Section B. Use of Other Forms of Tobacco

9. Have you ever used other forms of tobacco, not including cigarettes?
   - ☐ Yes
   - ☐ No → **Skip to Section C**

10. How often do you/did you use other forms of tobacco?
   - ☐ Every day → Number of times per day _____
   - ☐ Some days → Number of days _____ per ☐ Week ☐ Month ☐ Year

11. Which of the following products have you ever used regularly?
   Check all that apply
   - ☐ Cigarettes
   - ☐ E-cigarettes or other electronic nicotine delivery system
   - ☐ Traditional cigars, cigarillos or filtered cigars
   - ☐ Pipes
   - ☐ Waterpipe
   - ☐ Hookah
   - ☐ Clove cigarettes or kreteks
   - ☐ Bidis
   - ☐ Smokeless tobacco, like dip, chew, or snuff
   - ☐ Snus
   - ☐ Paan with tobacco, gutka, zarda, khaini
   - ☐ Other, Please specify:_____

12. If you do not currently use other forms of tobacco, but did in the past, how long has it been since you last used other forms of tobacco regularly?
   - ☐ Within the past month (0 to 1 month ago)
   - ☐ Between 1 and 3 months (1 to 3 months ago)
   - ☐ Between 3 and 6 months (3 to 6 months ago)
   - ☐ Between 6 and 12 months (6 to 12 months ago)
   - ☐ Between 1 and 5 years (1 to 5 years ago)
   - ☐ Between 5 and 15 years (5 to 15 years ago)
   - ☐ More than 15 years ago
   - ☐ Don't know/Not sure
   - ☐ Never used other forms of tobacco regularly

Section C. Second-Hand Smoke Exposure

13. Are you currently living with a smoker?
   - ☐ Yes
   - ☐ No

14. In the past 30 days, have you lived in a place where other people smoked cigarettes indoors?
   - ☐ Yes
   - ☐ No

15. In the past 30 days, have you worked in a place where other people smoked cigarettes indoors?

☐ Yes
☐ No

16. Thinking of all your childhood and adult years, have you ever lived in a place where other people smoked cigarettes indoors?
    ☐ Yes In total, for about how many years?_____ If less than 1, write "1."
    ☐ No

17. Thinking of all the years you have worked, have you ever worked in a place where other people smoked cigarettes indoors?
    ☐ Yes → In total, for about how many years?_____ If less than 1, write "1."
    ☐ No

Coordinator Signature _____ Date __ __ / __ __ / __ __ __ __
(MM/DD/YYYY)

APPENDIX F

Alcohol and Tobacco Use Assessment
ALCOHOL ASSESSMENT - FOLLOW-UP

Instructions:
For the following questions about drinking alcoholic beverages, a drink means a 12 oz. beer, a 5 oz. glass of wine, or one and a half ounces of liquor.

1. During the past 30 days, did you drink any alcoholic beverages?
   - ☐ Yes
   - ☐ No **(End)**
   - ☐ Refused **(End)**
   - ☐ Don't know/Not sure

2. During the past 30 days, how many days per week or per month did you drink any alcoholic beverages, on the average?
   _____ (Enter number of days you drank based on the timeframe checked below. Enter 0 if you did not drink.)
   - ☐ Week
   - ☐ Month
   - ☐ Refused
   - ☐ Don't know/Not sure

3. On the days when you drank, on average, about how many drinks did you have?
   _____ (Enter the average number of drinks you had per day.)
   - ☐ Refused
   - ☐ Don't know/Not sure

4. In the past 30 days, on how many days did you have 5 or more drinks per day?
   _____Number of times
   - ☐ None
   - ☐ Do not know/Not sure

Coordinator Signature _____ Date __ __ / __ __ / __ __ __ __
(MM/DD/YYYY)

APPENDIX F

Alcohol and Tobacco Use Assessment

TOBACCO ASSESSMENT - FOLLOW-UP

1. Do you NOW smoke cigarettes?
   - ☐ Everyday
   - ☐ Some days
   - ☐ Not at all → **Skip to Question 3.**

2. On average, when you smoked, about how many cigarettes do you (or did you) smoke a day? (A pack usually has 20 cigarettes in it).

   _____ Number of cigarettes per day

3. How long has it been since you last smoked a cigarette (even one or two puffs)?
   First check which one of the following choices applies to you. Then, if applicable, write a number on the line for how many days, weeks, months, or years it has been since your last cigarette.
   - ☐ I smoked a cigarette today (at least one puff)
   - ☐ 1-7 days → Number of days since last cigarette _____
   - ☐ Less than 1 month → Number of weeks since last cigarette _____
   - ☐ Less than 1 year → Number of months since last cigarette _____
   - ☐ More than 1 year → Number of years since last cigarette _____
   - ☐ Don't know/Don't remember

4. Since your last visit, have you used other forms of tobacco, not including cigarettes?
   - ☐ Yes
   - ☐ No (**End)**

5. How often do you/did you use other forms of tobacco?
   - ☐ Every day → Number of times per day _____
   - ☐ Some days → Number of days _____ per ☐ Week ☐ Month ☐ Year

6. Since your last visit, which of the following products have you used? ***Check all that apply***
   - ☐ Cigarettes
   - ☐ E-cigarettes or other electronic nicotine delivery system
   - ☐ Traditional cigars, cigarillos or filtered cigars
   - ☐ Pipes
   - ☐ Waterpipe
   - ☐ Hookah
   - ☐ Clove cigarettes or kreteks
   - ☐ Bidis
   - ☐ Smokeless tobacco, like dip, chew, or snuff
   - ☐ Snus
   - ☐ Paan with tobacco, gutka, zarda, khaini
   - ☐ Other, Specify_____

7. If you do not currently use other forms of tobacco, but did in the past, how long has it been since you last used other forms of tobacco regularly?
   - ☐ Within the past month (0 to 1 month ago)
   - ☐ Between 1 and 3 months (1 to 3 months ago)
   - ☐ Between 3 and 6 months (3 to 6 months ago)
   - ☐ Between 6 and 12 months (6 to 12 months ago)
   - ☐ Between 1 and 5 years (1 to 5 years ago)
   - ☐ Between 5 and 15 years (5 to 15 years ago)
   - ☐ More than 15 years ago
   - ☐ Don't know/Not sure
   - ☐ Never used other forms of tobacco regularly

The following instructions pertain to questions 8 - 10. During each of the following time frames, please indicate whether you smoked cigarettes every day, some days, or not at all.

8. During study treatment
   - ☐ Smoked every day
   - ☐ Smoked some days
   - ☐ Did not smoke at all
   - ☐ Don't know/not sure
   - ☐ Not applicable

9. After the end of study treatment
   - ☐ Smoked every day
   - ☐ Smoked some days
   - ☐ Did not smoke at all
   - ☐ Don't know/not sure
   - ☐ Not applicable (I have not completed the study treatment)

10. Since your last visit to this clinic
    - ☐ Smoked every day
    - ☐ Smoked some days
    - ☐ Did not smoke at all
    - ☐ Don't know/not sure
    - ☐ Not applicable (This is my first visit to this clinic)

Coordinator Signature _____ Date __ __ / __ __ / __ __ __ __ *(MM/DD/YYYY)*

APPENDIX G

Publicly available safety information of inactive ingredients from FDA website

Table 1. Composition of gel product
(A) Composition of endoxifen gel product (500 mL, MRIGlobal Inc.)

1.0% E/Z-Endoxifen Gel

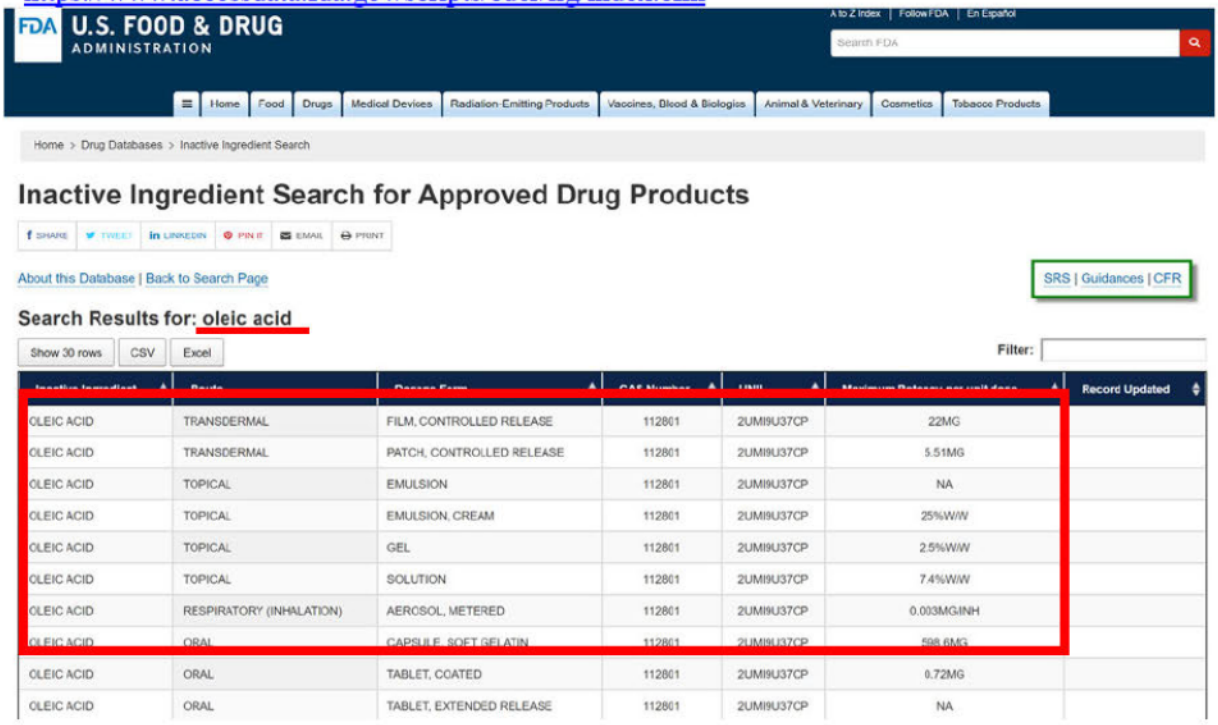
Components of Endoxifen Gel	Molecular weight (g/mole)	%(v/v), mL/500mL	Density (g/mL)	1.0% (w/v), g/500 mL of gel product
(E/Z) Endoxifen free base	373.49			5.00
Oleic Acid	282.46	0.5	0.895	2.25
Ethanol (200 proof)	46.07	300	0.79	237.00
Phosphate buffer, pH 7.0		200	1	197.50
Hydroxypropyl cellulose (Klucel HF)				7.50
				500 mL gel = 449.25 g gel
1 mL of gel delivers 0.8985 g of gel, and 1 mL of gel will contain 5 mg or 10 mg Endoxifen.				

(B) % (w/w) of each component of excipients

Components of excipients	formulation in the gel product	g/500 mL of gel product 500 mL = 449.25 g gel	(w/w) % in the gel product	Unit dose per breast (g/1 mL)	Total Daily dose (2 mL to cover both breasts)
Oleic acid	0.5% (v/v)	2.25 g	0.5%	0.0045 g	0.009 g
Ethyl alcohol (200 proof)	60% (v/v)	237.00 g	52.75%	0.474 g	0.948 g
Phosphate buffer, pH7.0	40% (v/v)	197.50 g	43.97%	0.395 g	0.79 g
Hydroxypropyl cellulose (Klucel ™ HF)	1.5% (w/v)	7.50 g	1.67%	0.015 g	0.03 g

Table 2. Oleic acid in approved drug products

https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm



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Inactive Ingredient Search for Approved Drug Products

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SRS | Guidances | CFR

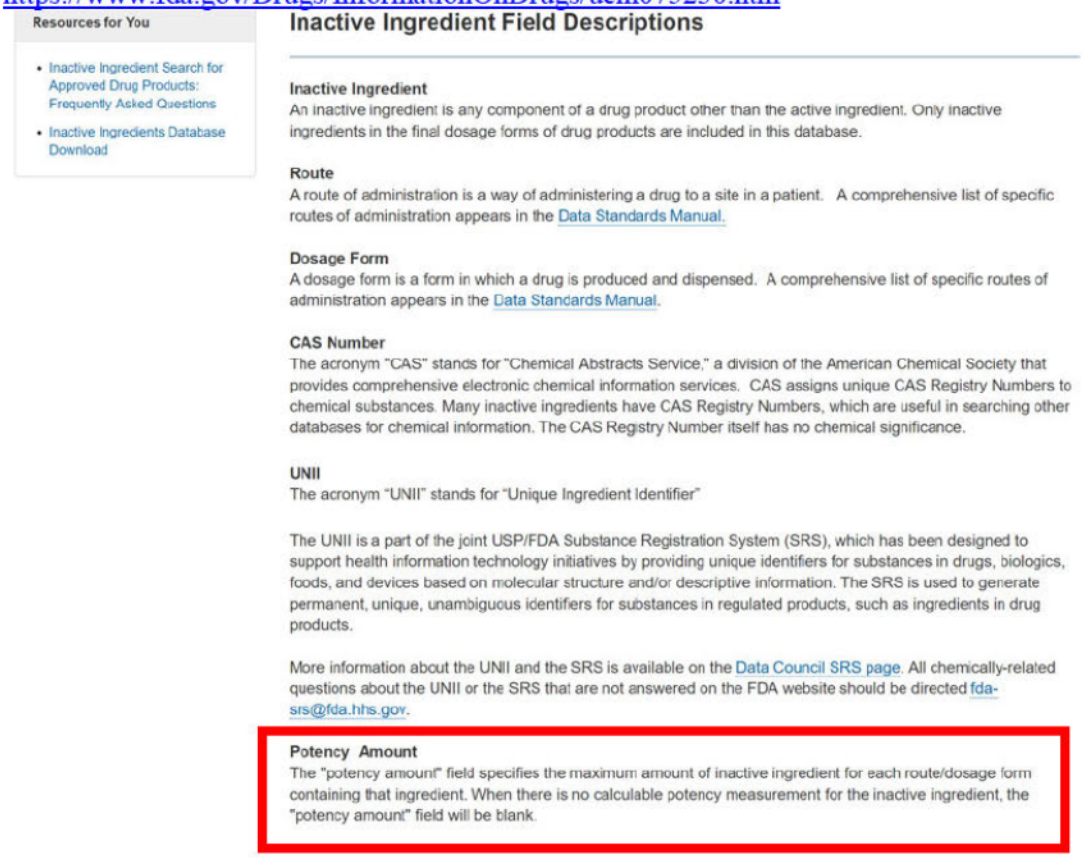
Search Results for: oleic acid

Show 30 rows | CSV | Excel

Filter:

Inactive Ingredient	Route	Dosage Form	CAS Number	UNII	Maximum Potency per unit dose	Record Updated
OLEIC ACID	TRANSDERMAL	FILM, CONTROLLED RELEASE	112801	2UMI9U37CP	22MG	
OLEIC ACID	TRANSDERMAL	PATCH, CONTROLLED RELEASE	112801	2UMI9U37CP	5.51MG	
OLEIC ACID	TOPICAL	EMULSION	112801	2UMI9U37CP	NA	
OLEIC ACID	TOPICAL	EMULSION, CREAM	112801	2UMI9U37CP	25%W/W	
OLEIC ACID	TOPICAL	GEL	112801	2UMI9U37CP	2.5%W/W	
OLEIC ACID	TOPICAL	SOLUTION	112801	2UMI9U37CP	7.4%W/W	
OLEIC ACID	RESPIRATORY (INHALATION)	AEROSOL, METERED	112801	2UMI9U37CP	0.003MG/INH	
OLEIC ACID	ORAL	CAPSULE, SOFT GELATIN	112801	2UMI9U37CP	598.6MG	
OLEIC ACID	ORAL	TABLET, COATED	112801	2UMI9U37CP	0.72MG	
OLEIC ACID	ORAL	TABLET, EXTENDED RELEASE	112801	2UMI9U37CP	NA	

https://www.fda.gov/Drugs/InformationOnDrugs/ucm075230.htm



Resources for You

- Inactive Ingredient Search for Approved Drug Products: Frequently Asked Questions
- Inactive Ingredients Database Download

Inactive Ingredient Field Descriptions

Inactive Ingredient
An inactive ingredient is any component of a drug product other than the active ingredient. Only inactive ingredients in the final dosage forms of drug products are included in this database.

Route
A route of administration is a way of administering a drug to a site in a patient. A comprehensive list of specific routes of administration appears in the Data Standards Manual.

Dosage Form
A dosage form is a form in which a drug is produced and dispensed. A comprehensive list of specific routes of administration appears in the Data Standards Manual.

CAS Number
The acronym "CAS" stands for "Chemical Abstracts Service," a division of the American Chemical Society that provides comprehensive electronic chemical information services. CAS assigns unique CAS Registry Numbers to chemical substances. Many inactive ingredients have CAS Registry Numbers, which are useful in searching other databases for chemical information. The CAS Registry Number itself has no chemical significance.

UNII
The acronym "UNII" stands for "Unique Ingredient Identifier"

The UNII is a part of the joint USP/FDA Substance Registration System (SRS), which has been designed to support health information technology initiatives by providing unique identifiers for substances in drugs, biologics, foods, and devices based on molecular structure and/or descriptive information. The SRS is used to generate permanent, unique, unambiguous identifiers for substances in regulated products, such as ingredients in drug products.

More information about the UNII and the SRS is available on the Data Council SRS page. All chemically-related questions about the UNII or the SRS that are not answered on the FDA website should be directed fda-srs@fda.hhs.gov.

Potency Amount
The "potency amount" field specifies the maximum amount of inactive ingredient for each route/dosage form containing that ingredient. When there is no calculable potency measurement for the inactive ingredient, the "potency amount" field will be blank.

Table 3. Ethyl alcohol in approved drug product
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

Home | Previous Page

New Drug Application (NDA): 021074
Company: 3M

Over-The-Counter (OCT) drug contain ethyl alcohol

EMAIL

Products on NDA 021074

CSV | Excel | Print

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	TE Code	RLD	RS
AVAGARD	ALCOHOL; CHLORHEXIDINE GLUCONATE	61%;1%	SOLUTION;TOPICAL	Over-the-counter	None	Yes	Yes

Showing 1 to 1 of 1 entries

Approval Date(s) and History, Letters, Labels, Reviews for NDA 021074

Original Approvals or Tentative Approvals

CSV | Excel | Print

Action Date	Submission	Action Type	Submission Classification	Review Priority; Orphan Status	Letters, Reviews, Labels, Patient Package Insert	Notes
06/07/2001	ORIG-1	Approval	Type 3 - New Dosage Form	STANDARD	Label (PDF) Letter (PDF) Review	

Showing 1 to 1 of 1 entries

Figure 1. Drug label of Avagard

Clean Copy of 9216 Label

3M™ Avagard™ (Chlorhexidine Gluconate 1% Solution and Ethyl Alcohol 61% w/w)
Surgical and Healthcare Personnel Hand Antiseptic, NDA 21-074

Avagard™ Product Information

PRODUCT TITLE
Avagard™
(Chlorhexidine gluconate 1% and ethyl alcohol 61%, w/w)

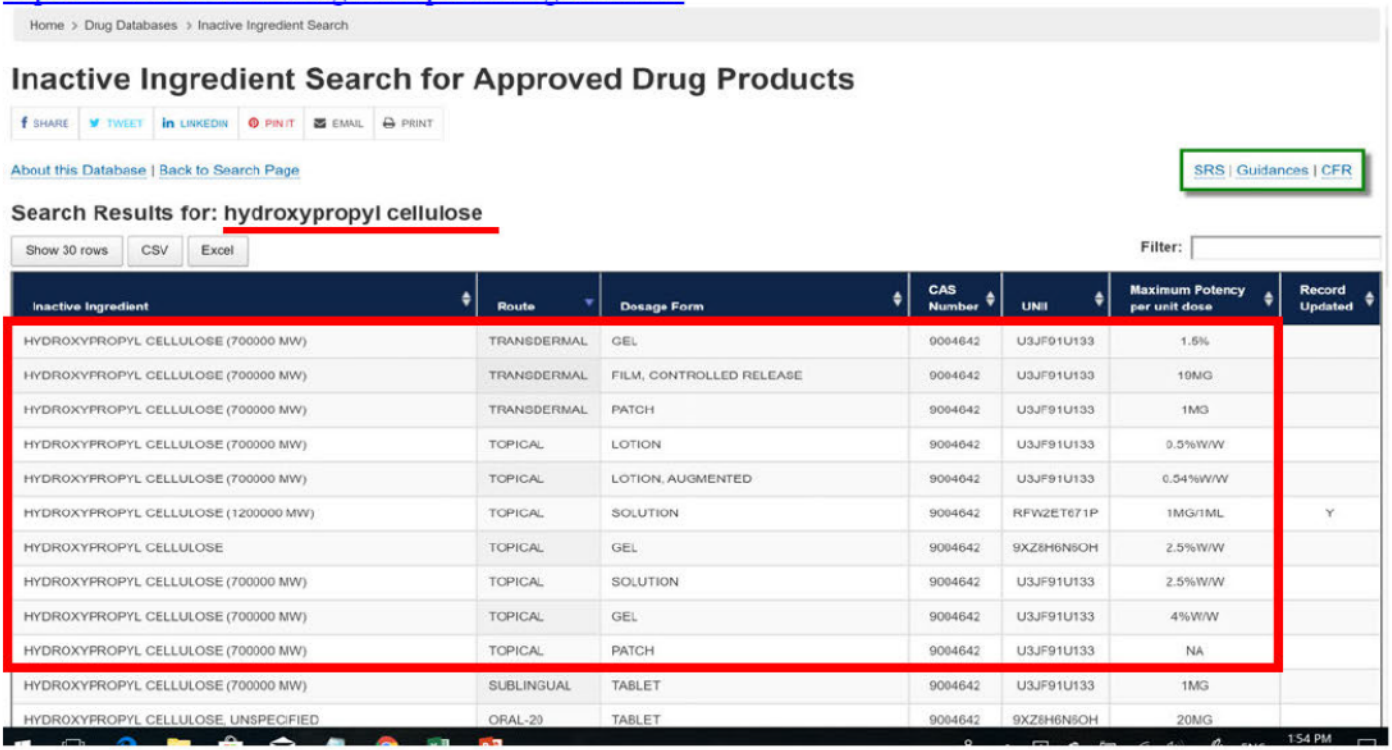
Surgical and Healthcare Personnel Hand Antiseptic
with moisturizers

DESCRIPTION
Avagard Antiseptic Hand Preparation with moisturizers for surgical and healthcare disinfection, provides rapid bactericidal action and persistent antimicrobial protection against a broad spectrum of organisms. Avagard antiseptic hand prep contains 1% (w/w) chlorhexidine gluconate, and 61% (w/w) ethyl alcohol in an emollient-rich lotion base.

This product is flammable, keep away from fire or flame, heat, sparks and sources of static discharge.

Avagard antiseptic hand prep does not require the use of water, or mechanical scrubbing with a surgical brush to achieve the bactericidal effect. Water should not be used in its application.

Table 4. Hydroxypropyl cellulose in approved drug product
https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm



Inactive Ingredient	Route	Dosage Form	CAS Number	UNII	Maximum Potency per unit dose	Record Updated
HYDROXYPROPYL CELLULOSE (700000 MW)	TRANSDERMAL	GEL	9004642	U3JF91U133	1.5%	
HYDROXYPROPYL CELLULOSE (700000 MW)	TRANSDERMAL	FILM, CONTROLLED RELEASE	9004642	U3JF91U133	10MG	
HYDROXYPROPYL CELLULOSE (700000 MW)	TRANSDERMAL	PATCH	9004642	U3JF91U133	1MG	
HYDROXYPROPYL CELLULOSE (700000 MW)	TOPICAL	LOTION	9004642	U3JF91U133	0.5%W/W	
HYDROXYPROPYL CELLULOSE (700000 MW)	TOPICAL	LOTION, AUGMENTED	9004642	U3JF91U133	0.54%W/W	
HYDROXYPROPYL CELLULOSE (1200000 MW)	TOPICAL	SOLUTION	9004642	RFW2ET671P	1MG/1ML	Y
HYDROXYPROPYL CELLULOSE	TOPICAL	GEL	9004642	9XZ8H6N6OH	2.5%W/W	
HYDROXYPROPYL CELLULOSE (700000 MW)	TOPICAL	SOLUTION	9004642	U3JF91U133	2.5%W/W	
HYDROXYPROPYL CELLULOSE (700000 MW)	TOPICAL	GEL	9004642	U3JF91U133	4%W/W	
HYDROXYPROPYL CELLULOSE (700000 MW)	TOPICAL	PATCH	9004642	U3JF91U133	NA	
HYDROXYPROPYL CELLULOSE (700000 MW)	SUBLINGUAL	TABLET	9004642	U3JF91U133	1MG	
HYDROXYPROPYL CELLULOSE, UNSPECIFIED	ORAL-20	TABLET	9004642	9XZ8H6N6OH	20MG	

Table 5. Approved topical/transdermal drugs using phosphate buffer as dissolution method
https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_getalldata.cfm

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Diclofenac Epolamine	Topical patch	V (Paddle over Disk) with a watchdish (a diameter of 6 cm)	50	pH 6.8 phosphate buffer at 32 ± 0.5 C	500	15, 30, 45, 60, 90, 120 and 180	10/21/2010
Fentanyl	Transdermal	VII (Reciprocating holder)- cylinder.	30 cycles per minute. amplitude of about 2m.	Equimolar mixture of 0.005 M phosphoric acid solution, and 0.005 M sodium phosphate, monobasic monohydrate (pH ~ 2.6). at 32 C. Change the test samples into fresh pre-equilibrated release medium at the time points indicated. Remove the protective liner and place the film onto a piece of nylon netting with adhesive facing the net. Secure the netting and transdermal system using nylon tie wraps at the top and bottom of the cylinder on the holder. The adhesive side faces towards the media.	250 mL for the 75 and 100 mcg/hr, 200 mL for the 50 mcg/hr and 150 mL for the 25 and 12.5 mcg/hr dosage strength.	0 5, 1, 2, 4 and 24 hours	06/09/2011
Selegiline (40 mg/40 cm2)	Transdermal	Rotating Cylinder (Apparatus 6)	50	0.1 M Phosphate buffer, monobasic, pH 5 at 32 C	1000	1, 2, 4, 8, 12, 16, 20 and 24 hours	07/15/2009
Selegiline (20 mg/20 cm2 and 30 mg/30 cm2)	Transdermal	Paddle over Disk (Apparatus 5)	50	0.1 M Phosphate buffer, monobasic, pH 5 at 32 C	500	1, 2, 4, 8, 12, 16, 20 and 24 hours	07/15/2009
Rotigotine	Transdermal	Paddle over Disk (Apparatus 5)	50	Phosphate Buffer, pH 4.5 at 32 C	900	15, 30, 60, 90, 120, 150 and 180	07/15/2009