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INTRA-MAMMARY DISTRIBUTION OF TRANSDERMAL TELAPRISTONE VERSUS ORAL TELAPRISTONE: A RANDOMIZED WINDOW TRIAL IN WOMEN UNDERGOING MASTECTOMY

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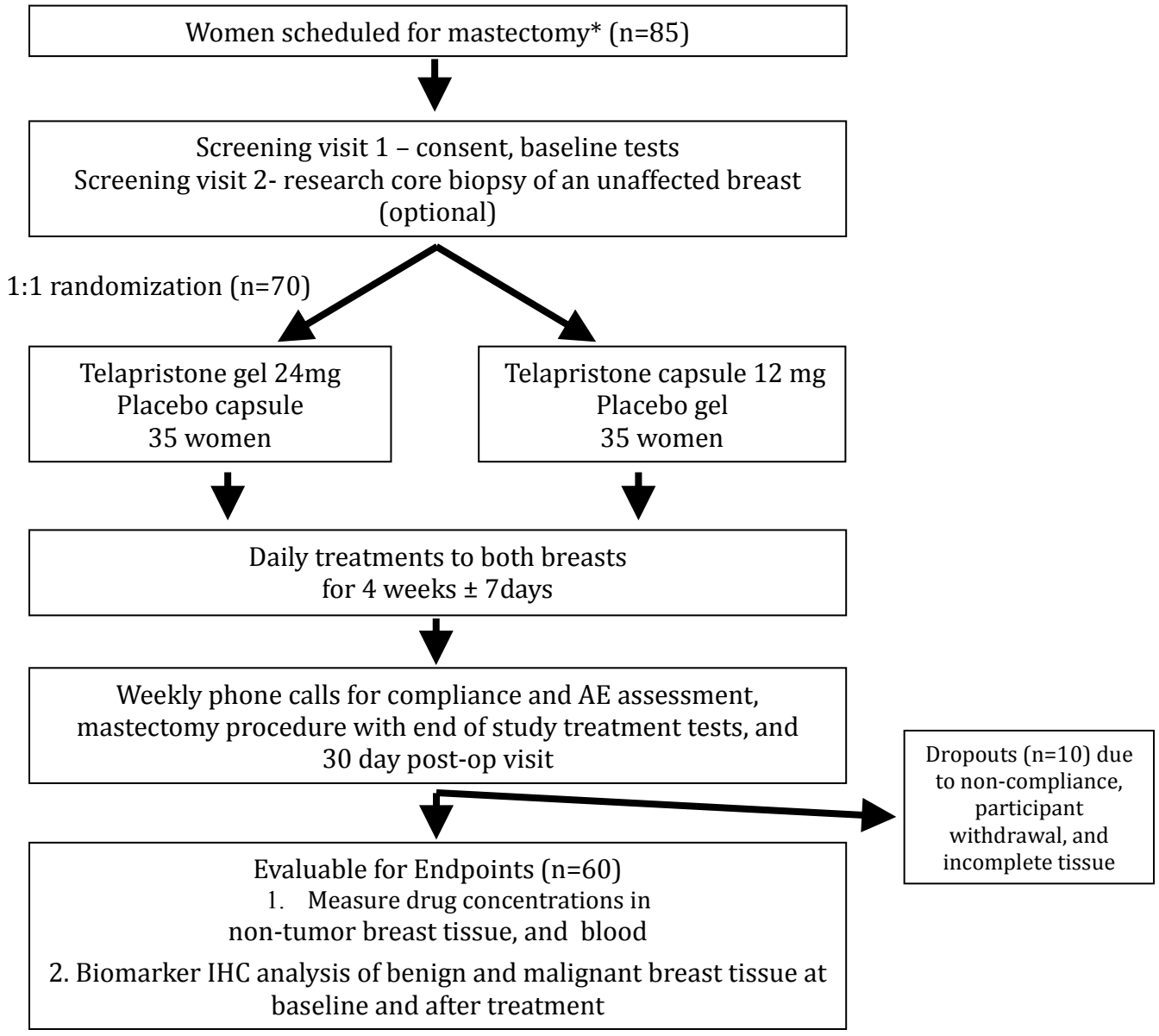
SCHEMA

Intra-mammary distribution of transdermal telapristone vs. oral telapristone: a randomized window trial in women scheduled for mastectomy



*Mastectomy for stage 0-II breast cancer therapy or prophylaxis (for *BRCA1/2* mutation carriers, women with strong family history or lobular carcinoma in situ or other conditions where prophylactic mastectomy has been elected)

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1. OBJECTIVES

1.1 Primary Objectives

To demonstrate that mean levels of telapristone in breast tissue following gel application will result in levels that are not more than 50% lower than those following oral administration.

1.2 Secondary Objectives

1) To assess whether plasma concentrations of telapristone are significantly lower with transdermal than oral therapy.
2) To compare within-breast variation of breast tissue concentration in transdermal and oral groups.
3) To measure changes in cell proliferation (Ki67 labeling index).
4) Explore changes in gene expression in breast tissue related to telapristone therapy.
5) Assess change in serum progesterone associated with telapristone therapy.
6) Assess the safety and tolerability of oral and transdermal administration.
7) Assess symptom measurements using BESS Questionnaire

2. BACKGROUND

2.1 Study Disease

A pressing need in breast cancer prevention is the availability of safe, acceptable preventive interventions for premenopausal women, whose only proven pharmacologic option at the moment is tamoxifen. Ideally, such an agent would prevent breast cancer regardless of hormone receptor status, accommodate the contraception needs of younger women, but also allow use in women who are planning to conceive. Tamoxifen has none of these attributes.

Progesterone receptor modulation for breast cancer prevention: Progesterone (P4) and progestin exposure is increasingly recognized as instrumental in the breast cancer risk associated with exposure to the reproductive hormones. The evidence supporting an important promoting role for progesterone and progestins extends from epidemiological investigations showing that the number of ovulatory cycles that a woman is exposed to is a stronger determinant of breast cancer risk than the length of time between menarche and menopause [1], and that combination post-menopausal hormone therapy (estrogen and progestin, or E+P) carries a larger breast cancer risk than therapy with estrogen alone [2]; the short-term increase in breast cancer risk following pregnancy, at least partially attributed to the high progesterone exposure of pregnancy [3]; furthermore, several studies have documented that postmenopausal E+P increases mammographic density to a greater extent than estrogen alone [4] and that density is greater in the luteal phase of the menstrual cycle [5]. In premenopausal women, current oral contraceptive use has long been associated with a modest increase in breast cancer risk [6], but recent data on the use of depo-medroxyprogesterone acetate (DMPA) shows a 2-fold increase in breast cancer risk, with a trend towards higher grade and triple negative tumors [7,8]. Other supporting data include the higher cell proliferation indices during the luteal phase of the menstrual cycle as compared with the follicular phase [9], and the observation among postmenopausal women, that users of E+P have higher epithelial proliferation indices than those taking E alone [10]. Together, these data suggest a specific pro-tumorigenic effect of P4 on the breast. Finally, E+P related breast cancers are more lethal than those related to use of E alone, in both premenopausal [11] and postmenopausal women [12, 13].

Tumors appearing in a progesterone-rich environment are more lethal: E+P related postmenopausal breast cancers are more lethal than those related to use of E alone [14], a trend which is also reflected in data on studies of DMPA use, where the risk for hormone receptor (HR) negative and triple negative (TN) breast cancer was found to be higher than for HR positive breast cancer [7, 8]. Finally, the intense P4 exposure of pregnancy may be partially responsible for the increased breast cancer susceptibility in the interval following pregnancy; this is a profoundly negative effect since post-partum tumors have been shown to have poorer prognosis [15], to be more frequently HR negative and triple negative [16], and to be mammographically occult [16].

The clinical and epidemiological data cited above is bolstered by the proliferative and tumorigenic effects of progesterone (P4) on the mouse mammary gland. Tumor formation in the DMBA mouse model is heavily progesterone–dependent, and is markedly reduced in PRKO mice [17]. An intact BRCA-1 protein appears to protect the mammary gland against the proliferative effects of P4 [18], and *BRCA1* deletion in the mouse mammary gland leads to overexpression of PR and a hyper-proliferative response to P4. The PR antagonist RU486 prevents development of these tumors, indicating that mammary tumor formation in *BRCA1*-null mice is dependent on PR [19]. Additionally, recent hypotheses regarding the tumorigenic potential of P4 exposure have invoked the ability of progesterone to expand mammary stem cell pools which may accumulate sufficient mutations to transform into tumor initiating cells; notably, this effect is seen only with the combination of E+P, and not with E alone [3].

In particular, a study of a rodent model of BRCA1 deficient breast cancer, where the progesterone antagonist RU-486 was successful in preventing hormone receptor negative tumors [20], raises the possibility that the success of oophorectomy in preventing breast cancer in *BRCA1* carriers [21,22] may be driven by progesterone rather than estrogen deprivation. Recent data on a newer generation of the selective progesterone receptor modulators (SPRMs) suggest a tumor-protective effect of progesterone receptor (PR) blockade with the SPRM telapristone (Proellex, Repros Therapeutics) in rat mammary carcinogenesis models [23,24]. These new SPRMs are of significant interest because PR blockade is more specific than RU486 and the toxicity profile is sufficiently favorable that telapristone and CDB2914 are being tested in the United States and Europe for benign gynecologic conditions such as endometriosis and uterine fibroids [25, 25-31].

2.2 Study Agent

Telapristone (Proellex), a 21-substituted analog of 19-norprogesterone (**Figure 1**), is a selective progesterone receptor modulator (SPRM). Telapristone opposes progesterone at the molecular or receptor level and exhibits potent anti-progesterone effects without significant anti-glucocorticoid activity. Telapristone has been tested on 7,12,-dimthylbenz(a)anthracene (DMBA)-induced mammary carcinogenesis in rats in comparison with RU486. The animals were treated for 28 days with vehicle, mifepristone, progesterone, and telapristone at various doses, or telapristone + progesterone (P4). RU486 and telapristone treatment caused regression of existing tumors, suppressed the development of new tumors and reduced tumor multiplicity. Progesterone treatment, however, increased tumor size and multiplicity. Mifepristone (RU486) and telapristone lowered tumor burden and median tumor size 5-fold in the case of mifepristone ($p<0.01$) and 10-fold for telapristone ($p<0.001$) compared to the control group. Telapristone, at the same dose, is more efficacious than mifepristone, possibly because the latter has also been shown to act as an anti-glucocorticoid. It should be noted that some tumors regressed completely and were no longer palpable by treatment of anti-progestins (RU486 and telapristone). When telapristone (10mg/kg) was combined with high dose of progesterone (10mg/kg), cell proliferation was lower than that observed with P4 alone ($p=0.030$). Moreover, the increased apoptosis seen with telapristone treatment was not abrogated by the

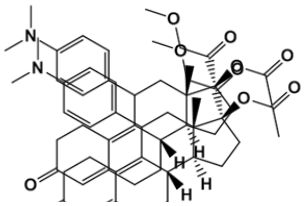


Figure 1. Molecular structure of telapristone

addition of P4, suggesting that tumor apoptotic response to telapristone occurs even in the presence of high dose P4. These results indicate that telapristone should be developed for the prevention and treatment of hormone-responsive breast cancer [23, 24].

In another study of N-methyl-N-nitrosourea (MNU)-induced mammary carcinogenesis in rats, telapristone administered at 30 mg over 84 days increased tumor latency from 66 ± 24 days to 87 ± 20 days ($P < 0.02$), decreased incidence from 85% to 35% ($P < 0.001$), and reduced multiplicity from 3.0 to 1.1 tumors/animal ($P < 0.001$). Tumor burden decreased from 2.6 g/animal to 0.26 g/animal ($P < 0.01$). Telapristone inhibited cell proliferation and induced apoptosis in MNU-induced mammary tumors, which correlated with a decreased proportion of PR+ tumor cells and with decreased serum P4[23,24].

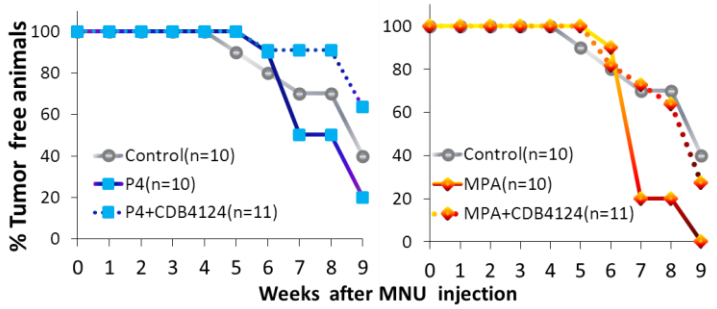


Figure 2. Mammary gland tumor-free survival in response to the treatments. Female Sprague-Dawley rats were received a single intraperitoneal injection of MNU (50 mg/kg) between 4 and 5 weeks of age. 30 mg CDB-4124, and 25mg hormone (P4 or MPA) pellets (90 days release) were s.c. implanted in lateral side of neck of rats 3 and 4 weeks after MNU injection, respectively.

Table 1. Tumor latency, incidence, multiplicity, and burden in mammary tumors at termination of the study.

Treatments	Incidence (%)	Latency (days)	Multiplicity	Burden (g)	p	p*	p#	p‡
Control	60	72.2 ± 25.8	1.4 ± 2.1	2.55 ± 5.67				
P4	80	62.9 ± 21.3	2.1 ± 1.9	3.29 ± 5.00	0.20		0.38	
MPA	100	50.8 ± 7.70	2.5 ± 0.7	6.02 ± 4.85	**0.01**		**0.07**	
P4 + CDB-4124	36	85.2 ± 21.5	0.7 ± 1.3	0.50 ± 0.77	0.11	**0.01**	0.14	**0.06**
MPA + CDB-4124	73	70.9 ± 24.5	2.0 ± 2.0	3.05 ± 4.16	0.45	**0.01**	0.41	**0.08**

Statistical significance(p value) between treatment groups was calculated with t-test($\alpha = 0.05$, un-equal variance and one tail method): p= tumor latency (control vs. other groups); p*= tumor latency (hormone vs. hormone+CDB-4124); p# =tumor burden(control vs. other groups); p‡ = tumor burden (hormone vs. hormone+CDB-4124).

Telapristone did not affect serum estradiol in rats. In a mechanistic study employing T47D cells, telapristone suppressed G1/G0–S transition by inhibiting cdk2 and cdk4 expressions, which correlated with inhibition of estrogen receptor (ER) expression [23,24]. Of the progesterone antagonists that have been evaluated for effects on breast development and breast cancer promotion, preclinical data suggests that telapristone is superior to RU-486, with more selective anti-progestin activity, greater inhibition of cell growth in T47D cells, and demonstrated growth suppression of established ER+ mammary tumors in rats [23,24]. *Taken together, these data, along with our data presented below, indicate that telapristone can suppress the development of mammary tumors in rodents, and suggest its utility for prevention and treatment of human breast cancer*.

Ongoing studies in our laboratory are intended to elucidate the mechanisms of action of telapristone against breast cancer and identify candidate biomarkers. We have tested the anti-tumor efficacy of telapristone in an orthotopic xenograft model of T47D cells in mammary glands of athymic rats. One day after implantation of T47D cells, all animals were treated with either s.c. telapristone pellet (30mg/pellet, 60-day release formula) or s.c. placebo pellet. Treatment duration was 6 weeks. We found that tumor formation was reduced in the telapristone treatment group compared to the placebo group (tumors formed in 10% of telapristone group vs. 63% of placebo group, p=0.008), confirming that telapristone inhibited establishment of T47D xeno-grafts in rats.

In a second experiment, we tested the ability of telapristone to retard tumor growth promoted by P4 and MPA in the widely used model of N-methyl-N-nitrosourea (MNU)-induced mammary carcinogenesis in the rat (**Figure 2**). MNU treated rats developed 70% ER+/PR+, and 30% ER-/PR- tumors [4]. Tumor incidence, latency, multiplicity, and burden were recorded weekly; plasma concentrations of telapristone and its metabolite CDB-4453 were determined by LC-MS/MS. The experiment was terminated at 9 weeks after MNU injection since all MPA treated mice, 80% of P4 treated mice, and 60% of control mice developed tumors.

Overall tumor incidence, latency, multiplicity, and tumor weight at euthanasia are summarized as mean ± SD in **Table 1**. Tumor latency was increased with telapristone treatment, whereas tumor incidence and burden (g) was decreased, compared to P4 and MPA treated groups. Plasma telapristone and CDB-4453 were 11.6 ±5.88 ng/mL and 3.4±1.68 ng/mL, respectively. Our results indicated that P4 promoted MNU-induced mammary tumor formation similar to MPA in rats. In this tumor permissive environment, telapristone showed prevention efficacy, suggesting good potential as a breast cancer prevention agent (Manuscript in preparation).

We have also tested functional activity for progesterone receptor (PR) in ER/PR positive breast cancer cell lines by progesterone response element -luciferase reporter (PRE-Luc) activity. To determine the relative agonist and antagonist activities of telapristone with respect to PR-mediated transcriptional activation, we performed dual- luciferase reporter assays (Promega, Madison, WI) in T47D, BT474, and MCF7 cell lines. As seen in **Figure 3**, treatment of ER+/PR+ cells with telapristone over a wide concentration range (10–1000nM), did not result in any detectable induction of PRE-Luc activity (i.e. no agonist effect). In contrast, progesterone (P4) and MPA dramatically induced expression of PRE-Luciferase. Cells were also treated with a single dose of P4 or MPA (10 nM) in the absence or presence of increasing concentrations of telapristone. Telapristone inhibited P4 and MPA induction of PRE-Luc expression in a dose-dependent manner. Specifically, 100 nM telapristone completely inhibited 10 nM of P4 and MPA induction of PRE-Luc expression. Collectively, these results, along with the epidemiological and laboratory evidence supporting the role of progestational agents in breast cancer development, provides strong rationale for the development of the newer generation of progesterone receptor modulators for breast cancer prevention and therapy.

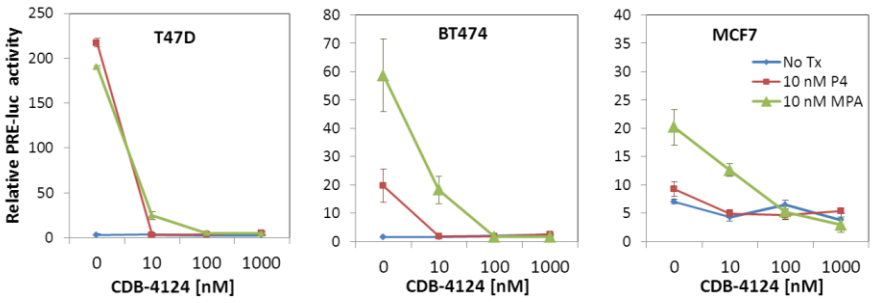


Figure 3. CDB-4124 dose-dependent inhibition on PRE-Luc activity. A range of 10-1000 nM CDB-4124 were tested with a supplementation of 10 nM of P4 or MPA. The relative PRE- luciferase activity was expressed as the ratio of the firefly luciferase/Renilla luciferase/µg of cell protein. All experiments were performed in triplicate.

Are SPRMs safe? The most well-developed safety data on SPRMs is available on CDB-2914 (ulipristal acetate) and telapristone. Ulipristal has been tested in a placebo-controlled randomized trial. When used for a 12-week period, it showed excellent tolerability with the major adverse effect being breast tenderness and headache, equally frequent in treated and placebo women [33]. The most common side effects associated with a 12 mg dose of telapristone are amenorrhea, hot flushes, cystic endometrial thickening (hyperplasia has not been observed), nausea, constipation, abdominal pain, and headache.

Overall, the safety profiles of both telapristone and ulipristal appear very favorable; both drugs show efficacy against benign uterine fibroids and endometriosis. Unlike mifepristone [34], telapristone does not increase plasma levels of estradiol or corticosteroids in rats and has much less antiglucocorticoid activity. However, it does increase liver enzymes at high doses (Repros ZPU-003 study and Repros investigator brochure for telapristone). It is now being tested under IND in a Phase II study of endometriosis (a three-arm trial with daily placebo, 6mg, and 12 mg); notably, no hepatic toxicity has been observed at an oral dose of 12 mg daily. Nonetheless, systemic adverse effects remain a concern since there is no data on the safety of long-term use (i.e. years), and with chronic use, these anti-progestin drugs may increase the potential for endometrial cancer through reductions in progesterone activity. They also cause irregular menstrual bleeding patterns and suppression of ovulation, which have reproductive implications for premenopausal women. Suppression of ovulation is expected to interfere with fertility and conception [29, 35]. On the other hand, there is clear potential that oral telapristone may provide contraception, and thus serve a dual purpose along with breast cancer prevention among high risk women not wanting to conceive.

Transdermal delivery for safer prevention: Since safety and acceptability is a paramount concern for preventive therapy, alternative drug-delivery approaches that minimize systemic exposure need to be considered. One of these is local transdermal delivery (LTT) of active drugs to the breast parenchyma through its skin envelope. Anticipated major advantages are: 1) the reduction or elimination of systemic toxicity; 2) the aversion of problems related to variations in drug metabolism which have been shown to hamper the efficacy of tamoxifen. The LTT approach for breast cancer prevention can be explored for any anticancer drug where systemic toxicity limits use in healthy individuals if it penetrates the skin and concentrates in the breast parenchyma with low systemic levels. This concept has had very limited testing in the breast; preliminary validation was achieved in a small Phase II study [36] which demonstrated that an active metabolite of tamoxifen, 4-hydroxytamoxifen (4-OHT), applied to the breast skin as a gel, provides local tissue concentrations that reduces breast tumor cell proliferation to the same extent as oral tamoxifen, with low circulating levels. That this constitutes local rather than systemic therapy was demonstrated through experiments that compared drug concentrations in the breast following application on the skin of the breast versus skin of the shoulder; significantly higher breast tissue concentrations were achieved when 4-OHT was applied to the breast skin [37]. Added support for the LTT concept for breast cancer prevention is provided by data demonstrating the embryological origins of the breast as a skin appendage [38], suggesting that the parenchyma and overlying skin are a single unit, so that drugs applied to the breast skin will not only be concentrated in the underlying parenchyma, but also distributed throughout the breast through a rich internal vascular and lymphatic network. We have further evaluated the LTT concept in two clinical studies; in the first, transdermal 4-OHT was compared to oral tamoxifen in a window trial of 26 women with DCIS (PI Seema Khan, NCT 00952731). This showed that similar breast concentrations of 4-OHT were obtained with transdermal and oral delivery, with equivalent suppression of Ki-67 labeling in DCIS lesions (manuscript in preparation). In the second, 30 women undergoing mastectomy were randomized to a diclofenac patch applied to the breast skin versus the abdominal skin. Preliminary results point to two- to three-fold higher breast concentrations of diclofenac with breast application of the patch than with abdominal application ($p<0.01$).

Telapristone is a small, lipophilic molecule that is suitable for transdermal delivery. We have tested its permeation in the laboratory, alone and with mixtures of permeation enhancers such as ethanol and 0.5 v/v % oleic acid (OA) for in vitro human skin permeation, using split-thickness skin from mastectomy specimens. We found that the permeation of telapristone through human breast skin was about 3.1 ± 0.86%, and that 0.5% OA enhanced permeation 4-fold compared to that of telapristone alone i.e. 11.6 ± 1.45% at 24 hr; additionally the rate of telapristone permeation was 5-fold faster than the drug alone within 12 hr (**Figure 4**). These results compare favorably with the level of skin permeation of estradiol (results from our laboratory) which is a well-established and efficacious transdermal agent.

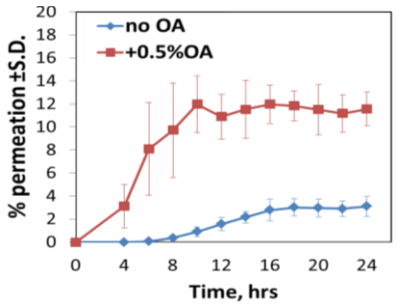


Figure 4. in vitro human skin permeation of telapristone was enhanced with the addition of 0.5% oleic acid.

Building on these results, Repros Therapeutics has formulated a transdermal alcoholic colloidal suspension of telapristone which is modified from commercially available transdermal formulation for testosterone (AndroGel®, AbbVie Inc., North Chicago, IL) (FDA approved and marketed). Repros replaced sodium hydroxide with Tromethamine due to poor gel formation. Also, they added butylated hydroxytoluene, 0.02% (w/w), as antioxidant to improve the stability. The gel (100%=100g) is composed of 12.9% telapristone, 60% ethanol, 10% benzyl benzoate, 3% isopropyl miristate, 13.08% water,1% carbopol 980 (a polymer for texture thickening), and 0.02% butylated hydroxytoluene. The high concentration of telapristone in this initial formulation was designed to allow testing of the limits of toxicity in female mini pigs (1mL of the drug suspension contains 129 mg of telapristone). This was massaged into the skin for 30-60 seconds daily at the same time (±1 hr), to the same location (a 2 cm diameter circle of skin centered on the nipple). Each pig was treated with vehicle gel to a left mammary gland, and telapristone gel to a right mammary gland. Blood samples of single dose were collected pre-dose, and 1, 2, 4, 8, 12, 16, and 24 hr post administration from five pigs. Prior to the 4 month study with daily repeated doses, a one-week wash-out period was given for each animal. Mammary glands were harvested from 2 pigs for drug concentration data following 4 weeks of therapy, and the remaining three continued to be treated, to a total of 4 months. Weekly blood collections were obtained (day 7, 14, 21, 28, 35, 42, 49, 101, 108, and 112) prior to each application. Drug concentration in plasma and tissue samples was analyzed using by liquid chromatography with tandem mass spectrometry (LC-MS/MS) by Dr. Miguel Muzzio at the Illinois Institute of Technology Research Institute (IITRI).

During 24 hours following a single dose, plasma concentrations of telapristone with single application were below quantitation limits (< 1 ng/mL); after 7 days of daily treatments these rose to 1.1± 0.97 ng/mL of telapristone and 0.36 ± 0.28 ng/mL of CDB-4453 (mono-demethylated metabolite of telapristone and biologically active). Thus, low levels of telapristone were detected in the circulation after 7 days of transdermal dosing. Following 4 weeks of daily treatment, mammary glands of two pigs were collected, and these pigs were terminated from the study. Tissue concentrations were 271ng/g for telapristone, and 4.11ng/g for CDB-4453 in one pig, 928ng/g of telapristone, and 4.8 ng/g for CDB-4453 in the other pig, and no further increase in plasma concentrations was observed (0.624 ±0.177 ng/mL for telapristone, and 0.508 ± 0.121 ng/mL for CDB-4453). Following four months of daily treatment, tissue concentration of telapristone from three remaining pigs was highest (~9.4 µg/g) in telapristone gel treated glands, followed by vehicle gel treated glands, and lowest in untreated (control) areas (**Table 2**). Each animal had three study teats: telapristone, vehicle, and untreated; the presence of some drug in the vehicle-treated and untreated teats suggests that there is drug diffusion through the mammary fatpad. However, plasma concentration of telapristone remained low (0.883 ±0.263 ng/mL for telapristone, and 0.068 ±0.033ng/mL for CDB-4453). Overall, it seems that telapristone accumulated in mammary tissues, but plasma level of

telapristone remained low (1 ≤ ng/mL).

Table 2. Mammary tissue concentration of CDB-4124 and CDB-4453 after 4 month daily treatments (mean ± SD).

Treatments\ Analytes	CDB4124(ng/g)	CDB4453(ng/g)
CDB4124 gel	9357 ± 11979	46.3 ± 66.6
Vehicle gel	2399 ± 3693	11.7 ± 13.4
Control(untreated)	531 ± 149	10.0 ± 8.2

Evaluation of skin irritation by application of transdermal gels in mini pigs: During the first 4 weeks of the study, the gel-treated areas were not washed between applications, and minor skin irritation was observed in treated areas. Two of five animals developed minor erythema at the application site (equal with telapristone and blank gel), likely related to the accumulation of the gel on the skin following multiple applications. Two pigs were terminated from the study at 1 month for mammary tissue collection and the remaining three pigs were observed for 4 months. The protocol was modified to allow washing of the skin with soap and water prior to next gel application; following this change, the erythema resolved, and during weeks 4-16 (day 29-112), no erythema was observed. No edema was seen in telapristone treated sites in all pigs, but one pig developed a very mild edema of the teat at the vehicle gel application site at 4 weeks of treatments, which resolved at week 11. Other changes were noticed in the vehicle gel application sites of two animals: one pig appeared to have enlarged teats at 11-14 weeks; the other pig experienced a decrease of teat size until the end of study. Overall, no significant skin irritation reaction was observed in telapristone gel treated sites compared to the vehicle gel treated sites.

A short-term photosafety test on rabbit skin: The pig study described above used very high concentrations of telapristone to test the toxic limit; in a second rabbit study, the dose of CDB4124 was lowered to a range to be used in the human protocol. This new gel formulation (100g =100 %) contains 0.9% CDB-4124, 58.67% ethanol, 19.34% benzyl benzoate, 3.88% isopropyl miristate , 15.19% water, 0.02% butylated hydroxytoluene , and 1.99% Carbopol 980. 1mL of this gel contains 10 mg telapristone. Since the telapristone absorbs between 290 and 700 nm of the electromagnetic spectrum (a peak maximum at 300-310nm), photosafety tests were performed in rabbits, the preferred species for use in dermal irradiation tests in preparation for human studies. Three female New Zealand white rabbits (2.3-2.8 kg weight) were prepared by shaving the mammary area of each rabbit free of hair (an area of approximately 10 cm^2 total). Four sites were outlined on each rabbit (2 cm in diameter and close together) in indelible ink, using a template, with care taken to avoid abrading the skin. Hair was clipped as needed throughout the study. Prior to treatment all animals were anesthetized with ketamine (10-15mg/kg) in order to allow for equal irradiation times of the test sites and to protect the rabbit's eyes from the UV light. The rabbits were given a single administration of the test substance on day 0 on the marked sites, applied evenly as a thin and uniform layer. Site 1) untreated (control); Site 2 telapristone transdermal gel (5 mg dose= 0.5 mL of the gel telapristone 10mg/mL); Site 3) SPF30 rated sunscreen; applied as a thin film in the same way as the test substance; Site 4) telapristone transdermal gel (5mg dose), followed by application of sunscreen to the same area 1 minute later. All sites were irradiated simultaneously with a single 2 minute exposure of UV light (254nm) (#G20T10 Germicidal, Preheat, Ozoneless, Eiko Inc.) from a handheld lamp, using a template to prevent exposure of skin other than the identified sites. Four hours later, the treated area of each animal was examined for evidence of erythema, edema, and for dermal irritation using the Draize technique for primary dermal irritation scoring. Additional observations were made daily for 4 days, following which the treated and control area of the skin of each animal was excised, formalin-fixed and paraffin-embedded for evaluation of skin histopathology. Two slides from each rabbit skin sample were used (one stained by H&E and the other for Ki-67 labeling). A pathologist (Dr. Konstantin Christov, at University of Illinois at Chicago) evaluated skin histology in a blinded fashion from treatment groups.

Four hours after UV exposure, one of three animals developed barely perceptible erythema in all skin areas (control and treated). At 24 hrs, all three animals developed slight erythema in the skin areas of control and telapristone gel treatments and two animals also had the same degree of erythema in sunscreen applied areas (sunscreen, and sunscreen+ telapristone gel). Two days after UV exposure, all three animals exhibited the same degree of erythema in the skin areas of control and telapristone gel treatments, but not in sunscreen applied areas. On Days 3 and 4 after UV exposure, erythema resolved in all three animals in treated areas, but persisted in the untreated skin areas (control). No edema or other skin reaction was found during the duration of the study. For the skin histology evaluation, attention was paid to the following biomarkers: a) Epidermis thickness, b) Development of papillary structures c) Differentiation of epidermis, d) Lymphocyte infiltration, e) Deposition of keratin masses, f) Cellular debris. Variability in the thickness and papillary structures was found in individual rabbits, with differences in keratin and debris deposition. Inflammation, determined by lymphocyte and macrophage infiltration, was similar in all slides. Based on the histo-morphology, no significant alteration was found in individual treatment groups.

Pharmacokinetics of transdermal delivery: Drug concentrations in breast tissue following transdermal delivery of 4-OHT have been measured in several studies (28 and Lee NWU07-9-02 manuscript in preparation) and show that concentrations are sufficient to modulate cell proliferation; however, measurements have only been performed in one location per breast

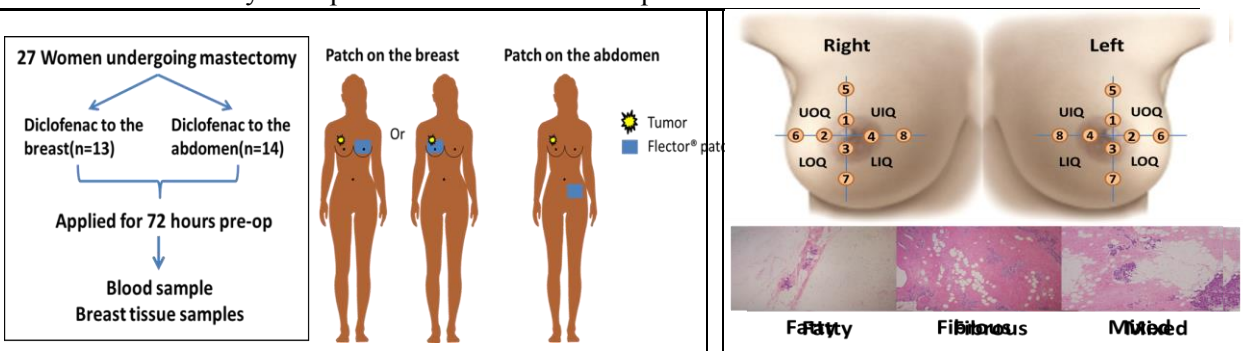
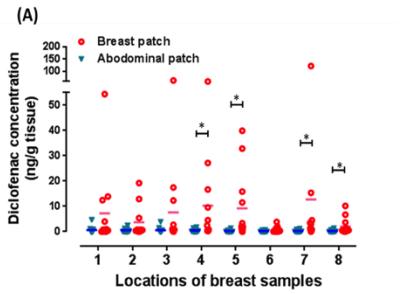


Figure 5. Diclofenac (Flector®patch) study design (left panel), Breast sampling schema (right panel), and characteristic tissue compositions (bottom of right panel).

An important question regarding the kinetics of transdermal delivery to the breast relates to the uniformity of delivery throughout breast tissue. There is presently no information as to the uniformity of drug concentrations through the breast with systemic agents; we have developed pilot data on this question in a proof-of-principal trial with the objective of demonstrating that transdermal delivery to the breast is a local phenomenon if the drug is applied to the breast rather than elsewhere on the body. The schema of this trial is shown in **Figure 5**; women undergoing mastectomy were randomized to a breast patch or an abdominal patch group and drug concentrations were measured at eight different locations in the breast. Drug concentrations in the two groups are shown in **Figure 6A**, demonstrating significantly higher, but also quite variable (**Figure 6B)**, diclofenac concentrations in the breast, possibly related to the complex composition of breast tissue (fat, fibrous tissue, parenchyma), and variable distance from the skin. In contrast, diclofenac concentrations in the abdomen group (which approximates systemic delivery to the breast) showed relatively low concentrations, and low variation.



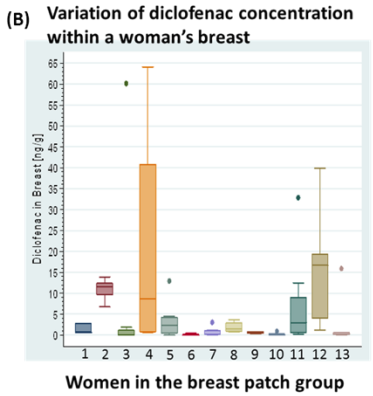


Figure 6. Diclofenac concentration in the breast tissue samples. (A) Diclofenac concentrations of fresh tissues according to the eight locations of the breast and the patch groups. * P<0.01. Breast location KEY: 1=upper central; 2= outer central; 3= lower central; 4= inner central; 5 = upper peripheral; 6= outer peripheral; 7= lower peripheral; 8= inner peripheral area.(B)Breast patch group represented high variations within a woman's breast .

We will investigate this aspect of oral versus transdermal therapy for the first time by measuring drug concentration at multiple locations through the breast. An oral therapy control group is required since there are presently no data defining the variation of drug concentrations at different locations in the breast with systemic delivery. Therefore, we are proposing a randomized comparison of drug concentrations achieved in the breast with oral and transdermal delivery; we will measure drug concentrations in several locations in the breast, which will be selected for distance from the skin envelope. We anticipate some inherent variability in breast tissue drug concentrations related to breast composition (and possibly breast size) in both transdermal and oral groups. Drug concentrations in breast tissue will be measured by Dr. Miguel Muzzio (IITRI); he has established assays of tissue concentration for CBD4124 and has also collaborated with us in a study of transdermal diclofenac.

2.3 Rationale

Hypothesis: 1) Transdermal delivery of CDB 4124 will result in breast tissue concentration similar to those achieved by oral delivery with distribution throughout the mammary gland.
2) Transdermal delivery of telapristone will be effective in modulating candidate biomarkers of anti-progesterone efficacy similar to oral administration.

Study design considerations: Our overall goal is to develop anti-progestational agents for breast cancer prevention in premenopausal women whose only proven pharmacologic option at the moment is tamoxifen. Thus, there is a pressing need for safe, acceptable preventive interventions. Ideally, such an agent would prevent breast cancer regardless of hormone receptor status and accommodate the contraception needs of younger women, but also allow use in women who are planning to conceive. Our interest in telapristone is driven by data summarized on pages 8-14. In contrast, little preclinical data exists regarding ulipristal effects on breast neoplasia. Telapristone is therefore the best candidate SPRM for development for breast cancer prevention and therapy. The present proposal addresses the testing of transdermal delivery of telapristone to provide a potentially safer alternative for healthy young women, which may allow them to continue ovulation and decrease other side effects. In the present proposal we focus on drug distribution within the breast, which has never been previously compared to systemic therapy. In a recent External Advisory Board review of our research program, there was consensus that the distribution of drug through the breast must be demonstrated prior to further development of transdermal delivery of this or other drugs. Below, we will address aspects of study design and our rationale for making the choices we did.

1) Pre-surgical window design: the need for extensive sampling of breast tissue for drug concentrations can only be accommodated in women undergoing mastectomy; for this purpose, the tumor stage and the menopausal status of the subjects is not relevant, therefore we are including pre and postmenopausal women, and those with Stage I-II breast cancer as long as there is no skin invasion or inflammatory

disease. Additionally, there is insufficient data to determine a priori that postmenopausal women will not benefit from treatment.

2) Dose and duration of therapy: the oral dose is based on data from Repros, derived from their endometriosis and leiomyoma studies; the transdermal dose of 24 mg is based on data from transvaginal delivery (24 mg doses). In a Phase II transvaginal telapristone study (ZPV200), daily 24 mg transvaginal treatment for 16 weeks was tested in 10 premenopausal women with uterine fibroids. 5 of 10 women completed study, and no women discontinued from the study due to treatment-related AEs. Pharmacokinetic analysis found that subjects treated with telapristone at 12mg/day achieved the largest mean Cmax(12.ng/mL) and resulting AUC(242ng*hr/mL). The 24 mg vaginal suppository was too large, did not melt evenly in the vagina, and the AUC was therefore lower. This is not expected to be a problem with the topical gel which will be spread evenly over the skin. However, penetration through the intact stratum corneum is expected to be significantly lower that through the vagina (our in vitro studies show about 10% of applied dose permeates through human skin), and the porcine studies described above (page 12) have demonstrated extremely low plasma values after multiple dosing (0.883 ±0.263 ng/mL for telapristone, and 0.068 ±0.033ng/mL for CDB-4453), despite the high dose of telapristone applied (129 mg/day). These concentrations are a fraction of what was generated by the 50 mg oral doses previously associated with liver toxicity. In contrast, the C_{max} values seen with a 12.5 mg daily dose of telapristone were over 400 ng/ml (Repros ZPU001). We will use an oral dose of 12 mg and a transdermal dose of 12 mg to each breast, (total dose 24 mg daily), since the most effective vaginal dose was 12 mg daily, and there is not expected to be significant cross-over from one breast to the other. Our transdermal permeation studies in vitro (human skin) and in vivo (pig skin) suggest that with this total daily dose of 24 mg, systemic exposure will still be far lower than that associated with hepatic toxicity. In our previous NWU07-9-02 protocol, surgical patients were willing to accept 4 weeks of therapy, and women undergoing mastectomy at Northwestern University have an average 4 week window between surgical consultation and surgery. This window will also allow attainment of steady state drug concentrations. Although we would have liked to include several doses (2, 4, 6 mg), sample size and budgetary constraints limit this. Additionally, the proof of principle does not require varying transdermal dose.

3) Sampling schema of the breast: although it is possible to obtain a large number of tissue samples from mastectomy specimens, the key question is whether drug penetrates to the deepest portion of the breast, furthest from skin. The sampling schema therefore includes five non-tumor samples: a superficial location in the upper outer quadrant, a subareolar location, two additional samples from the middle depth of the breast at 4 cm from the nipple, and one from the deepest portion of the breast, adjacent to the pectoral fascia and in line with the nipple. These five samples will form a basis of comparison between the oral and transdermal treatment groups. The tumor sample will not be included in the main comparison between groups, but will be used for additional analyses.

4) Should we measure biomarkers? Although we cannot test primary hypotheses regarding biomarker modulation with this sample size (60 evaluable subjects) and design (no untreated control group), the evaluation of candidate biomarkers will provide extremely useful data for the design of subsequent studies. The field of progesterone signaling in the human breast and the consequences of its interruption are relatively young; most of the work in this area has been accomplished in rodent models and, therefore, the accumulation of preliminary data regarding breast tissue-based biomarkers will provide new insights, lead to new hypotheses, and facilitate future studies.

5) IND considerations: We have obtained an investigator-initiated IND (#123864) through Northwestern University, cross-referencing the IND to Repros Therapeutics.

Biomarker selection: Breast tissue drug concentrations: Therapeutic drug concentrations are a primary requirement for efficacy. For the development of this novel prevention approach, the demonstration of

similar drug delivery to breast tissue, similar variability in drug concentrations within the breast, and significantly lower systemic exposure are required.

Cell Proliferation: Data on the effects of P4 blockade in the human breast are sparse, but a study of a 3-month course of telapristone in women undergoing surgery for uterine fibroids showed a significant decrease in breast cell proliferation (measured by Ki-67 labeling) when compared to placebo (29). Ki67 is a well-established efficacy biomarker for breast cancer treatment trials. In addition, telapristone has demonstrated growth suppression of established ER+ mammary tumors in rats by reduction in Ki67 and increase in TUNEL (11, 12). However, in a recently window trial of telapristone, the measurement of TUNEL in core biopsy samples proved to be challenging and eventually not feasible, therefore we will not pursue in the present study.

Hormone receptors: Although the presumption so far is that SPRMs act to retard breast cancer growth and development through PR modulation, this has not been definitively established. Progesterone-responsive tissues of premenopausal women differ greatly from each other in their levels of PR during the menstrual cycle (34). The PR exists in 2 molecular isoforms, PR-A and PR-B (33, 34) which have similar hormone-binding properties but different transcriptional activities (36, 37). In fact, PR-B is believed to activate P4-responsive genes, while PR-A functions as repressor of PR-B activity and a modulator of steroid hormone receptor action in general (36, 37). However, there is currently no consensus on reliable isoform-specific antibodies to PR-A and PR-B, and measurement of these isoforms in the present study does not seem feasible. On the other hand, total PR expression is a widely recognized indicator of estrogen response and, therefore measurement of ERα is important when assessing anti-progesterone efficacy. Furthermore, telapristone treatment has decreased ERα expression in ER+ mammary cancer in rats (11, 12); ERα and PR expression will be measured by NanoString nCounter Assay.

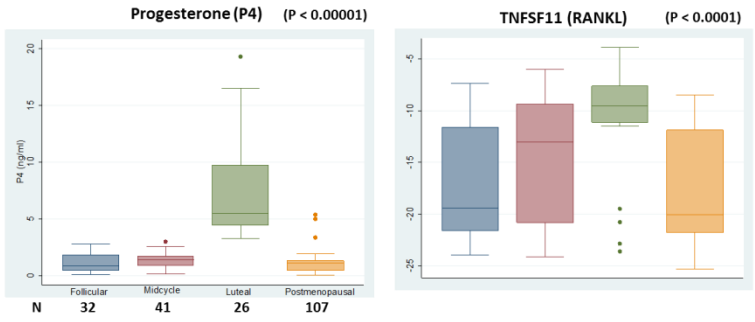


Figure 7. Concentration of progesterone and expression of RANKL in rFNA samples from premenopausal (at follicular, midcycle or luteal phases) or postmenopausal women. Healthy women, (premenopausal 92 and postmenopausal 107) with clinically normal breasts. Breast samples were obtained by random fine needle aspiration (rFNA). Menopausal and menstrual status was well-annotated (dates of last and next period, and serum hormones on the day of breast sampling).

Progesterone response proteins: Progesterone-driven effects in the human breast include increased proliferation observed in the luteal phase in premenopausal women and the higher proliferative rates seen in postmenopausal women on E+P treatment (42). P4-induced paracrine factors that promote proliferation have been identified in the mouse; one of these is RANK ligand (RANKL), which is secreted by cells that express PR and causes proliferation of neighboring cells that are negative for PR. Furthermore, RANKL has been shown to mediate progesterone-induced expansion of mammary stem cells through paracrine signaling (43, 44). Studies elucidating the role of RANKL mediated, P4-driven growth, have been performed primarily in mouse models, and more recently in human breast samples [39]. We have observed that expression of RANKL is significantly upregulated in normal breast tissues in relation to serum progesterone (p=0.015) and during the luteal phase of the menstrual cycle (see **figure 7**). The expression of RANKL in normal breast epithelium also correlated with expression of PR, prolactin receptor (PRLR), and cyclin D1. Other investigators have shown that RANKL treatment causes increased proliferation and rapidly increases cyclinD1 mRNA and protein levels in mouse mammary tumor virus (MMTV)-RANK transgenic mice

mammary epithelial cells in vitro (45). Our data from the healthy breast demonstrates a similar strong correlation between Cyclin D1 and RANKL at the mRNA level. Since Cyclin D1 has been known to play an essential role in tumor development and progression (46), it suggested that RANKL may activate cyclin D1 to stimulate proliferation in human breast tissue. These data strongly implicate a relationship between RANKL and P4 action in the human breast. We will investigate the effects of telapristone therapy on the expression of RANKL, prolactin receptor, and cyclin D1 gene expression, to identify a potential signature for progesterone response modulation in the breast following telapristone therapy. In addition to these specific genes of interest, we will use our recent RNA sequencing results from our recently completed window trial of telapristone in Stage I/II breast cancer (NU12B09) to identify 50 genes that are correlated with telapristone effect. We will use Nanostring nCounter analysis for this purpose; we will confirm differential expression of genes responding to telapristone therapy in benign samples and tumor found on microarray, and also look at specific genes selected a priori: cyclin D1, PRLR, RANK, RANKL for a total of 50 genes based on the microarray analysis.

RNA sequencing of benign breast samples from prophylactically mastectomy samples: the future use of telapristone includes breast cancer prevention. However, there are, as yet, no data regarding changes in high-risk breast tissue in response to telapristone. We expect to have prophylactic mastectomy samples from 20-24 women, some of whom will have BRCA1/2 mutations. We propose to use these samples for RNA sequencing, to develop pilot data on gene expression changes in being high risk breast tissue. These will serve as the discovery platform for biomarkers to be validated in future studies.

Serum hormones: We also plan to measure serum concentrations of estradiol, progesterone, and FSH at baseline and after treatment. Oral telapristone treatment lowered serum P4 level in premenopausal women (CDB investigator's brochure) and rats (11, 12), thus it is a predictive circulating biomarker which responds to drug treatment. We will compare alteration of sex hormone level by transdermal vs. oral telapristone; if transdermal telapristone does not affect sex hormone level, this would support the notion that transdermal therapy is a local therapy, not a systemic therapy.

Pharmacogenomics: We will store peripheral blood collected at screening visit 1 to derive DNA for future pooled analyses with other planned studies to assess the significance of genetic variation in telapristone metabolism and efficacy. Rapid metabolism of telapristone occurring by extensive hydroxylation and demethylation may reduce the efficacy of oral telapristone and women with rapid metabolism of this drug may have reduced therapeutic exposure, potentially affecting treatment outcome. Since transdermal administration of telapristone will bypass extensive hepatic metabolism, direct delivery to the breast is unlikely to be affected by enzyme polymorphisms; we lack power to test this hypothesis in the current study, but plan to address it in pooled analyses with ongoing and future studies.

Laboratory Correlates, Biomarkers: Details of collection and processing are in **Section 7**.

Drug concentration measurements in breast tissue: Tissue from the mastectomy specimen will be obtained for tissue drug concentration measurement. Samples will come from the areas indicated in **Figure 12**.

Breast tissue biomarkers: Tumor tissue samples will be taken from the CNB specimen as well as the mastectomy specimen post intervention for performing Ki67 immunohistochemistry (IHC) and genomic analysis. IHC for Ki-67 at baseline and after treatment will be performed in the Research Histology and Tissue Imaging Core (RHTIC), University of Illinois at Chicago; 4 sections will be reserved for IHC and H&E staining; the remainder will be used for LCM, RNA extraction, and genomic analyses.

Blood samples for sex hormone assays (estradiol, progesterone, and follicle stimulating hormone (FSH)) and for drug concentration measurement will be collected at the beginning and end of intervention.

Compliance and symptom measurement will occur at visit 1, by telephone contact 2 weeks following start of intervention, at visit 2 and post-operative visit 3. Compliance assessment will occur through subject diaries, pill count, and weighing of gel dispensers.

3. SUMMARY OF STUDY PLAN

This is a randomized, double blind, placebo-controlled pre-surgical window trial of oral vs. transdermal telapristone treatment daily for 4 weeks ± 7 days in women who are scheduled for unilateral or bilateral mastectomy for breast cancer therapy or prophylaxis. A total of 70 women will be randomized in a 1:1 ratio to either transdermal telapristone gel or oral telapristone, resulting in 35 subjects in each group. We plan to recruit at least 30 premenopausal women who are scheduled for mastectomy (unilateral or bilateral). *BRCA1/2* mutation carriers scheduled for prophylactic bilateral mastectomy are also eligible. We plan to recruit at least 15 subjects in this group. In the oral group, the dose will be 12 mg daily and placebo transdermal application to each breast daily. In the transdermal group, it will be 12 mg per breast daily (total dose 24 mg daily) and placebo capsule once daily. We will allow for attrition of 10 subjects (for insufficient samples and non-compliance) and expect to have 60 evaluable subjects. The duration of intervention will be 4 weeks ± 7 days with the last dose taken on the day before surgery. Study subjects who meet all entry criteria will be consented either at their initial surgical consultation or on a subsequent visit. Women who are undergoing contralateral or bilateral prophylactic mastectomy (CPM or BPM) will be asked if they are willing to undergo a random CNB of the unaffected breast (research biopsy). Those who are willing will return for Screening Visit 2. Telapristone will be administered for 4 weeks± 7 days prior to mastectomy. Subjects must begin study medication within 8 weeks of core biopsy diagnosis. There will be three study visits; for women requiring the research core biopsy there will be four study visits.

Screening Visit 1 At entry for consent, review of eligibility, instructions on how to take the study drug and gel application, baseline symptom assessment, and blood draw for clinical and research labs. Urine or serum pregnancy test in women of child bearing potential and dispensing study drug for women not undergoing optional biopsy.

Screening Visit 2 Will occur only in women who are having at least one prophylactic mastectomy (i.e. CPM or BPM) and are willing to undergo a research core biopsy. This visit will involve random CNB of the unaffected breast, a urine or serum pregnancy test in women of child bearing potential, a serum hormone test, and dispensing of the study drug.

Study Visit 1 Day of surgery for review of symptoms, review of intake of study medication, collecting unused medication, blood draw for clinical and research labs, and urine or serum pregnancy test. Breast size and body mass index will be recorded.

Study Visit 2 Post-operative, 1-2 weeks following the end of intervention.

Accrual will occur within the duration of 24 months with expected accrual rate of 3-4 subjects per month across 3 sites. The study will be terminated when 60 evaluable participants have completed all study procedures (30 of whom are premenopausal, and 15 of whom are *BRCA1/2* mutation carriers, either pre or postmenopausal).

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-II (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.

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.

Total bilirubin	<1.5 XULN
AST (SGOT)	<2.5 XULN
ALT (SGPT)	<2.5 XULN
Creatinine	< 2 X ULN
Alkaline phosphatase	< 2.5X ULN
Blood Urea Nitrogen	< 2 X ULN

4.1.5 Women who are premenopausal, are on a stable contraceptive regimen, and are planning to continue the same regimen through surgery are eligible to participate. For women who are on hormonal contraception regimens that have a placebo phase, the following should be recorded regarding the day of baseline core biopsy and the day of surgery: the agent, whether they are in active or placebo phase, the day of the phase (e.g. day 13 of 21-day active phase or day 4 of 7-day placebo phase). This information will have to be back-calculated for the day of core biopsy, but best attempt should be made.

4.1.6 Women who are using postmenopausal hormones, and are planning to continue the same regimen through surgery are eligible to participate. If the hormone therapy regimen is cyclical, the following should be recorded regarding the day of baseline core biopsy and day of surgery: the agent, the day of the phase (e.g. day 13 of 14-day estrogen phase etc). This information will have to be back-calculated for the day of core biopsy, but best attempt should be made.

4.1.7 Women with child-bearing potential who are not on hormonal contraception should be willing to use non-hormonal contraception (adequate barrier-type contraception or IUD) from the time the pregnancy test is performed for the duration of study participation, and 30 days after study drug cessation (for women of childbearing potential only).

4.1.8 Ability to understand and the willingness to sign a written informed consent document.

4.1.9 Willing and able to schedule mastectomy 4 weeks (_± 7_days) following start of study agent.

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

4.1.11 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; OR has had a menstrual period at any time in the preceding 12 consecutive months).

4.1.12 Willing to use alcohol in moderation while taking study agent.

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) on the breast

4.2.4 A history of thromboembolic disorder or cerebral vascular disease.

4.2.5 Women who were using oral contraceptives or postmenopausal hormones within eight weeks prior to core needle biopsy, and then stopped following core needle biopsy, are not eligible. Use of hormone coated IUD like Mirena is allowed.

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 telapristone (i.e. other progesterone antagonists).

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. Previous unilateral radiation in women scheduled for mastectomy of the contralateral side is allowed.

4.2.11 Pregnant or breastfeeding.

4.2.12 Currently taking spironolactone.

4.2.13 Recent history (within 6 months) of alcoholism or drug abuse.

4.2.14 Known active infection with HIV, Hepatitis A, B, or C.

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 progesterone-driven carcinogenesis has not been studied in men and the number enrolled (if any) would be too few to analyze.

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. Enrollment will be weighted towards eligible premenopausal women, with a goal of enrolling at least 30 women in this category. 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 $150 for incidental expenses associated with these studies (for women who need to complete Screening Visit 2 for core biopsy of an unaffected breast, the compensation will be $300). 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).

5. AGENT ADMINISTRATION

Intervention will be administered on an outpatient basis. Reported adverse events (AEs) and potential risks are described in Section 6.2.

5.1 Dose Regimen and Dose Groups

Seventy participants will be randomized into one of 2 groups: 35 participants will receive 12 mg telapristone capsules per day along with placebo gel applied daily to each breast; 35 participants will receive 12 mg telapristone in an alcohol-based gel, applied daily to each breast (total 24 mg daily) along with a placebo capsule per day. Dosing will extend for 28 ±7 days

5.2 Study Agent Administration

All participants will receive both gel and capsule each day and will be blinded to which delivery modality is a placebo and which contains the active study drug. Both the capsule and gel will be self-administered.

One capsule (telapristone/placebo) should be taken once a day by mouth with 8oz (one glass) of water in the morning about an hour before breakfast at about the same time every day.

The gel (telapristone/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 breast 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 or take the pill in the morning, administration later in the day is acceptable, as long as the skin has been washed since the last application. 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.

The day of surgery, participants should refrain from taking 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

Not applicable.

5.4 Contraindications

Participants are to avoid exposure of the treated breast skin to natural or artificial sunlight. This includes sunbathing or the use of tanning beds with the breasts exposed. Also, women who have dermatologic conditions causing the breakdown of skin in the area of gel application should not use telapristone gel or placebo gel.

5.5 Concomitant Medications

There are no other known incompatibilities with prescription or non-prescription medications. Isoflavone-rich herbal supplements are a possible exception because they have known phytoestrogen properties. Soy bean/vegetable-derived estrogen compounds (OTC) and Chinese herbs or other OTC herbal products, including St. John's Wort should not be used along with the study medication.

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 study procedures (*e.g.*, biopsy, surgery) should not be included.

5.6 Dose Modification

No dose modifications are planned. However, study agent will be discontinued if the subject reports grade 3 or 4 adverse events that are probably or definitely related to study agent, or grade 4 adverse events that are possibly related to study drug.

5.7 Adherence/Compliance

The participants will be asked at registration if they would like to utilize a phone application in place of paper forms. According to subject preference, participants will either utilize phone application or fill out paper forms daily to monitor compliance. For participants utilizing the phone application, study coordinator will be notified after 2 days of missed entries and these participants will be contacted by study coordinator. For individuals using paper forms, email messages will be sent daily for the first week; in following weeks, messaging will be targeted to women having difficulty remembering their dose. Since agent compliance is very important during the final week, email messages will be sent to all study participants.

Capsule counts and weighing of gel dispensers will be performed at the conclusion of therapy. Drug and metabolite levels will be measured in blood and tissue on the last day of administration. If less than 80% of the dose has been consumed during the study period, or if more than one of the last three doses of therapy are missed, the subject will be considered non-compliant and will not be evaluable for secondary endpoints. All participants that receive a study agent for any period of time will be evaluable for toxicity.

6. PHARMACEUTICAL INFORMATION

6.1 Study Agent (IND #123864, Dr. Seema Khan, Northwestern University)

This study was submitted under a new IND sponsored by Northwestern University. It cross-references INDs 112576, 70535, and 76631, held by Repros Therapeutics, Inc., and IND 117378, held by Northwestern University.

Oral Component:
The drug product is comprised of telapristone supplied as a powder in Size 3 hard gelatin capsules, white opaque, with 12 mg telapristone in a dry blend with microcrystalline cellulose and 2% of magnesium stearate to make a total capsule fill weight of 100 mg including the active ingredient. Capsules are manufactured under current good manufacturing practice regulations (cGMPs). The PI has filed IND 117378 for the oral formulation for the on-going oral telapristone vs placebo trial. For the present protocol, a IND 123864 (covering both transdermal and oral formulation)cross-referencing IND 117378 has been obtained from the FDA.

Placebo will be supplied as a powder in Size 3 hard gelatin capsules, white opaque, with no active ingredient and containing microcrystalline cellulose and magnesium stearate. Telapristone and placebo gelatin capsules are identical in appearance. The route of administration and dosing schedule will be the same as for telapristone. Placebo will also be provided by Repros Therapeutics Inc.

Transdermal Component:
Transdermal telapristone: Building on animal studies results, Repros Therapeutics has formulated a transdermal alcoholic colloidal suspension of CDB- 4124 which is modified from a transdermal formulation for testosterone (AndroGel®, AbbVie Inc., North Chicago, IL), which has been FDA approved and marketed since 2010. The gel (100%=100g) is composed of 1.4% CDB-4124, 60% ethanol, 20% benzyl benzoate, 4% isopropyl miristate, 0.8% tromethamine, 12.5% water, 2% carbopol 980 (a polymer for texture thickening), and 0.02% butylated hydroxytoluene.

Transdermal placebo: The placebo is the same gel suspension minus the active ingredient.

6.1.1 Summary of non-clinical in vitro/in vivo studies

The NICHD has evaluated telapristone for a wide range of hormone-related activities, including assays for in vivo and in vitro anti-progestin, glucocorticoid, estrogenic, androgenic, anti-glucocorticoid, anti-estrogen, and anti-androgen activities, in addition to in vivo measurements of post-coital (anti-implantation) and anti-ovulatory activities. Results show that telapristone is more effective in the rabbit uterus compared to mifepristone, and has effective anti-ovulatory and anti-implantation activities in the rat. Telapristone lacks estrogenic, androgenic, anti-estrogenic, and anti-androgenic activities. Its poor anti-glucocorticoid activity (indicated by an inability to oppose glucocorticoid-induced thymus involution in the rat) distinguishes telapristone from mifepristone (R. Blye, NICHD, personal communication). An in vitro assessment of metabolism comparing human, dog and rat hepatocytes showed similar metabolites produced by all species. A hERG channel assay was also conducted testing doses from 3 to 30μM. A dose dependent inhibition was detected up to 46% at the highest dose. Telapristone is highly bound to proteins and the in vitro assay did not translate to QTc prolongation in initial human studies. No drug-related cardiovascular side effects have been observed in human studies completed to date.

Three different methods were used to evaluate the mutagenic activity of telapristone. In the first method, telapristone was tested in Salmonella typhimurium strains TA 1535, TA 1537, TA 98 and TA 100 and Escherichia coli strain WP2uvrA at concentrations ranging from 10 to 3333 ng/mL per plate. Two mutation assays (direct plate and a pre-incubation assay) were conducted on agar plates in the presence and absence of an Aroclor1254-induced rat liver preparation and the co-factors required for mixed-function oxidase activity. No mutagenic activity was observed in any of the 5 bacterial strains, in either activation condition.

Secondly, the in vivo genotoxic potential of telapristone was evaluated in a micronucleus test in bone marrow erythrocytes of young male and female CD-1 mice following a 0 hr+24 hr oral dosing and 48 hr

sampling regimen at 3 exposure levels (70, 140, and 280 mg/kg/day). Bone marrow samples were collected at 48 hr. No micronucleus induction was detected in bone marrow erythrocytes of mice dosed with telapristone.

Finally, telapristone was assayed in the mouse lymphoma L5178Y cell line, clone-3.7.2.C, scoring for forward mutations at the thymidine kinase locus. Tests were conducted both in the presence and absence of a post-mitochondrial supernatant fraction obtained from Aroclorl254-induced livers of adult male rats (S9). The results indicate that telapristone is not mutagenic in mouse lymphoma L5178Y cells, when tested to toxic concentrations.

Under the SBIR grant "Inhibition of Breast Cancer with Antiprogestins", R43CA/HD91483-O1A1, Repros Therapeutics investigated the potential of antiprogestins for the treatment of breast cancer. Results showed that telapristone significantly reduced the size of established 7,12-dimethylbenz(a)anthracene (d)-induced tumors of the rat mammary gland and prevented the appearance of new tumors over the course of a 28-day treatment period. The drug effects correlated with suppression of cellular proliferation and increased apoptosis [24]. Rat models of breast cancer have been shown to respond to both anti-estrogens and antiprogestins with a decrease in tumor size. The use of anti-estrogens, is a major therapeutic option currently available for the adjuvant therapy of hormone-responsive breast cancer in women. The data above suggest that antiprogestins such as telapristone could be used as first-line monotherapy, as second-line therapy in women whose tumors have become resistant to anti-estrogen therapy, or in combination with an anti-estrogen.

A study of telapristone treatment in mice showed that the acute oral LD50 for telapristone is greater than 1250 mg/kg. In a second mouse study, repeated oral dosing of telapristone at 50 mg/kg of body weight for a period of 4 weeks produced no adverse effects. These studies established the upper limits for acute and chronic dosing of telapristone.

The pivotal repeat-dose studies involving chronic oral dosing in rats (10, 40, 200 mg/kg/day) and in dogs (4, 12, 40 mg/kg/day) have been completed. Most of the findings observed during the pivotal chronic dosing studies are associated with the pharmacological activity of telapristone. At the end of a 6-month study, telapristone was shown to be well tolerated in rats. The results of a 9-month study indicate that telapristone is also well tolerated in dogs. A dose of 4 mg/kg/day resulted in no toxicity; effects observed are related to the pharmacology of the drug.

Two independent studies of the effects of telapristone on the cynomolgus monkey endometrium demonstrated a lack of anti-glucocorticoid activity and absence of effects on serum estrogen and ovulation. In these animals, telapristone induced a reduction in the height of the endometrium and its development, an altered mitotic index, and changes in the glands and stroma concomitant with antiprogestational effects.

In a nine month trial, episodes of vaginal bleeding were decreased with the telapristone treatment, but returned within 4 weeks of treatment cessation for most animals. No serious drug-related pathological changes in the individual animal necropsy. After nine months of treatment, monkeys demonstrated decreased proliferation in uterine epithelium and stroma but not in the breast. Apoptosis was increased in both uterine epithelium and breast.

6.1.2 Summary of relevant clinical studies

Completed Phase I studies show that telapristone is orally available and achieves maximum circulating concentrations within two hours. The drug is rapidly metabolized. In Phase I and Phase II studies two subpopulations were identified, with high and low clearance rates of telapristone. Within these two groups

telapristone exposure is dose dependent. However there are distinct differences between the groups. For example, the ½ life of telapristone in the high clearance group is 11.46 hours, compared to 37.77 hours in the low clearance group.

The initial metabolite of telapristone is a mono-demethylated form. This form is also active. Maximum concentrations of the parent compound and the metabolite are the same in both high and low clearance groups. The liver toxicity observed seems to be associated with the maximum concentration of the combined compounds and is clearly dose dependent. Interestingly, there does not appear to be a difference in efficacy of telapristone between the high and low clearance groups.

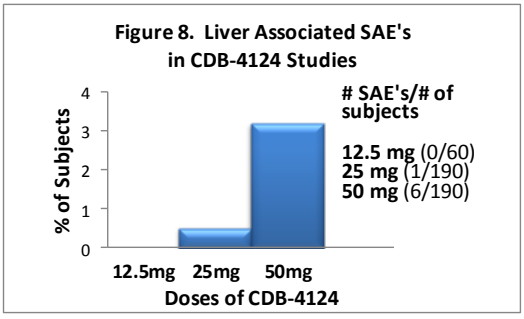
The efficacy of telapristone may be linked to its ability to induce a state of amenorrhea. Whether or not this amenorrheic state is more readily achieved by high or low clearance individuals at low doses remains to be seen. Repros Therapeutics Inc. has evaluated safety and efficacy of telapristone at the doses of 12.5, 25, or/and 50 mg P.O. daily for 3-12 months in several Phase I/II studies (ZPU-003, ZPE-002, and ZPU-003 ext). Telapristone therapy has exhibited statistically significant improvements in the debilitating symptoms of both uterine fibroids and endometriosis at all three doses. There was a slight decrease in efficacy at the 12.5 mg dose; however, the difference in results as compared to the 25 mg dose did not reach statistical significance within the study (ZPU-003). The primary endpoint, change from Baseline to Month 3 in menorrhagia (PBAC score, menstrual pictogram) demonstrated large reductions in bleeding from Baseline scores to Month 3 in both active-treatment groups for the modified ITT population. These reductions were both clinically and statistically significant compared to placebo for both Telapristone doses, but no differences between these dose groups could be established. Mean values of PBAC score were -75.6±87.3 for 12.5 mg (n=34) and -95.9 ±15.5 for 25mg (n=33) (p= 0.1417).

6.1.3 Summary of toxicity data

6.1.3.1 Safety status of subjects previously exposed to telapristone

On March 10, 2010, Repros provided a safety closeout of the roughly six month follow-up of subjects that were previously exposed to telapristone. On August 3, 2009 all clinical sites were notified to stop dosing of all subjects in the telapristone studies. Sites were instructed to have subjects return to the clinic for exit safety assessment (including liver function tests) and return of all study drug. Previously, on July 1, 2009 Repros ceased dosing of the 50 mg dose strength due to observations of increasing liver toxicity-associated adverse events associated with that dose, which included two subjects that satisfied Hy's Law criteria.

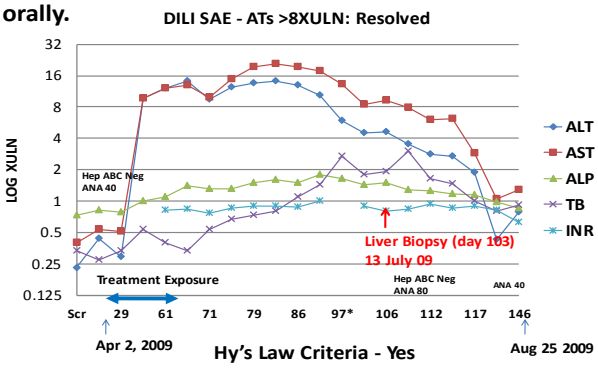
All subjects in the follow-up safety database have now exhibited liver enzymes within the normal range. These include the seven subjects that previously experienced serious adverse events. Six were exposed to 50 mg (includes the two Hy's law cases). The one subject that experienced a liver related SAE at 25 mg was from an earlier Phase II study, during which she received 50mg for a 2 week period. Study close-out report dated February 2, 2010, in IND 70,535 SSN-175, summarizes the findings. **Figure 8** represents the liver related SAE's observed to date. Table 4 provides liver related chemistry results for all 14 subjects that exhibited liver enzyme elevations > 3XULN.



The most severe reaction noted at 50 mg was with subject 07-004 (37 yrs-old, African American) from study ZPU-304. She was exposed to 50 mg telapristone for 32 days. On July 13, 2009 (103 days), she underwent a liver biopsy which exhibited hepatocellular pathology indicative of hepatitis. A viral

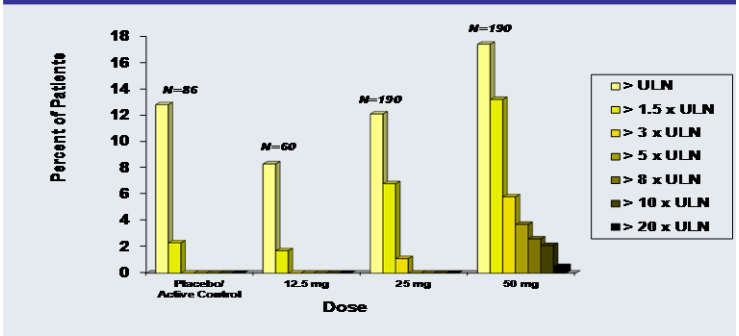
antibody screen (Hepatic ABC ANA80) was conducted and found to be negative. The conclusion was that her condition was the result of a drug induced event. She was referred to a liver transplant center as a precaution and placed on oral medication. Fortunately, after withdrawal of telapristone, her liver enzymes returned to normal and no further treatment was required. **Figure 9** graphically presents the course of her liver toxicity experience.

Figure 9. The course of liver toxicity experience of the subject 07-004 (ZPU-304 study). The subject 07-004 was treated with CDB-4124 (telapristone), 50 mg orally.



6.1.3.2 Relationship of dose and duration of telapristone of exposure on liver toxicity

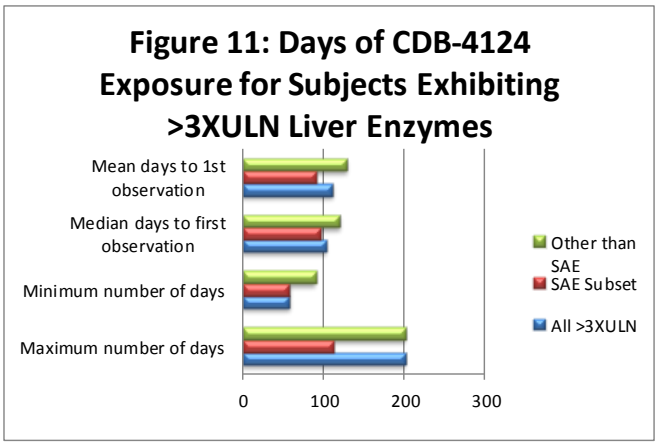
Figure 10. Overall Summary of Any Abnormal Liver Function Tests During Treatment Period



In addition to tracking SAE's Repros also tracked liver enzyme elevations that fell outside the normal range. A review of the excursions above the normal range is exhibited in **Figure 10**. A clear dose response is apparent. These findings are particularly relevant in light of the observation that the longest duration of exposures occurred in the 25 mg group as part of the ZPU-003 extension study (IND 70,535 SSN-133). In study ZPU-003 extension, 32 subjects were exposed to telapristone for between 361-720 days. Another 18 subjects were exposed for between 181-360 days. There were three subjects that experienced adverse events associated with elevated liver enzymes. Most notable was subject 11-018, previously reported as an SAE. She was randomized to the 25 mg group in the double blind study ZPU-003. Study ZPU-003 was designed to initiate trial participants with a dose 2X their intended randomized dose. Therefore 11-018 was dosed initially with 50 mg for two weeks before finishing the three month study at 25 mg per day. The two other subjects that exhibited elevated liver enzymes in the ZPU-003 extension were subjects 05-028 and 11-008. Both of these subjects were assigned to the placebo treatment group during the double blind portion of the study. Subject 11-008 reached ALT elevations of 1.3XULN for ALT before discontinuing from the study. The investigator noted the potential for gall stones contributing to the observation. Subject 05-028 exhibited ALT elevations of 7.5XULN for ALT but she was assessed to be positive for hepatitis C exposure based on the presence of antibodies against the virus.

It should be noted elevations listed as greater than a specific value are a subset of the next lowest value group. In general a trend is seen with increasing dose that is indicative of an increased frequency and

severity of liver toxicity. At a dose of 12.5 mg the frequency and severity of liver enzyme excursions is similar to the control group based on the limited data available. An assessment of time of exposure to onset of first detected liver enzyme elevations was conducted for those subjects that reached 3XULN and/or a liver associated SAE (**Figure 11 and Table 4**). The subjects whose telapristone doses were listed as 50/25 were initially randomized to 50 mg but reduced to 25 mg when Repros ceased administration of the 50 mg dose.



Study Number	Subject Number	Proellex Dose (mg)	Baseline Visit Date	First Detected LFT Value (u/L)	LFT Elevation Detection Date	Days of Exposure Before Elevation Detection	Hy's Law Case (Yes/No)	SAE (Yes/No)
ZPU-003	11-018	25	6/28/2006	ALT - 244	9/21/2006	86	No	Yes
ZPE-201	08-018	50	9/5/2008	ALT - 487	1/12/2009	101 (missed 29 doses)	Yes	Yes
ZPU-305	30-063	50	2/18/2009	ALT - 1042	6/9/2009	112	No	Yes
ZPU-305	27-002	50	3/11/2009	ALT - 503	6/23/2009	105	No	Yes
ZPU-304	07-004	50	4/2/2009	ALT - 526	5/29/2009	58	Yes	Yes
ZPU-304	20-004	50 / 25	4/10/2009	ALT - 314	7/1/2009	84 days (82 d - 50 mg; 2 d - 25 mg)	No	Yes
ZPU-303	02-001	50	3/6/2009	ALT - 243	6/9/2009	96	No	Yes
ZPU-305	009-005	50	12/18/2008	ALT - 167	4/13/2009	116	No	No
ZPU-302	04-001	25	10/14/2008	ALT - 175	1/12/2009	91	No	No
ZPU-305	003-008	50	10/30/2008	ALT - 335	5/18/2009	201	No	No
ZPU-305	024-016	50	2/3/2009	ALT - 264	6/2/2009	120	No	No
ZPU-305	016-005	25	1/7/2009	AST - 143	6/19/2009	163	No	No
ZPU-305	004-005	50 / 25	4/2/2009	ALT - 197	6/30/2009	91 days (89 d - 50 mg; 2 d - 25 mg)	No	No
ZPU-305	30-021	50 / 25	2/24/2009	ALT - 210	6/30/2009	127 days (90 d - 50 mg; 27 d - 25 mg)	No	No

Table 4. The individual data for the 14 subjects exhibiting liver enzyme elevations >3XULN in figure 11

Aside from the liver toxicity, telapristone was well tolerated. However, at doses of 12.5 mg and higher, the resultant induction of amenorrhea, the endometrial glands became atritic resulting in cystic dilatation. This dilatation can be confused with endometrial thickening or hyperplasia. However, histological examination of endometrial biopsies shows clear cellular differences between the two conditions. Hyperplasia, which is usually the result of a hormonal environment consistent with unopposed estrogen, is characterized by glandular crowding and densification of the stroma. In the case of an anti-progestin induced condition, the endometrium, though visibly thicker than normal endometrium as determined by

measurement of the endometrial stripe via ultrasound, is best characterized as atrophic with cystic dilatation. The glands are fluid filled and cystic and the intervening stroma is less dense. Assessment of cellular activity shows a marked reduction in markers of proliferation and an increase in apoptotic events. Over time this fragile structure breaks down and begins to be shed as evidenced by unexpected vaginal bleeding. Depending on the length of time that a woman has been continuously dosed with telapristone this bleeding may require intervention (dilation and curettage), but can be prevented by stopping dosing every four months and allowing the drug to washout. In this "off-drug interval" a normal menses will occur within roughly 35 days. After menses, the resultant reformed endometrium is normal (based on biopsy assessment) and the woman can begin another course of telapristone treatment, if needed. In the ZPU-003 extension study, women were dosed for up to 720 days successfully using the "off drug interval". No breakthrough or unexpected bleeding was observed. If telapristone is eventually approved, it will be dosed for periods of 4 months followed by off-drug intervals to allow for menses. Following menses, additional four month cycles can be prescribed over the course of a woman's reproductive lifespan. Telapristone has exhibited statistically significant results in relieving the debilitating symptoms of both uterine fibroids and endometriosis at doses of 12.5, 25 and 50mg, but the liver toxicity associated with drug at higher doses has focused evaluation on lower doses.

The ZP-204 Phase I/II study examined the safety and efficacy of low dose administration of telapristone (1, 3, 6, 9 and 12 mg) in healthy women. Subjects were dosed daily for 10 weeks following a placebo run-in period to establish baseline parameters. A linear dose-dependent increase in AUC of both telapristone and major metabolite were found. Markers for effects on the liver (total bilirubin, ALT, AST, and alkaline phosphatase) showed no changes during the study. Overall, although there were more numerical increases than decreases in the mean liver function test (LFT) values, those values did not exceed the upper limit of normal. The differences between dose groups were sporadic and random. The mean values did not show dose-dependency. Individuals showed occasionally high LFT values which were either (a) isolated spikes that returned to normal, or (b) a consequence of their pre-drug condition. No subject exceeded 2X the upper limit of normal due to use of the drug. There were no drug related changes in clinical chemistry, hematology, or urinalysis. From Visit 2 to Visit 12 all dose groups showed slight increases in endometrial thickness, but these changes were not statistically significant. There were no clinically significant changes in vital signs.

The FDA lifted a full clinical hold of oral telapristone to a partial hold, allowing Repros to conduct a Phase II study of oral telapristone for endometriosis (a three-arm trial, daily placebo, 6mg, and 12 mg).

6.2 Reported Adverse Events and Potential Risks

Of the progesterone antagonists that have been evaluated for effects on breast development and breast cancer promotion, preclinical data suggest that telapristone (Repros Therapeutics, Inc.) is superior to mifepristone, with greater and more selective anti-progestin activity, greater inhibition of cell growth in T 47D cells, and demonstrated growth suppression of established ER+ mammary tumors in rats [23]. Unlike mifepristone it does not increase plasma levels of estradiol or corticosterone in rats and has much less antiglucocorticoid activity. However, with chronic use, these compounds will cause reductions in progesterone activity and may increase the potential for endometrial cancer. They also cause irregular menstrual bleeding patterns which may discourage premenopausal women from continuing its use. A recent study in women with uterine fibroids and endometriosis showed efficacy in these conditions, but with hepatic toxicity (abnormal liver enzyme functions) at the 50 mg dose. Telapristone (Proellex), a 21-substituted analog of 19-norprogesterone, is a selective progesterone receptor modulator (SPRM, antiprogestin). In May 1999, a licensing agreement was finalized between Repros Therapeutics, Inc., and the National Institute of Child Health and Human Development (NICHD) to develop "21-Substituted Progesterone Derivatives as New Antiprogestational Agents", Serial Number 60/0 16,628. Preliminary evidence indicates that one or more of this new class of antiprogestins may be the ideal drug for the

treatment of endometriosis and uterine fibroids. Telapristone is currently being developed for these indications under that agreement.

Based on clinical studies with orally administered Telapristone to date, potential adverse events of treatment with Telapristone may include the following: increased liver enzymes, amenorrhea, endometrial thickening, uterine bleeding or spotting, vaginal discharge or infection, breast pain, nausea and/or vomiting, constipation, abdominal pain or distension, dyspepsia, headache, dizziness, arthralgia, back pain, extremity pain, neck pain, and hot flashes.

Many of these adverse effects (AEs) are seen rarely or intermittently, and few SAEs have been seen except the liver toxicity seen with the high oral dose in settings where more than 6 weeks of therapy was used.

The ZPU-001 - Phase I/II study examined the safety, and efficacy of 3 doses of Telapristone (12.5 mg, 25 mg, and 50 mg) daily for three months compared to Lucrin Depot (3.75 mg). The frequency of AEs was 16.7% in the 12.5 mg group. The majority of AEs were mild to moderate in intensity. The overall incidence rates of treatment-emergent adverse events were 83.3% for each of the Telapristone treatment groups and 100% for the LUC *and placebo* groups. **These rates indicate that the placebo subjects showed a higher incidence of adverse events than did the Telapristone treatment subjects**. In the 12.5 mg telapristone group, the most frequently reported adverse events, by preferred term, were: headache *16.7%*; vaginitis *16.7%*, and abdominal pain 16.7%. **All adverse events were mild to moderate in intensity except for 3 severe events that occurred in the 50mg Telapristone group, 2 considered as serious, but all considered as not related to treatment. No deaths were reported during the study**.

As reported by Repros in their Investigator's Brochure, in the ***ZPU-003 Trial***, 127 women were randomized to telapristone 12.5 mg, 25mg, or placebo. AE data that differed between the 12.5 mg group versus placebo is summarized below:

- Headache– 16% in telapristone group vs. 9% in placebo group
- Back pain – 7% in the telapristone group and 2% in the placebo group
- Arthralgia, back pain, pain in the extremities- 19% in telapristone group vs. 12% in placebo group
- Hot flashes 20% in the 12.5 mg group versus 2% in the placebo group.

Many of these adverse effects (AEs) are seen rarely or intermittently, and few SAEs have been seen excepting the liver toxicity seen with the high oral dose in settings where more than 6 weeks of therapy was used. In a previous phase I/II single-blind, placebo run-in, dose escalating study ***(ZP-204)*** comparing 5 oral doses of telapristone, *82% of the adverse events reported were of mild intensity as well as unlikely related to study treatment*. The most frequent AEs (occurring in 3 or more of 29 subjects) were musculoskeletal pain, nausea, headache, emesis, URI, mittelschmerz, abdominal cramps/discomfort or pain, dizziness, menorrhagia, rhinitis, and hot flashes. These were mostly mild (44 of the 52 events) and mostly unrelated to treatment (43 of the 52 events). *Amongst all adverse events, nausea and hot flashes are reported as probably or possibly related to 12mg telapristone dose*.

In our ongoing window trial of telapristone 12 mg versus placebo in women with early stage breast cancer, adverse events are reported by approximately 50% of women, the most frequent of which are headache, arthralgias, and hot flashes.

Telapristone gel has not been used in humans before, so AEs/risks are unknown; however, systemic AEs are expected to be lower, and preclinical studies in rabbits and pigs have not shown any skin

toxicity.(Repros Investigators' Brochure version 2, page 32-35). Study agent will be discontinued if the subject reports grade 3 or 4 adverse events that are probably or definitely related to study agent, or grade 4 adverse events that are possibly related to study drug.

6.3 Availability

Telapristone and matching placebo are investigational agents supplied to investigators by the Division of Cancer Prevention (DCP), NCI.

Telapristone and matching placebo will be supplied to the NCI/DCP by Repros Therapeutics as a 12 mg, white opaque Size 3 hard gelatin capsule for oral administration. Telapristone 12mg and matching placebo will be packaged with 30 count 12 mg capsules/bottle. Each participant will receive 2 bottles.

Telapristone gel and matching placebo will be supplied to the NCI/DCP by Repros Therapeutics in a metered dispenser for topical administration. Each dispenser will contain telapristone/placebo sufficient for 34 days of gel application.

Telapristone is provided to the NCI under a Clinical Supply Agreement (CSA) between Repros Therapeutics and the DCP, NCI (see Section 12.7).

Telapristone oral and transdermal formulations are expected to be available by June 1, 2014.

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 Pharmacist (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) 360-5369
FAX: (816) 753-5359
Emergency Telephone: (816) 360-3800

All gel dispensers must be weighed before distributing to the participant, and again after the participant returns the used dispensers to the pharmacy (prior to being destroyed). The dispensers should be weighed with the cap on, and with all local labels applied. The weight should be recorded on the Weight of Agent Dispenser form. If the cap is not returned, weigh the dispenser without the cap and mark this on the Weight of Agent Dispenser form.

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). This Investigational Product Accountability Form will track kit transactions. Record all sections on the form as indicated. Document all shipments received, date, quantity received, balance, lot number and recorder's initials. Upon dispensing, record date, subject initials, subject number, quantity dispensed, balance, lot number, and recorder's initials. Fill out Investigational Product Not Returned by Subject and Investigational Product missing by any other reason sections if situations warrant documentation. The study agent will be dispensed to the subject at Screening Visit 1 or 2 either in person or via mail or courier delivery.

In addition, record the weight of the dispenser on the Weight of Agent Dispenser Form by kit number as described in section 6.4. Use one form per kit.

6.6 Packaging and Labeling

The telapristone and placebo capsules will be packaged as 12 mg, or placebo capsules, in bottles of 30 capsules. Each bottle will have a label printed with the treatment kit number, number of capsules, expiration date, and the statement "Caution: New Drug- Limited by Federal law (US) to investigational use". Each participant will be dispensed 2 bottles.

Transdermal telapristone or placebo gel: A dispensing pump system that allows the administration of the correct amount of topical gel will be used. This dispenser is from a commercially-available unit Topi-Pump®. Instructions for use will be provided as outlined in Appendix E.

Telapristone (capsule and gel) will be packaged and labeled by Repros Therapeutics. Repros will ship the supplies at ambient temperature. The Research Pharmacy should store the material at 2-8°C upon arrival. Each site will package the supplies to protect drug from heat and moisture for mail/courier delivery to subjects. Each woman will be provided with two bottles containing 30 capsules (placebo or 12 mg telapristone), and 2 gel dispensers (sufficient for 68 days). One gel dispenser contains at least 68 doses of telapristone which is sufficient for 34 day gel application. Each participant will apply one dose of gel per breast daily.

The labeling for telapristone capsule bottle will be as mentioned above. In the case of telapristone gel, the dispensers will be labeled with the new study number and "placebo or 12 mg telapristone gel" along with the statement "Caution: New Drug- Limited by Federal law (US) to investigational use". Detailed instruction for gel application will be provided.

One kit will be assigned to each subject. Each kit contains: 2 bottles of telapristone/placebo 12 mg capsule and 2 telapristone/placebo dispensers. Dispensing pharmacist shall open the kit, affix prescription labels to both capsule bottles and dispensers with written direction according to the prescribing instruction. Fill out blank sections on the bottles and dispensers indicating subject number and subject initials. Weigh both dispensers and record final gross weight on the space provided on the dispenser itself and on the form. Detach peel-off label from each kit and save it according to the protocol.

6.7 Storage

All telapristone/placebo capsules and gel dispensers will be stored in a safe, secure area with limited and controlled access by only the investigator and staff. Although telapristone capsule can be kept at room temperature, the drugs all come in ONE BOX and the Research Pharmacy will have to store the entire kit in the refrigerator (2-8 ºC) until time for dispensing. Once dispensed, the subjects will be instructed to store the capsules and the gel at room temperature in homes protected from light, and moisture. The DCP Drug Repository, MRI Global, will distribute the study agent directly to each participating site. Repros

Therapeutics will conduct a 3-year stability protocol to test telapristone gel. If the results of stability at any time points are getting close to the limits of specification, Repros will prepare a new batch for the clinical trial.

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. For registrations requiring immediate randomization, the study coordinator should send an email to ncpc@northwestern.edu. Immediate randomizations can only be completed between 9:30am-5:00pm central time.
4. After registration, participants will be assigned a participant identification number and a study agent kit number.
5. The clinical research coordinator and the research pharmacist will receive a participant identification number code and kit number for the patient via email.
6. The research pharmacist will dispense all drugs in the kit, two bottles of telapristone capsules and 2 bottles of transdermal telapristone gel to the subject in its original kit with label.
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 NU, MSKCC, and CSMC. The study statistician will set up randomization blocks.

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 only occur when it is deemed medically necessary, 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 destroyed. Used gel dispensers must be weighed prior to destruction, as specified in section 6.4. Dispose of all dispensers according to the institutional policy for inflammable wastes.

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

Procedure	Screening Visit 1[1]	Screening Visit 2 (Optional)	Day 8±3, 15±3, 22±3 (1st day of study drug =day 1)	Study Visit 1 Day 29, ±7	Study Visit 2 (day 29-40)	Follow-Up Day[11] 60 ±7
Informed Consent	X					
Registration	X	X[8]				
Randomization[9]	X	X				
Assess Eligibility	X	X				
History[7]	X			X		
Last Menstrual Period	X			X	X	X
Physical Exam[7]	X			X		
Vital Signs/ Height and Weight[7]	X			X	X	
BESS Questionnaire administration	X			X		
Clinical Labs (LFTs and Renal function tests)[2]	X			X		
Urine or Serum Pregnancy Test[3]	X	X		X[10]		
Research Core biopsy[4]		X				
Research blood specimen collection	X	X		X		
Tissue procurement for research purposes[5]	X			X		
Concomitant Medications	X		X	X	X	
Dispense Study Agent and diary[6]	X	X				
Collect Study Agent				X		
Review Agent Diary/Record				X		
Adverse Events assessment			X	X	X	
Telephone/Email Contact			X			X

[1]Screen 1 will occur within 6 weeks of starting study agent.
[2] LFTs and Renal function tests within 6 weeks prior to registration.
[3]Required within 5 days prior to starting study treatment for females of child-bearing potential. Will be performed at Screening Visit 2 for women requiring this visit. Women of child-bearing potential who do not have a Screen 2 Visit, and whose Screen 1 Visit 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.
[4]Performed to obtain pre-intervention tissue for women consenting to a research CNB prior to prophylactic mastectomy.
[5]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.

[6] Subjects who are unable to pick up the study medication will receive it via mail or courier delivery requiring signature to confirm receipt.
[7] Within 6 weeks prior to registration.
[8]Registration will occur prior to receiving the biopsy at the Screen 2 Visit, to ensure participants receiving the biopsy are eligible.
[9]See section 7.2.2 for details on when randomization will occur.
[10]Urine or serum pregnancy test is routinely performed for females of child-bearing potential prior to the surgery.
[11]For premenopausal participants to collect last menstrual period.

7.2 Timeline for Enrollment

7.2.1 Registration can occur at Screen 1 visit. No more than 6 weeks should elapse between Screen 1 visit and start of study drug.

7.2.2 For women with child-bearing potential: the pregnancy test can be performed either at Screen 1 or at Screen 2 visits, so that it is known to be negative within 5 days prior to study drug start .
If more than 5 days have elapsed since a negative pregnancy test, and study drug has not been started, the subject must return for a pregnancy test within 5 days prior to study drug start, and will be compensated for this visit.

7.2.2 Randomization may occur at the same time as registration, or at any point following registration as long as the following conditions are met: surgery date is known, therefore drug start can be predicted; pregnancy test for women with child-bearing potential is within 5 days prior to study drug start date; Screen 2 visit (if planned) has been completed.

7.3 Baseline Testing/Prestudy Evaluation

7.3.1 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: Protocol-specific (hormone level measurement and DNA extraction): One 10 mL red top tube for serum hormones and one 10 mL lavender top tube (K2 EDTA) for DNA will be collected.
9. Review of conformance with Inclusion / Exclusion criteria
10. BESS questionnaire (Appendix D)
11. Collection of last menopausal period date
12. Urine or serum pregnancy test for women with child-bearing potential (except for subjects who need Screening Visit 2).
13. Registration and randomization (except for subjects who need ScreeningVisit 2).
14. Dispensing study medication (for subjects who are not able to pick up 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.

15. Subject diary (Appendix B and C) will be reviewed and dispensed along with the study medication.
16. 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.

7.3.2 Screening Visit 2

Only for women undergoing CPM or BPM after eligibility is established based on Screening Visit 1, and subject consents to the optional research core biopsy.

1. Research core needle biopsy
2. Blood draw for hormone levels to determine menstrual/menopause status.
3. Urine or serum pregnancy test for women with child-bearing potential.
4. Registration and randomization
5. Dispensing study medication (for subjects who are not able to pick up 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.
6. Subject diary (Appendix B and C) will be reviewed and dispensed along with the study medication.

7.3.3 Pregnancy Test Visit

Participants of child-bearing potential, who do not participate in a Screen 2 Visit, and whose Screen 1 Visit does not occur within 5 days of starting study agent, will be asked to return to the office for a pregnancy test.

7.4 Evaluation During Study Intervention

Phone calls (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.

At these phone calls, the following with be collected:

1. Concomitant medication review
2. Adverse events - Participants will be asked if they have experienced any of the following symptoms to assess adverse events:
    a. Nausea/ Vomiting
    b. Stomach pain
    c. Constipation
    d. Headache
    e. Dizziness
    f. Hot flashes
    g. Vaginal discharge
    h. Uterine spotting/ Uterine bleeding
    i. New muscle or joint pain, and severity on VAS.
    - Additionally, any other symptom experienced by participants will be recorded to assess adverse events.

The participant contact on day 22 will include a reminder to switch to the new gel dispenser and to prime the bottle before first use.

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.

7.5 Evaluation at Completion of Study Intervention

7.5.1. Study Visit 1 (Day 29±7)

Participants will report to the hospital 3 hours prior to surgical time on day 29 ±7. Participants will fast from midnight on the evening prior to surgery.

On arrival the following procedures/evaluations will be performed:

1. Medical history per treating physician
2. Physical exam per treating physician
3. Vital signs assessment per anesthesia assessment or pre-operative nursing evaluation
4. Clinical labs for renal and hepatic function including total bilirubin, AST, ALT, alkaline phosphatase, blood urea nitrogen and creatinine
5. Blood collection for research purposes (hormone level measurement and drug concentration measurement). Blood collection should occur prior to completion of the mastectomy (ie if blood is not drawn prior to the patient entering the operating room, it can be drawn in the OR).
6. Urine or serum pregnancy test (for subjects of child bearing potential) - per standard of care prior to the surgery.
7. BESS questionnaire (Appendix D)
8. Collection of last menstrual period date
9. Concomitant medications and adverse events assessment
10. Compliance assessment (pill count and weighing gel dispensers) and collection of study agent
11. Collection of study diary.
12. Tissue will be obtained from the DCNB as well as the surgical resection specimen for study end points

7.6 Post-intervention Follow-up Period

7.6.1 Study visit 2 (Post-op visit in the breast surgery clinic, day 29-40) (The intent is to have this visit 7-14 days after study visit 1):

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. Date of last menstrual period for premenopausal subjects

7.6.2 Follow up

Telephone contact only on day 60±7 for premenopausal subjects.

1. Date of last menstrual period for premenopausal subjects.

7.7 Methods for Clinical Procedures

Core needle biopsy (CNB) of an unaffected breast will be performed at Screening Visit 2 in women who are scheduled for bilateral or contralateral prophylactic mastectomy. CNB procedure: this will be performed at the participating study sites as an office procedure. The skin will be prepared with antiseptic solution, a location in the mid-zone, upper outer quadrant will be infiltrated with 1% lidocaine, a 2 mm stab will be made with an 11 blade, and a 11 to 14 gauge core needle loaded on a spring-loaded or vacuum-assisted biopsy device will be used to obtain 8 cores of breast tissue. All of these will be fixed in 10% Neutral buffered formalin. The biopsy area will be subjected to firm pressure for 5 minutes, steri-strips applied, and the patient instructed to avoid vigorous physical activity and swimming for 3 days.

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

8.1 Primary Endpoint

Primary: To demonstrate that mean levels of telapristone in breast tissue following gel application will result in levels that are not more than 50% lower than those following oral administration. 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 12A**. 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.

8.2 Secondary Endpoints

8.2.1 To assess whether plasma concentrations of telapristone are significantly lower with transdermal than oral therapy.

8.2.2 To assess within-breast variation of breast tissue concentration in transdermal and oral groups.

8.2.3 To measure changes in cell proliferation (Ki67 labeling index) in breast cancer samples obtained at diagnostic core needle biopsy (of cancer) or research core needle biopsy (of unaffected breast) with tissue samples obtained at mastectomy.

8.2.4 To assess symptom measurements using BESS Questionnaire.

8.2.4 To measure changes in gene expression to identify treatment response. The same breast tissue samples used for IHC at baseline and after treatment will be used for measurement of gene expression using nanostring for selected genes (RANK, RANKL, prolactin receptor, cyclin D1) and for additional genes selected from the RNA sequencing results of NU 12B09.

8.2.5 Assess change in serum progesterone associated with telapristone therapy

8.2.6 Assess the safety and tolerability of oral and transdermal administration.

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. Participants who complete less than 80% of the planned dose or do not take more than one of the last 3 doses will be considered non-compliant and will not be evaluable for secondary endpoints; additionally, participants for whom fewer than 3 breast tissue samples are collected will be replaced.

8.4 Off-Study Criteria

Participants may go 'off-study' for the following reasons:

- Adverse Event
- Death
- Disease Progression
- Lost to follow-up/Participant Withdrawal
- Participant Refused Follow-up
- Physician Decision
- Protocol Defined Follow-up Completed
- Protocol Violation
- Study Complete
- Ineligible
- Other

Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events. Participants will be removed from study agent if investigators feel it is in the interest of subject to do so.

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 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.] We have successfully utilized LC/MS/MS method for plasma and breast tissue specimen in our previous prevention trial (NWU07-9-02, oral tamoxifen vs. 4-hydroxytamoxifen topical gel treatment on women with breast DCIS) and a pilot "Study to Test Uniformity of Transdermal Drug Delivery to the Breast Using Diclofenac Epolamine as a Model".

IHC for Ki67: 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 and apoptosis. Telapristone has demonstrated growth suppression of established ER+ mammary tumors in rats by reduction in Ki67 and increase in TUNEL (11, 12). We have attempted to use TUNEL as an apoptosis assay in a prior window trial (NU12B09) and found it to be

challenging because of low values and difficulty of scoring. Therefore, we do not plan to evaluate TUNEL in the present study.

mRNA gene expression assays*:* Since progesterone antagonists are novel agents for early breast cancer management and prevention, we have performed RNA sequencing for an unbiased assessment of gene expression changes with therapy in our previous window trial of telapristone in patients with Stage I/II breast cancer. The analysis of these data is in the final stages

A. Independent validation of potential *tumor biomarkers* for telapristone response: We will select 50 genes that are differentially expressed in tumor samples of treated and controls arms and are known to be involved in progesterone response. We will perform targeted gene expression assays to confirm their expression in the present NWU2013-01-03 (TopPACT) study using the NanoString nCounter analysis (Nanostring Technologies, Seattle, WA). This is a widely used and highly reproducible method for quantitative determination of differential mRNA expression. The mRNA gene expression profiling will be performed at NanoString headquarter for tumor samples. Refer to PK-biomarker document for more method details.

B. *Benign tissue biomarker* of benign high-risk breast for telapristone response by RNA sequencing assays: In addition, the present NWU2013-01-03 (TopPACT) also has a subset of patients who did not have cancer, as well as subjects who had cancer on one side, and underwent bilateral mastectomy. No tumor tissue is available from these breasts. Instead, we have benign breast tissue samples from both breasts of BRCA1/2 mutation carriers and contralateral unaffected breast tissue are available from BRCA1/2 mutation carriers as well as BRCA normal women. Since the effects of the drug on benign high-risk breast are of significant scientific interest, and RNA-seq results from PACT study tumors cannot be applied to this tissue, we are proposing to perform RNAseq on these benign breast samples for these women for discovery of genes modulated by telapristone (CDB4124). This work will be done at Center for Medical Genomics Sequencing Service, Indiana University School of Medicine, Indianapolis (RNAseq of PACT study was performed by this team). Refer to PK-biomarker document for more method details.

Genotyping assay for drug metabolism enzyme polymorphism analysis: Genotying 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.[1] We lack power to test this hypothesis in the current study. The WBC samples will be stored at -80 °C but plan to address the hypothesis in pooled analyses with ongoing and future studies.

9.2 Comparable Methods

A. Proposed methods represent standard technology for drug concentration measurement and for IHC. Targeted gene expression in tumor samples will be examined using NanoString nCounter assays. This is a relatively new but now fairly standard method for measuring gene expression in paraffin embedded samples. RNA sequencing for benign tissue will be performed using SMART-Seq v4 Ultra Low Input RNA Kit for cDNA library construction and HiSeq 4000 sequencing machine for 75b paired-end sequencing (Illumina, Inc.). This is a relatively new but now fairly worked well for measuring gene expression in paraffin embedded samples. Refer to PK-

biomarker document for more method details and references.

10. SPECIMEN MANAGEMENT

10.1 Laboratories

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

2. 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.
3. Hormone assays in serum will be performed at University of Virginia.
4. Telapristone concentration assays in plasma will be performed at Dr. Muzzio's laboratory at Illinois Institute of Technology Research Institute.
5. Telapristone concentration assays in breast tissue will be performed at Dr. Muzzio's laboratory at Illinois Institute of Technology Research Institute.
6. Tumor mRNA gene expression profiling will be performed at NanoString Headquarters, Seattle, CA.
7. RNA sequencing work will be done at Center for Medical Genomics Sequencing Service, Indiana University School of Medicine, Indianapolis, IN.

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

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 (Reported Adverse Events and Potential Risks) can be found in §6.2, Pharmaceutical Information, 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.

11.1.2 AE Data Elements:
The following data elements are required for adverse event reporting.

- AE verbatim term
- System Organ Class (SOC)
- Common Terminology Criteria for Adverse Events v4.0 (CTCAE) AE term
- Event onset date and event ended date
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a serious adverse event (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 NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE provides descriptive terminology and a grading scale for each adverse event 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 CTCAE grade associated with the AE 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.

*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 adverse event is related to study agent will be classified as one of the following: not related, unlikely, possible, probable, definite.

11.1.5 Follow-up of AEs
Follow-up of unresolved AEs at close of study (or another time point) will become part of the standard medical care.

11.2 Serious Adverse Events

11.2.1 DEFINITION: Fed. Reg. 75, Sept. 29, 2010 defines SAEs as those events, occurring at any dose, which meet any of the following criteria:

- Results in death
- Is life threatening (*Note: the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).*
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality/birth defect
- Important medical events that may not result in death, be life-threatening or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed.

11.2.2 Reporting SAEs to DCP and Northwestern University

11.2.2.1 The Lead Organization and all Participating Organizations will report SAEs on the DCP SAE 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 The Lead Organization and all Participating Organizations will send written SAE reports using the DCP SAE form within 24 hours of learning of the event to the following:

- DCP Medical Monitor, Dr. Marjorie Perloff, email (perloffm@mail.nih.gov)
- DCP's Regulatory Contractor, CCS Associates, email (safety@ccsainc.com)
- Lead Organization (Northwestern University), email (ncpc@northwestern.edu)

11.2.2.3 Include the following information with the completed SAE report:

- 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 and expectedness
- Determination of whether or not the event qualifies as an Unanticipated Problem Involving Risks to Subjects or Others (UPIRSO). For the definition of a UPIRSO, please see section 11.2.2.6.

11.2.2.4 The IND holder, Dr. Seema Khan, the Northwestern University quality assurance staff, and the Medical Monitor will determine which SAEs require FDA submission.

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.

11.2.2.6 A UPIRSO is an event that meets all three of the following criteria:

- Is unanticipated in terms of nature, severity, or frequency
- Places the research subject or others at a different or greater risk of harm
- Deemed to be related or possibly related to participation in the study

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 form in the appropriate format. Follow-up information should be sent to the DCP and Lead Organization as soon as available.

12. STUDY MONITORING

12.1 Data Management

Data will be managed by the study statistician, Dr. Jovanovic, 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 questionnaires completed in person may be completed directly on the paper 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, telapristone capsule, placebo capsule, telapristone gel, and placebo gel supplied by DCP, NCI, used in this protocol, are provided to the NCI under a Collaborative Agreement (CSA) between the Repros Therapeutics (hereinafter referred to as Collaborator(s)) and the NCI Division of Cancer Prevention. 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 combination 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

This is a phase II study of two application methods of the same drug. Randomization is double blinded; each patient ***gets both the pill and the gel vector***. There will be no early testing or stopping rules.

The primary objective of this study will be to demonstrate that mean levels of drug in benign breast tissue following gel application will not result in levels that are more than 50% lower than those following oral administration.

Data will be collected to address the following additional secondary objectives**:**

1. To compare whether plasma concentrations of telapristone are significantly lower with transdermal than oral therapy.
2. To compare within-breast variation of breast tissue concentration in transdermal and oral groups.
3. To measure changes in cell proliferation (Ki67 labeling index) using IHC at baseline and after treatment.
4. To explore changes in gene expression in benign and malignant breast tissue related to telapristone therapy
5. To measure change in serum progesterone associated with telapristone therapy
6. To compare the safety and tolerability or oral and transdermal administration.
7. Assess symptom measurements using BESS Questionnaire.

13.2 Randomization/Stratification

Patients will be randomized by the study statistician. Randomization will be stratified by two factors: pre/post menopausal and accruing institution. Within each combination of these two factors we will balance the two treatments 1:1. Enrollment is expected to be (but not limited to) a 70:30 ratio of pre-menopausal:post-menopausal women. Randomization will be done in blocks of 2 and 4 as appropriate and possible. Subgroup analysis will be performed after main analysis. We will use Intent to Treat analysis as a principle in identifying treatment assignment.

13.3 Accrual and Feasibility

Assumed accrual rate is 2-3/month, and the planned recruitment duration is 30-36 months, for total of n=70 randomized patients. We expect to have 60 evaluable patients. Power and precision arguments are provided below.

13.4 Primary Objective, Endpoint(s), Analysis Plan

Analysis: A total of 70 women undergoing mastectomy will be randomized, 35 to each of two arms: transdermal and oral drug therapy. We expect an attrition of 10 women, yielding a total of 60 evaluable women. We will use block randomization with varying block sizes of two and four, to ensure balance of treatment assignments over the course of accrual. Drug concentration in tissue will be measured at five non-tumor sites and in one blood draw at the time of surgery. The primary analysis compares the *mean breast tissue drug concentration at non-tumor sites between the two treatment groups*. We expect the transdermal breast tissue drug concentration to be within 50% of that in the oral group. The sample size is determined so that >50% difference may be discovered if it exists. Means and standard deviations will be reported for the summary breast tissue drug concentration outcome for all participants and separately for the treatment groups. The mean tissue concentrations between treatment groups will be compared using Student t-test. In addition, we will compare the two groups for clinically relevant characteristics including

age and race, breast size cup size, body mass index, and sample adiposity as assessed on the histologic sections of the tissue used for drug concentration measurements since skin permeation may vary with these parameters.
Additionally we will compare levels of drug in plasma with the level of drug in the tissue, separately for each treatment group. We expect to observe higher concentration per gram of tissue than per ml of plasma in both groups, but we expect that the ratio of tissue: plasma concentrations will be 3:1 in the oral group and 10:1 or higher in the transdermal group. The comparison will be within each woman, and the outcome of interest will be average expression in the tissue in comparison with one measurement made in plasma.

Sample size considerations. Primary outcome: We want to explore equivalence for tissue concentration between the transdermal and oral groups using a confidence interval for the differenced in mean concentrations between groups. We estimate that the mean tissue concentration will be about 45.3ng/g tissue with SD=30 in the oral group. We define equivalence as the transdermal group mean being approximately within 50% of the oral group mean with 95% confidence. Thus, with n1=n2=30, n1+n2=60, and SE(Diff(means))= SDxsqrt(2)/sqrt(60) = 30x1.41/7.75 = 10.9, the approximate 95% CI (difference(means)) will have half width of 1.96x10.9= 21.4, which is roughly a half of 45.3ng/g tissue postulated for oral group. Thus if in analysis the aforesaid CI of the difference in group means covers zero, we will declare equivalence as defined above with 95% confidence.

13.5 Secondary Objectives, Endpoints, Analysis Plans

Further, we wish to establish that difference exists between levels of each administered method of delivery of drug **between tissue and plasma**. This will be done separately for each treatment group. The information we have is for oral group suggests a 1:3 ratio as follows: In tissue mean = 45.3, SD=30; in plasma, mean=13.35, SD=5.1. We hypothesize that in the transdermal group the ratio of means will be 10:1. For 30 patients, in oral group, to test the null hypothesis of no difference in drug level versus an alternative of Diff=30, with SD(diff)=10, we will have power of over 80% to reject the null hypothesis, under various possible scenarios regarding variance. Similar considerations would apply to the transdermal group.

To assess within-breast variation of breast tissue concentration in transdermal and oral groups, we will register SD(i,j)) = standard deviation for subject i, based on depth position j, where j=1,2,3 in Figure 12 are three non-tumor observations. Then we will do descriptive statistics on n=30 values for each treatment group and each depth. Finally we will have a map of can compare ‘average dispersion’ in two treatment groups and various locations (j=1,2,3) as well as other locations j=4,5,6,7, using a ANOVA. The end result will be description of SDs in groups/locations/depths as well as p-values suggesting whether groups significantly differ from each other.

Further analyses will include serum P4 as well as protein expression of Ki67 using IHC at baseline and after treatment. Changes in gene expression before and after treatment will be compared, in the expectation that changes will be similar in the two groups. Descriptive statistics and two sample tests will be applied. Lack of significant difference will not be taken to mean equivalence. **To establish possibility of “equivalence**” we will use the rule of thumb where a 20% or lesser difference in expression will be considered evidence of equivalence between two treatment groups. Power to establish so defined equivalence will vary from case to case with expression level and variability inherent in such expression measurement. Changes in gene expression detected in array experiments will be confirmed using NanoString nCounter analysis.

The patient-reported BESS will be administered twice: before and after the treatment. Summary scores for each of the eight symptom clusters will be calculated by summing the scores of the component items.

Response frequencies will be summarized for each individual item within each arm before and after treatment. Descriptive statistics (mean, SD, range) will be calculated for the eight symptom cluster scores. The mean change, with 95% confidence intervals, will be calculated for each scores within each group, as will the mean differences between arms.

Pooled analysis of biomarkers. Finally we will use data from NU-12B09 (our on-going telapristone trial with 25 patients receiving oral drug and 25 controls) to combine the two oral groups for a pooled analysis of biomarkers, comprising a total of 30+25 = 55 oral drug patients and 25 placebo controls. This will allow a more robust biomarker analysis than would be possible in the present study alone.

13.6 Reporting and Exclusions

Compliance will be measured by observing patient diaries, and by considering the amount of pills and gel returned to the study coordinator and the pharmacy. Missing data will be imputed using a semi-parametric approach developed by I. Helenowski (Statistics and its Interface, 6 (2013) 399-412).
Compliance is defined as 80% of the total dose with at least 2 of the 3 last doses of the prescribed dosage taken.

13.7 Evaluation of Toxicity

All participants will be evaluable for toxicity and adverse events from the time of consent.

13.8 Evaluation of Response

All participants will be evaluated for concentration of telapristone in breast tissue and blood plasma, as long as 6/7 doses were used during the week prior to surgery, and no more than 1 of last 3 doses were missed.

13.9 Interim Analysis

There will be no planned interim analyses.

13.10 Ancillary Studies

N/A

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 Signed and dated 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.

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 (within two years) for all labs listed on Form FDA 1572 for the Lead Organization and all Participating Organizations.

14.2.4 Documentation of training in "Protection of Human Research Subjects" 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 the DCP Regulatory Contractor:

Paper Document/CD-ROM Submissions:
Regulatory Affairs Department
CCS Associates
2001 Gateway PL, Suite 350W
San Jose, CA 95110

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 the DCP 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

All research related costs associated with participating in this study will be paid for, and will not be the responsibility of the participant. Individuals who complete the of intervention will receive $150 for any incidental expenses. Subjects undergoing contralateral prophylactic mastectomy who complete Screening Visit 2 will receive an additional $150. Subjects who are required to return to the office for a pregnancy test visit will receive an additional $100. However, 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

(Insert Institution name)

Consent Form and HIPAA Authorization for Research

STUDY TITLE FOR STUDY PARTICIPANTS: A study testing if a potential breast cancer prevention medication applied to the breast skin reaches the breast tissue as well as when it is given by mouth.
PROTOCOL TITLE: NWU2013-01-03: Intra-mammary distribution of transdermal telapristone vs. oral telapristone: a randomized window trial in women undergoing mastectomy
PRINCIPAL INVESTIGATOR: *(insert name)*

SPONSORED BY: National Cancer Institute (NCI) – with support from Repros Therapeutics, Inc

Introduction

You are being asked to take part in a research study. This document has important information about the reason for the study, what you will do if you choose to be in this research study, and the way we would like to use information about you and your health.

Conflict of Interest Disclosure

The following disclosure is made to give you an opportunity to decide if this relationship will affect your willingness to participate in this research study:

If your doctor is also the person responsible for this research study, please note that she is interested in both your clinical care and the conduct of this research study. You have the right to discuss this study with another person who is not part of the research team before making your decision whether or not to be in the study.

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 treatment, including plans for surgery, will be decided by you and your breast surgeon. All study treatments 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 simply have your agreed upon medical treatment,
- you may choose to take part in a different study, if one is available

Why is this study being done?

The purpose of this study is to see if we can treat the breast with drugs applied to the skin of the breast rather than pills taken by mouth. 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 compare the amount of the drug that reaches different parts of the breast when it is taken as a pill (the usual way), or applied as gel to the breast skin (the new way). The drug is called telapristone.

The use of telapristone (the study drug) in this study is investigational, meaning that it is not approved by the Food and Drug Administration (FDA). Telapristone is currently being examined in clinical trials for uterine fibroids and endometriosis. It is a selective progesterone receptor modulator; in other words, it

works against the hormone, progesterone, which is thought to play a role in breast cancer development. All women who participate in this study will receive telapristone for about 4 weeks prior to surgery; half will receive it as a capsule, and half will apply a gel to the breasts. The researchers in this study would like to compare how well the drug gets into the breast, and how much gets into the blood, when taken as a capsule or gel. Additionally, the researchers will compare the effectiveness of the two forms of telapristone in reducing the growth rate of cancer cells (and of benign breast cells in women having preventive surgery) .

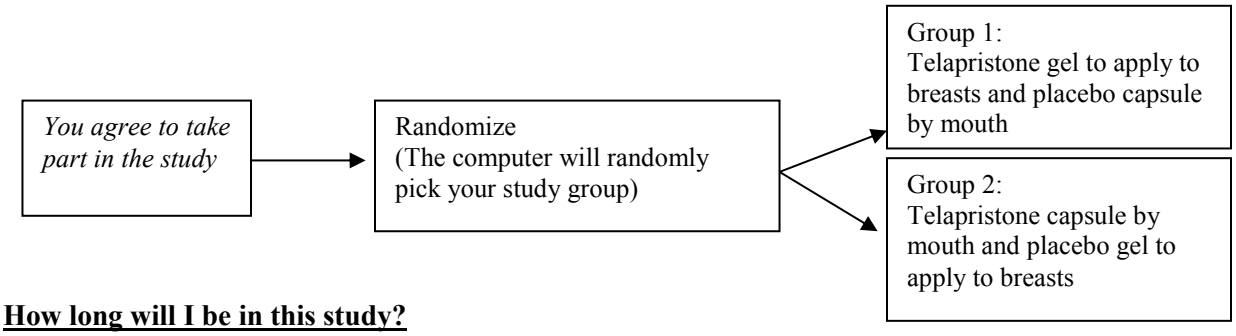
The study investigators hope to enroll 70 participants at Northwestern University, Memorial Sloan Kettering Cancer Center, and Cedars-Sinai Medical Center.

What are the study groups?
This study is a phase IIb study, which means we will be looking at both safety and effectiveness, so in addition to comparing the effectiveness of telapristone, researchers will also compare side effects in women taking telapristone as a capsule or a gel.

Women who participate in this study will also receive a placebo; those in the capsule group will use a gel placebo, and those in the gel group will use a placebo capsule. (A placebo is gel/capsule made to look like the study drug, but it does not contain active medication). All participants will receive active telapristone study medication in gel form or active study telapristone study medication in a capsule.

This study has two study groups. Group 1 will receive telapristone 12mg capsule by mouth and placebo gel to apply to each breast. Group 2 will receive telapristone gel 12 mg applied to each breast and placebo capsule by mouth.

A computer will randomly put you in a study group—like a coin toss—to decide what group you get placed into. This is done because no one knows if one study group is better, the same, or worse than the other group. Once you are put in a group, you cannot switch to the other group. Neither you nor your doctor will know if you are receiving telapristone as a capsule or as a gel. Your doctor cannot choose which group you will be in.



How long will I be in this study?

You will receive the study medication for 4 weeks±7 days. The final follow-up is on day 60 (± 7 days) over telephone for premenopausal women. While on study medication you must agree to use alcohol in moderation.

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*.

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. Most of these are part of regular care for breast conditions such as the one for which you have been diagnosed and would be done even if you do not join the study. 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

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 3 ½ tablespoons or 56mL)

Your initial study visit for screening will last approximately 60 to 90 minutes. If you are found to be eligible and are randomized to receive the study drug, the study drug 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.

Because it is important that you are not pregnant while taking this study drug, you will need to have a negative pregnancy test within 5 days prior to starting the study drug. If you are able to become pregnant and 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.

For women undergoing preventive mastectomy of one or both breasts: before beginning to take your study drug, we ask that you allow us to obtain *needle biopsy tissue samples* from this breast, for research purposes. This biopsy takes about 10 minutes to do, it causes minimal discomfort, and it will allow us to better assess the effects of the drug on normal breast tissue where cancer has not yet developed. It will be done in the office by a qualified surgeon. Local anesthesia (medicine to numb the skin) will be given to an area of the breast where the sample will be taken. A 2 millimeter (this big -) incision will be made in the skin of the breast and a needle will be used to obtain specimens of the breast tissue which are about an inch long and the thickness of a pencil lead. Up to 6 samples may be taken. A urine or serum pregnancy test will also be performed at this visit (for women who are able to become pregnant). Additionally, collection of blood for research purposes will occur (a total of about 3 ½ tablespoons or 56mL).

You will come to _____*(site specific address)* for this procedure. The visit will last about 60 minutes. This procedure will take place within 6 weeks prior to start of the study drug. Study medication will be given to you on that same day, or it will be mailed to you.

Please circle your answer to show whether or not you would like to take part:

I agree to participate in the needle biopsy and collection of tissue samples.

YES NO N/A (not undergoing preventive mastectomy)

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 take the telapristone 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 take/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. Telapristone capsule and placebo gel
2. Telapristone gel and placebo capsule

Instructions to apply gel: You will apply 1 pump (12 mg) of gel to each breast (total 24mg) daily in the morning after shower, allow it to dry for one minute and dress as usual. Do not bathe, swim, or shower for at least 4 hours after gel application. You may wash the area 4 hours post-application. After washing with soap and water, other individuals who contact your breast will not be affected. If you do not shower, wash the breasts with soap and water using a wash-cloth, and dry, before applying the gel. Please avoid fire, flame or smoking during gel application since the gel contains 60% ethanol which can catch fire.

Instructions to take the capsule: You will take the medication daily orally (by mouth) preferably in the morning at about the same time every day with 8 oz of water.

If you forget either the gel or the capsule in the morning, take it whenever you remember, later in the day, and record this in your study diary.

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. You should mark any missed or skipped doses in this diary, as well as any side effects that you are experiencing.

You will take the capsule and gel for 4 weeks/28 days (± 7 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. 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.

On the day of your surgery, the baseline tests will be repeated. These tests include a questionnaire, 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 3 1/2 tablespoons or 56 mL will be collected). You will fast starting at midnight before this visit. The study diary will be reviewed and collected and all unused study medication will be collected at this visit, but 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 telapristone treatment.

Follow up
The follow up visit for the study will be at your post-op visit in the clinic to review your progress. The last contact will be one month 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. This final phone call will last approximately 15minutes.

What are some of the possible risks and discomforts?
Your involvement in this study may involve the following risks:

Risks Associated with telapristone
The telapristone used in this study may affect how different parts of your body work, such as your liver. The study doctor will be testing your blood and 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 and will not have side effects.
- Some side effects may go away soon and some may last longer.

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.

Below are the most common side effects that we know about telapristone, most of which are mild. 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. There is an approximately 1 in 5 chance that you will experience one or more of these side effects while you are on the study drug.

Common (out of every 100 women receiving the drug, more than 20 may experience):

- Menstrual period that is absent or abnormal
- Hot flushes
- Joint aches and pain

Occasional (out of every 100 women receiving the drug, from 4 to 20 may experience):

- Endometrial thickening (abnormal overgrowth of the lining of the uterus and the most common symptom is abnormal uterine bleeding),
- Gastrointestinal disorders like nausea and constipation,
- Abdominal pain,
- Headache
- Breast pain

Rare (out of every 100 women receiving the drug, less than 3 may experience

- an abnormal increase in laboratory tests of the liver. This increase has been serious in some patients that have received a dose of 50mg by mouth (4 times the dose in the current study). No serious liver toxicity has been seen with the 12.5mg dose by mouth, which is used in this study. Your liver function will be monitored while you are on the study.

Risks with gel application: there might be irritation to the skin at the site of application.

Blood Collection
There may be pain, swelling, or bruising around the vein where your blood is collected. You may feel dizzy or you may faint. You may get an infection at the place on your body from which the blood is collected.

Tissue sampling from breast: The risks of the needle biopsy procedure include pain (this is mainly from the injection of the numbing medicine), bleeding, bruising of the breast, small lump, or soreness around the needle site. These symptoms are reported in about 3% (1 in 30) of women undergoing the procedure. Firm pressure will be applied to minimize the bruising and bleeding and you should avoid vigorous physical activity and swimming for 3 days. Rarely, some women feel faint for 15 minutes or so and recover spontaneously. You will be in a clinic/hospital setting and immediate care will be provided if needed. There is also a rare chance of infection at the biopsy site.

What do I need to know about reproductive health/sexual activity if I am in this study?
When taken during pregnancy, the effects of telapristone on the developing baby are unknown, including risk of birth defects and effects of drug may not be found before birth. Women who are pregnant, attempting to become pregnant or breastfeeding may not participate in the study.

If sexually active, both women and their male partners should use an effective method of birth control while taking the study drug. Barrier contraceptives (condoms or diaphragm) with spermicide, non-hormonal intrauterine devices (IUD's), Mirena or prior surgical sterilization are examples of safe methods. Hormonal contraceptives such as the birth control pill cannot be used while on this study. If you or your partner become pregnant while taking the study drug, it is important that you tell your study nurse/doctor immediately. You may have to stop the study drug. Other treatment options will be discussed with you if you stop the study drug.

What are the Possible Benefits for Me or Others?
You will not benefit from participating in this research study. The results from this study will provide information that will help scientists to better understand how telapristone and similar drugs work, which could help prevent or treat breast cancer in the future.

Are there any financial costs to being in this study*?*
There will be tests and procedures that are done only for this study and other tests and procedures that are part of your routine medical care (not part of the research).

You will receive telapristone and placebo free of charge for this study. You will also receive research-related tests free of charge, including liver function tests, a baseline pregnancy test (if required), and any tests performed on your blood or tissue for research purposes only.

The cost of your standard medical care will be billed to you or to your health insurance company in the usual way. However, some health insurance plans will not pay the costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular treatment. If your

insurance does not pay, you will be responsible for the charges of your routine medical care.

Will I receive payment for participation in this study?
To compensate for time and inconvenience, you will receive $150 upon completion of study participation when you have completed taking study medication. If you are undergoing mastectomy of the healthy breast and are being asked to complete needle biopsy of that breast, you will receive $300 upon completion of study participation when you have completed taking study medication. If you need to make an extra visit for a pregnancy test, will receive $100 for this visit, in addition to the above payments. The payment will be made in the form of check. Please allow 6-8 weeks time for the check to be mailed to you after the completion of the study.

The Accounting Services at (insert name) will be given your name, address, and Social Security Number in order to issue a check for your study participation. Study payments are considered taxable income and reportable to the IRS. A Form 1099 will be sent to you if your total payments are $600 or more in a calendar year.

What should I do if I am injured as a result of being in this study?
If you become ill or injured as a result of study (medications or procedures), you should seek medical treatment through your doctor or treatment center of choice. You should promptly tell the study doctor about any illness or injury.

The hospital *[university, researchers]* will not pay for medical care required because of a bad outcome resulting from your participation in this research study. This does not keep you from seeking to be paid back for care required because of a bad outcome.

If I have questions or concerns about this research study, whom can I call?
You can call us with your questions or concerns.

If you have any illness or injury during your time on this study, you should call us promptly.

In case of an emergency (Insert name) is in charge of this research study. You can call him/her at (insert contact number) during Monday through Friday, from 9:00 a.m. to 5:00 p.m. You can contact him/her at (insert contact number) during the evenings and weekends.

What are my rights as a research subject?
If you choose to be in this study, you have the right to be treated with respect, including respect for your decision whether or not you wish to continue or stop being in the study. You are free to choose to stop being in the study at any time.

If you choose not to participate in this study or decide to stop participating, you will not suffer any penalty or loss of benefit to which you are entitled. Specifically, your choice not to be in this study will not negatively affect your right to any present or future medical treatment, your class standing (for students enrolled at *X university*), or your present or future employment (for employees at *X* or its affiliates).

Any new findings developed during the course of this research that may affect your willingness to continue in this study will be shared with you.

If you want to speak with someone who is not directly involved in this research, or have questions about your rights as a research subject, please contact the Institutional Review Board (IRB) Office. You can call them at (insert phone number).

Your participation in this study may be ended without your consent by the study doctor for reasons including, but not limited to, the following:

1) if you develop a dangerous side effect;
2) if you do not follow the study doctor's instructions;
3) if you become pregnant; or
4) if the study doctor decides to end the study for other reasons

If you decide to stop your participation in the study, contact the study coordinator. S/he will inform the study doctor so that you may be advised regarding any follow-up care that you may need.

What about my confidentiality and privacy rights?

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number, stored blood and tissue. Your health information we may collect and use for this research includes:

1. All information in a medical record
2. Results of physical examinations
3. Medical history
4. Lab tests, or certain health information indicating or relating to a particular condition as well diaries and questionnaires
5. Records about study medication or drugs

The following groups of people may give the researchers information about you:
All current and previous health care providers, including but not limited to the Northwestern Medical Faculty Foundation (NMFF) and Northwestern Memorial Hospital (NMH).

Once we have the health information listed above, we may share some of this information with the following people. Please note that any research information shared with people outside of Northwestern University and its clinical partners (or affiliates) will not contain your name, address, telephone or social security number or any other direct personal identifier unless disclosure of the direct identifier is required by law [except that such information may be viewed by the Study sponsor and its partners or contractors at the Principal Investigators office]

1. Authorized members of the Northwestern University workforce, who may need to see your information, such as administrative staff members from the Office for Research, Office for Research Integrity and members of the Institutional Review Board (a committee which is responsible for the protection of the rights and welfare of human research subjects),

2. Clinical affiliates, including but not limited the Rehabilitation Institute of Chicago (RIC), Northwestern Medical Faculty Foundation (NMFF), Northwestern Memorial Hospital (NMH), Northwestern Memorial Physicians Group (NMPG), and the Ann & Robert H. Lurie Children's Hospital of Chicago (Lurie Children's). Your participation in this clinical trial will be tracked in an electronic database and may be seen by investigators running other trials that you are enrolled in and by your healthcare providers.

3. Other University research centers and University contractors who are also working on the study,

4. Study monitors and auditors who make sure that the study is being done properly,

5. Pharmaceutical Company (Repros Therapeutics) who is providing support for the study, and that company's contractors and partners.

6. Government agencies and public health authorities, such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS) and National Cancer Institute (NCI).

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

Those persons who get your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission.

The results of this study may also be used for teaching, publications, or presentation at scientific meetings.

Where can I get more information?

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 U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Please note that:

You do not have to sign this consent form. If you do not, it will not affect your treatment by health care providers, or the payment or enrollment in any health plans, or affect your eligibility for benefits. However, you will not be allowed to take part in this research study.

You may change your mind and "take back" (revoke) this consent at any time. Even if you revoke this consent, the Principal Investigator may still use or share health information that was obtained about you before you revoked your consent as needed for the purpose of this study. To revoke your consent for the use of your health information, you must do so in writing to:

(Insert name and contact information)

Unless you revoke your consent, it will not expire.

If you "take back" (revoke) your consent to use any blood or tissue taken for the study, any samples that remain in the bank will no longer be used. Samples or related information that have already been given to or used by the researchers will not be returned.

Optional Sample Collections for Biobanking for Possible Future Studies

Researchers are trying to learn more about breast cancer. The researchers would like to ask your permission to store left over samples obtained during your participation in this study for future use. These are not additional samples that will be collected, but will consist of any material that remains after the tests described for this study have been conducted. If you agree, this blood and tissue will be coded and kept at Northwestern University.

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 in this study, the study doctor for the main study would like to collect tissue, blood, and DNA. 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". All the research tissue samples will be processed and stored in the Pathology Core Facility (Northwestern University, Olsen Pavilion, 8th floor) of the Robert H. Lurie Comprehensive

Cancer Center. All the research blood samples will be processed and stored in Dr. Seema Khan's Laboratory. Both Biobanks are being run by Northwestern University and supported by the National Cancer Institute.

What is involved?

Your samples and some related information will be sent to a researcher for use in the study described above. Remaining samples may be stored in the Biobanks, along with samples from other people who take part. The samples will be kept until they are used up or no longer needed. Qualified researchers can submit a request to use the materials stored in the Biobanks. A research committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Neither you nor your study doctor will be notified if/when research is conducted using your samples.

What are the possible risks?

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. 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.

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 Northwestern University staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom Northwestern University 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.

These reports will not be put in your health record. Sometimes blood and tissue are used for genetic research (about diseases that are passed on in families). Even if your blood and tissue are used for this kind of research, the results will not be put into your health records.

What are the possible benefits?

You will not benefit from taking part. Reports about the research done with your blood and tissue will not be given to you.

Are there any costs or payments?

There will be no cost to you for any blood and tissue collected and stored. Your blood and tissue samples will be used only for research and will not be sold. You will not be paid for allowing your left-over blood and tissue to be used in research. 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 and phone number)* 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, Seema Khan, at 312-503-2112.

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

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

YES NO

This is the end of the section about optional studies.

Consent Summary:
I have read this consent form and the research study has been explained to me. I have been given time to ask questions, and have been told whom to contact if I have more questions. I agree to be in the research study described above. A copy of the consent form will be provided to me after I sign it.
A copy of this signed consent document, information about this study and the results of any test or procedure done may be included in my medical record and may be seen by my insurance company.

_____ _____
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		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	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.
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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B

Study Diary Part 1

Protocol Number
Subject ID Name
Site Start date End Date

Dear research participant,
Thank you for participation in this study. It is important that you fill in the diary every day and bring it with you to your visit just before your surgery. If you do not have the diary with you, continue to record information on note paper and copy it onto the diary afterwards. If you lose the diary, please contact the study staff immediately to get another diary.

Please remember to apply the gel every morning. Each bottle should be used for only 22 days (even if some gel remains). Your cooperation in this study is greatly appreciated. Bring all bottles back with you on the last day before surgery, whether gel remains in the bottle or not.

Bottle number 1	Date of first use	Date of last use
Bottle number 2	Date of first use	Date of last use

Study Coordinator's Signature: _____ Date: _____

APPENDIX C

Study Diary Part 2

Protocol Number
Subject ID Name
Site Start date End Date

Day 1 of Study Date

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? yes no

Did you take your study pill as directed yes no

Did you take any over-the-counter medications, or supplements? If yes, please list below.

Medication name	dose	Number of times taken	Reason for taking

Study Coordinator's Signature/Date

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

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

GEL APPLICATION INSTRUCTIONS:

1. Flammable until dry: do not apply near fire, flame or heat

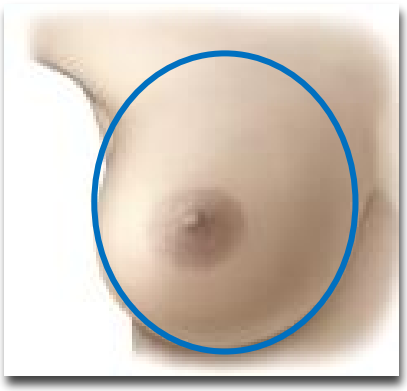
2. Apply the gel to your own breasts after bathing, in the morning and at approximately the same time each day.

3. To apply, remove the cap from the dispenser, which is like a hand-lotion dispenser. When you use a new pump for the first time, you must prime it by pressing the pump down 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). You should prime the pump only the first time that you use it.

4. Place the pump on a table or counter so that when you push on the pump, you can be sure to push down all the way. Place the palm of your other hand under the pump and push down fully once to get a full dose of the gel in your hand. Be sure to press down completely on the pump and release it completely to dispense one dose of gel. This is just like your hand-lotion dispenser, but you need to push all the way down for a full dose.

5. Apply **one dose of gel to each breast** (dosage is indicated on the bottle label). Start applying at the center of the breast and work outwards until you reach the edge of the breast. Do not apply more or less than one dose to each breast. Be sure to release the pump completely after you dispense gel..

6. **Spread the gel evenly over the entire surface of your breast** along the upper border (just under the collar-bone) to the outer edge in line with the armpit, underneath the breast to the crease below the breast, and along the inner border of the breast, to the edge of the breast bone. Do not rub it in, just let it dry. This will take about a minute. The study staff will outline the area of the breast to which the gel is to be applied.



7. Wash your hands with soap and water immediately after applying the gel.

8. 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). Do not expose your bare breasts to sunlight unless the gel has been washed off; if you plan to swim or sunbathe, you can wash off the gel 4 hours after application, but not before.

9. After use, replace the cap on the bottle.

INSTRUCTIONS FOR USE

1. Do not wash your breasts or immerse in water (shower, bathe, swim), for at least 4 hours following application of the gel. If you plan to bathe or swim in the morning, delay application of the gel that day until after water exposure. If you regularly swim or exercise, then shower in the morning, it is better to apply the gel afterwards, after your shower.

2. 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). Skin contact is fine after the breasts have been washed. Do not wash the breast skin for at least 4 hours after gel application. If you anticipate contact of breast skin with others within the next 4 hours, delay the application until after the contact.

3. Do not apply any other cream, lotion or moisturizer for at least 4 hours after gel application. If cream, lotion, or moisturizer is used between applications, wash the breast skin before applying the next dose.

WASHING INSTRUCTIONS:

1. It is best to apply **after bathing or showering, each morning**.

2. If you have not bathed or showered since the last dose, and it is now time for another dose, please wash the breast with soap and water before application of the next dose. If you applied lotion to your breast skin after the last dose, that should be washed off too, before application of the next dose. To wash, you can apply soap to the breasts with your hands and remove with a washcloth, or any other way you find convenient. The point is to not accumulate multiple doses of the gel on the skin without washing in between.

RECOMMENDATIONS:

1. If you forget to apply the gel in the morning, apply it whenever you remember, later in the day, and record this in your study diary.

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

3. Gel may appear cloudy for your first application – this is normal.

4. Please note on each bottle/dispenser label, the first and last day of use. Do not discard the pill bottles and the gel dispensers, they need to be returned to us on the day of surgery.

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 bottle and notify your study coordinator immediately.

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

STORAGE INSTRUCTIONS:

1. Keep your gel dispensers at room temperature. **Do not refrigerate.**

2. Keep the gel diepensers and pills 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 capsule and 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 take the capsule or 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: you institution may or may not allow for FedEx/UPS/courier delivery of the capsules and gel dispensers. If you are having the capsules and 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.