Study Title: A PHASE I/II STUDY OF DERMAPRAZOLE FOR RADIATION DERMATITIS IN POST-MASTECTOMY BREAST CANCER PATIENTS (TOPAZ)

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A PHASE I/II STUDY OF DERMAPRAZOLE FOR RADIATION DERMATITIS IN POST-MASTECTOMY BREAST CANCER PATIENTS (TOPAZ)

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1. PROTOCOL SUMMARY

Radiotherapy is a mainstay of treatment in breast cancer treatment, in the adjuvant setting. Radiation dermatitis occurs in up to 65% of these patients; currently, there is no standard of care for this treatment-related toxicity. The aim of this study is to investigate the safety and tolerability (Phase I) and preliminary efficacy (Phase II) of prophylactic esomeprazole cream (termed “Dermaprazole”) in patients who require radiation for breast cancer in the adjuvant setting.

All study participants will begin using Dermaprazole for 1-2 weeks prior to receiving radiation. During the CT Simulation, study participants will be instructed to apply Dermaprazole in a “patch test” area - an area of the chest outside of the field of radiation. This is to assess for immediate skin reactions including itching, irritation and allergy. If there are no immediate allergic reactions at the conclusion of the simulation visit, the study participant will be instructed to apply the cream in the patch test for 2-4 days to assess for contact dermatitis and if no itching or rash at that time (evaluation will be conducted via phone call). Patients will be questioned regarding any visible skin changes or irritation (itching, peeling, scaling), and patients responding in the affirmative will be asked to present for clinic visit or send photographs for visual classification according to the scale outlines in Table 1 below. Skin reactions matching a score of 3 will be evaluated with a second clinic visit between 2 to 7 days after initial application. Any skin reactions of score 4 or 5 at final assessment will be deemed to be positive for allergic contact dermatitis, and patients will be deemed positive for allergic contact dermatitis.

If no concern for allergic or contact dermatitis, patients will be advised to begin application in the area that will be irradiated in addition to the patch test area for 1-2 weeks until the radiation starts. Patients will be instructed to discontinue use immediately if any local skin reactions occur.

Table 1: Grading System for Patch Test Reactions (immediate allergic reactions and delayed contact dermatitis)

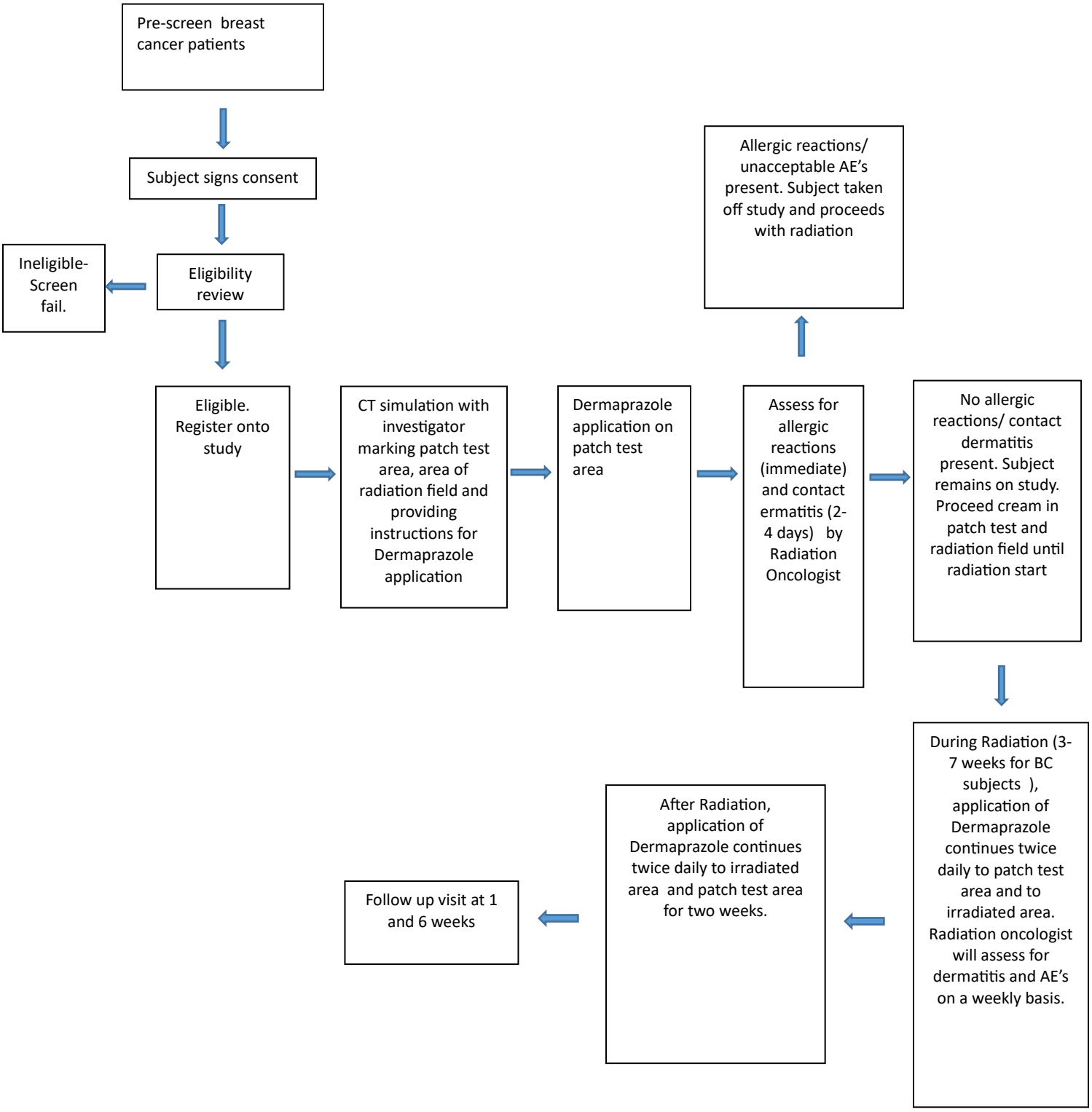
Score	Description
1	Negative reaction
2	Doubtful reaction, faint macular erythema
3	Weak, non-vesicular reaction with erythema, infiltration, and papules
4	Strong vesicular reaction with erythema, infiltration, and papules
5	Spreading bullous reaction

For the subset of patients determined to have allergic reactions or contact dermatitis, a second patch test will be conducted to determine whether the allergy is to dermaprazole itself or the vehicle used in the topical formulation. A topical application of the vehicle without the active ingredient (dermaprazole) will be applied to the patient’s forearm. Similar to the above protocol, patients will be assessed at 30 minutes and 2-4 days after topical application (in clinic for first assessment, phone call for second). Patients with skin reactions will send photos or present for clinic follow up and reactions greater than 3 in the scale above will be interpreted to mean the patient has an allergic reaction to the vehicle rather than dermaprazole. Alternative formulations with different carrier vehicles will be considered in the future, but for the purposes of this phase I/II study, such patients will be excluded.

After allergic reaction testing/contact dermatitis evaluation is complete, patients begin radiation and will continue daily application both in the patch test area and in the radiation field during radiotherapy, and for 2 weeks after they complete their radiation treatment. During the entire time while using the Dermaprazole, study participants will be evaluated for adverse events such as contact dermatitis in the patch test area as well as radiation dermatitis within the treatment field. All participants will be followed for 1 month after the final Dermaprazole application.

Two dose levels of Dermaprazole (1% and 2%) will be evaluated in the combination Phase I/II dose escalation/de-escalation BOIN design study evaluating preliminary efficacy at the Maximum Feasible Dose (MFD). The Dermaprazole will be initiated at a dose of 1% and escalated to 2% as appropriate based on the number of adverse events. A Dose Limiting Toxicity (DLT) will be any of the following: a) any **greater than** Grade 2 skin toxicity outside the radiation field (Macules/ papules covering 10-30% of the area with or without symptoms of pruritus, burning, tightness) b) any **greater than** Grade 2 radiation dermatitis (Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema) within the treatment field that is probably or definitely related to Dermaprazole. Dermatitis will be evaluated by a radiation oncologist on a weekly basis using the Common Terminology Criteria for Adverse Events (CTCAE) V5.0 criteria. Patient reported quality of life will be evaluated using a validated survey instrument called SkinDex16.

2. STUDY SCHEMA



3. OBJECTIVES

3.1. Primary Objective

3.1.1. Phase I - Safety

To define the safety and maximum feasible dose (MFD) of Dermaprazole in preventing radiation dermatitis for breast cancer patients. This will be evaluated by application of the cream:

1. Prior to, during and after radiation via patch testing to assess for baseline irritant or contact dermatitis.
2. Prior to, during and after radiation via monitoring treatment field receiving prophylactic Dermaprazole to assess for adverse events.

3.1.2 Phase II Efficacy

1. To evaluate clinically bothersome radiation dermatitis rate for breast cancer patients at maximum feasible dose.

3.2. Secondary Objective

1. To assess the rate of grade 2 or higher acute radiation dermatitis.
2. To assess time to occurrence of grade 2 or higher acute radiation dermatitis.
3. To assess the time to healing if grade 2 or higher acute radiation dermatitis develops.
4. To assess patient-reported quality of life outcomes using SkinDex16.
5. To assess radiation adherence; defined as the number of missed radiation treatments due to skin toxicity. Dose over time, i.e., total days from start of treatment to end of treatment will be recorded.

4. BACKGROUND AND RATIONALE

4.1. Study Disease

Radiation therapy (RT) is a mainstay of treatment in breast cancer (BC). Quantitatively, up to 95% of patients receiving RT experience some degree of acute radiation-induced dermatitis (RD). About 20-25% of patients develop severe skin reaction including: moist desquamation, ulceration, necrosis and scarring. About 65% of patients with breast cancer experience clinically significant radiation dermatitis (Grade II or higher) during treatment.[i] There is no gold standard treatment for RD and the use of corticosteroids is associated with considerable side effects including skin atrophy, further breakdown of skin integrity and possible superinfection.

Currently, the recommendation regarding RD is to use alcohol-free and fragrance-free water emollients (such as Aquaphor) after radiotherapy is administered to protect the skin barrier, though this has not been proven to be effective in preventing RD toxicity. Open wounds are often treated with Silvadene or other antibiotic cream due to concern of superinfection. If infection develops, topical and/or oral antibiotics are considered; if itching develops,

corticosteroids or antihistamines are considered. No topical ointments are allowed at least 2 hours prior to radiation due to theoretical increase in skin dose due to “bolus effect”, or the dose distribution being brought higher onto the epidermis due to unaccounted for tissue-equivalent material. However, there is no data to substantiate these common practices and RD is often thought to be an unavoidable consequence of radiotherapy.

Given the unmet medical need for therapies to address radiation dermatitis, our basic science team has been investigating candidate drugs to mitigate the problem. After screening a library of 130,000 compounds, we found that proton pump inhibitors (PPIs) have previously unrecognized yet potent effect in modulating inflammation and fibrosis induced by chemotherapy and ionizing radiation.

Radiation-induced dermatitis occurs in most patients following radiotherapy. According to the NCI-CTCAE and the RTOG toxicity scoring system, mild dermatitis (Grade I) is characterized by mild redness (erythema), epidermal thickening (hyperkeratosis) or dry desquamation and appears shortly after initiation of RT. [ii] [iii] [iv] Moderate dermatitis (Grade II) occurs within two weeks of radiotherapy and manifests painful and intense erythema, loss of hair from the root (epilation), blisters and edema. Of note, the presence of grade II toxicity is generally regarded as clinically significant toxicity. In severe dermatitis (Grade III and IV), moist desquamation occurs excessively and may lead to persistent inflammation, full-thickness skin necrosis and severely painful ulceration that is prone to infection. The acute effects occur almost immediately at radiation doses between 2 and 40 Gray (2-40 Gy) whereas chronic effects occur several months-to-years after exposure to high radiation doses (>45 Gy) and typical skin changes include atrophy, scarring and spider veins (telangiectasia).[v]

The effect of radiation on the skin is in part due to its effect in promoting the production of highly reactive free radicals that are involved in DNA damage.[vi] [vii] [viii] In addition, radiation upregulates inflammatory cytokines (e.g. TNFα, IL1β, IL6, VCAM1 and ICAM1) that can exacerbate sustained injury and compromise skin integrity. [ix] [x] [xi] About one third of breast cancer patients are profoundly affected by clinically relevant dermatitis (Grade II or higher) due to the development of serious skin reactions described above. The predictive risk factors for prolonged effect of severe dermatitis include age, sex, body mass index (BMI), site and volume of the body exposed to radiation, use of concurrent radiosensitizing drugs or chemotherapeutic regimen and presence of diabetes, autoimmune disorders, or genetic mutations.[xii] [xiii] [xiv] Severe dermatitis can result in discontinuation of the radiotherapy before completion of the prescribed dose and threatens the relapse of underlying cancer. [xv] [xvi] [xvii]

4.2. Rationale for Dermaprazole

Several non-pharmacological and pharmacological approaches have been evaluated for the prevention, treatment or management of severe radiation dermatitis. [xviii] - [xix] However, the use of many of these agents is not recommended either due to lack of efficacy or insufficient clinical data. Meanwhile, various pharmacological agents have been developed to mitigate radiation dermatitis. Of these, topical corticosteroids are the archetype. Among the steroid-based products, mometasone furoate (0.1%), betamethasone (0.1%) and hydrocortisone (1%) are extensively studied in clinical trials.[xx] - [xxi]However, the use of topical corticosteroid for radiation dermatitis is limited due to the risk of cutaneous atrophy, stretch marks (striae), allergy, secondary skin infection (e.g. cellulitis, candidiasis). In obese and diabetic patients (as in our population), the

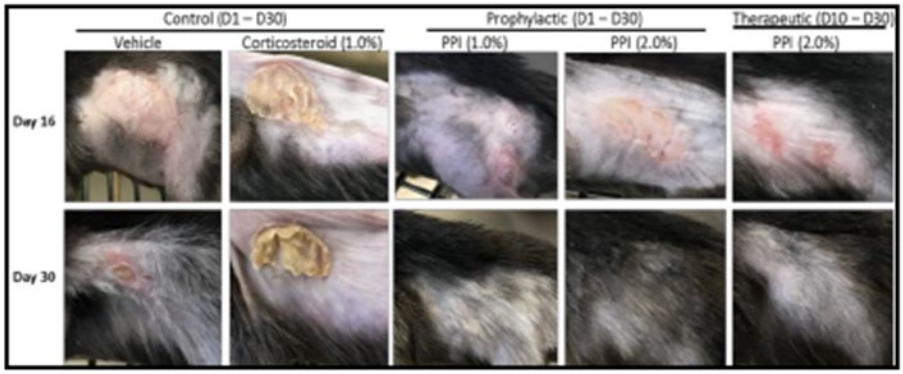
prophylactic use of corticosteroids leads to increased rates of candida infection with risk of bacterial superinfection if open wound develops during radiotherapy. Accordingly, there is an unmet clinical need to develop safe and effective products.

Our earlier research discovered that PPIs directly regulate the nitric oxide synthase (NOS) pathway via inhibition of the inducible isoform (iNOS) which is significantly expressed in skin cells in response to inflammatory stimuli as in radiation or chemotherapy.[xxii - xxiii] The nitric oxide (NO) catalyzed by iNOS is short-lived and rapidly oxidizes to peroxynitrite (OONO-); a highly reactive molecule that is involved in the generation of nitrotyrosine; a more stable product that is involved in tissue inflammation. Additionally, a number of inflammatory cytokines released during chemoRT are known to enhance NO production. We found that regulation of the iNOS pathway by PPIs is due to their direct interaction with dimethylarginine dimethylaminohydrolase (DDAH), an enzyme that breaks down asymmetric dimethylarginine (ADMA, the endogenous and competitive NOS inhibitor). Subsequently, we showed that esomeprazole is the most potent PPI that controls the pro-inflammatory enzyme DDAH and many classic pro-inflammatory cytokines (such as NFKB, TNFα, IL1β, IL6, VCAM1, and ICAM1) that are reported to be pathologically upregulated in radiation dermatitis.[xxiv]

Recently, supported by Dan L Duncan Comprehensive Cancer Center Pilot Grant, we reformulated esomeprazole sodium powder into a Lipoderm®-based equivalent to 2% active esomeprazole cream (Dermaprazole) that retained the inherent biologic antioxidant, anti-inflammatory, and anti-fibrotic effects of esomeprazole. This was executed by mixing esomeprazole powder with propylene glycol, and Lipoderm as a transdermal base. Notably, our LC-MS study showed that a relatively low strength of Dermaprazole (1-2%) was highly stable and biologically active in modulating esomeprazole target genes.

Accordingly, we evaluated the efficacy of this formulation in a mouse model of RD in a prophylactic and therapeutic settings in the presence of corticosteroid control. Remarkably, our study showed that while 90% of the animals in the corticosteroid group had grade II or higher dermatitis, topical PPI mitigated the radiation dermatitis in most of the animals with only 20% showing grade II or higher radiation dermatitis (Figure 1). We evaluated 1% and 2% strengths further after our efficacy studies showed lack of superiority at >2% Dermaprazole strengths.

Figure 1: Mouse Model of RD: Representative Digital photography Data

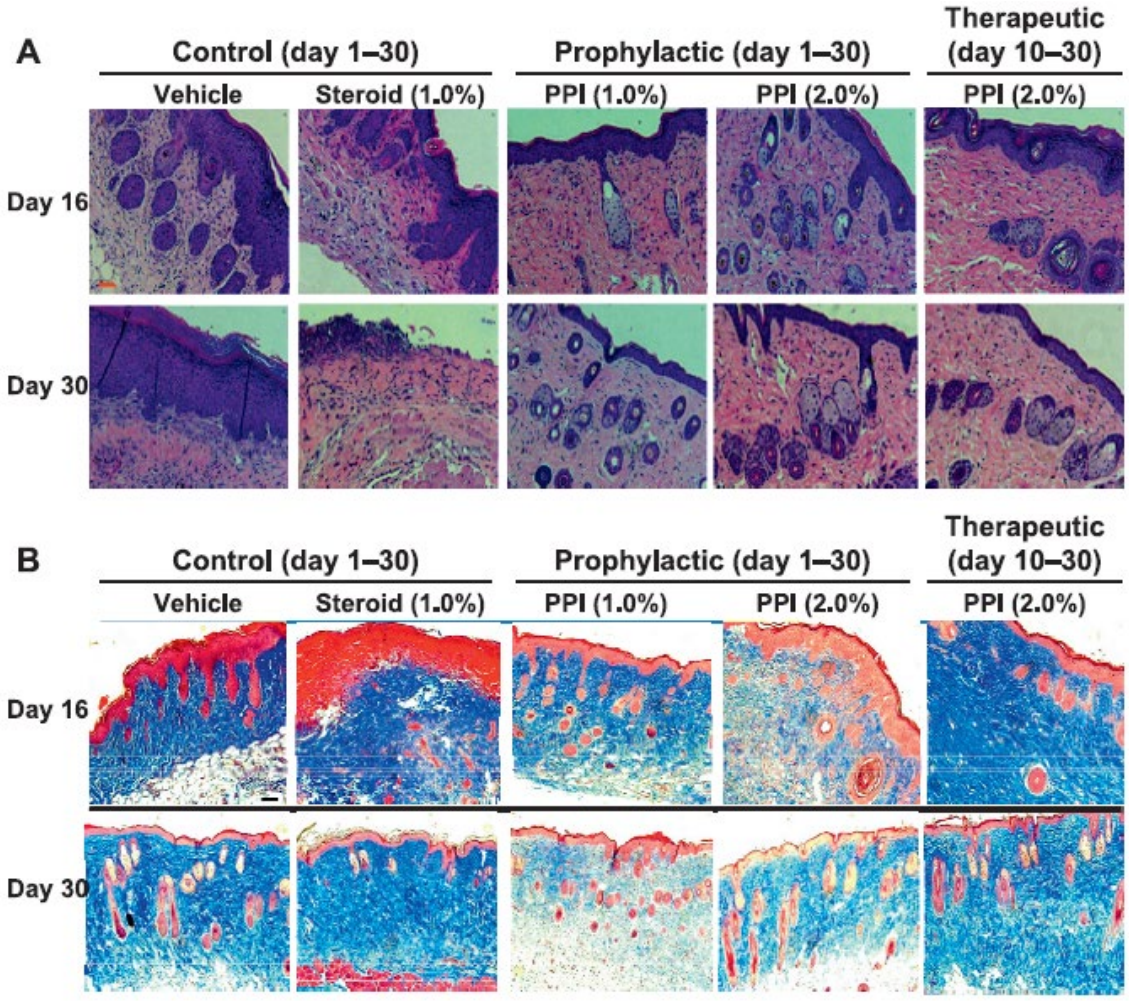


Topical application of Dermaprazole improves skin appearance in a model of radiation-induced dermal inflammation and fibrosis. Mice were irradiated (2 x 15Gy) on Days 0 and Day 7. Dermaprazole, vehicle (base) cream, or the corticosteroid hydrocortisone were applied once a day on the indicated days (D1-D30 for prophylactic

group and D10-D30 for therapeutic group). Representative images from the same animals are shown (n=10 animals/group).

We also observed that Dermaprazole use led to significantly lower ulceration, necrosis, inflammation, and fibrosis (Figure 2). Overall, most Dermaprazole treated animals showed complete or nearly complete closure of the wounds within 4 weeks following exposure to ionizing radiation.

Figure 2: Mouse Model of RD: Representative Histological Data



Panel A: H&E stained irradiated skin tissue from an animal model of RD treated with vehicle cream, Dermaprazole or hydrocortisone once daily on the indicated days.
Panel B: Masson's trichrome stain was used to assess the degree of dermal fibrosis in the animal model of RD. Increased collagen deposition (blue stain) is observed in the vehicle and steroid groups. Treatment with Dermaprazole inhibited collagen deposition. Representative images are shown at 20X magnification. The scale bar shown in the vehicle group at day 16 is 50 um and applies to all the images.

5. PATIENT SELECTION

5.1. Inclusion Criteria

a) Women with breast cancer, treated with ipsilateral*.
   ____ i) Simple (total) mastectomy OR
   ____ ii) Modified radical mastectomy, OR
   ____ iii) Radical mastectomy
   ____ iv) Segmental mastectomy
   ____ v) Skin Sparing/nipple sparing mastectomy
   *tissue expanders or implants or tissue flaps are acceptable

b) Histological diagnosis of invasive ductal or lobular carcinoma (diagnosed within 2 years of enrollment).

c) Planned to receive adjuvant chest wall radiation of at least 40Gy or higher biologically equivalent dose (BED).

d) Age 18 years or older.

e) Women of childbearing potential (any woman with menses in the last 12 months) must agree to pregnancy testing and contraceptive use throughout the study period. Testing consists of human chorionic gonadotropin (HCG) urine testing, which if suspected to be falsely positive may be confirmed by ultrasound. If ultrasound is negative, patient is considered not pregnant and eligible for inclusion in the study. In addition to routine contraception method such as barrier devices, hormonal methods, and intrauterine devices, heterosexual celibacy, and surgical sterility (hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or a partner with history of vasectomy) is considered acceptable. If a celibate patient chooses to become sexually active during the study period, she must use one of the listed methods of contraception throughout the study period.

f) Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.

g) Written Informed Consent.

h) History and Physical within 12 weeks of enrollment.

5.2. Exclusion Criteria

a) Prior chest wall radiotherapy.

b) Any serious medical condition or illness that would preclude the safe administration of the study drug including, but not limited to: active infection, symptomatic heart failure, unstable angina, psychiatric illness or social situations that would limit compliance with treatment.

c) Concurrent chemotherapy.

d) Biopsy-proven skin (epidermal) involvement or positive margins after surgery.

e) Open wound at time of consultation, or delayed surgical wound healing as defined as open wound >8 weeks post-op.

f) Known active collagen vascular disease such as systemic lupus erythematous, scleroderma or dermatomyositis.

g) Allergy or sensitivity to proton pump inhibitors.

h) Pregnancy or breast feeding.

i) Use of clopidrogrel, St. John's Wort, rifampin, or methotrexate.

d)

6. STUDY DRUG

Dermaprazole is a repurposed drug derived from esomeprazole powder and compounded into a topical formulation. The parent compound, esomeprazole is a widely available, safe and tolerable FDA-approved prescription (since 2001) and over-the-counter antacid medication (since 2014). Esomeprazole is not chemically modified in any form, and the excipients are compliant with the standards of the Professional Compounding Centers of America (PCCA).

6.1. Formulation and Preparation

Dermaprazole will be formulated at a strength equivalent to either 1% or 2% active esomeprazole powder in a topical liposomal-based cream in collaboration with a compounding Pharmacy. The compounding pharmacy is accredited by the Pharmacy Compounding Accreditation Board (PCAB) and fully compliant with USP <795>, USP <797> and USP <71> compounding standards. The name, address and contact information of the compounding pharmacy is:

Village Compounding Pharmacy
975 Corbindale Rd,
Houston TX, 77024
P: 713-464-5069
F: 713-464-5099
email bpylant@villagecompounding.com

6.2. Stability

Timetable studies performed in a standard container unit dose system indicate that under refrigerated conditions (2°C to 8°C), potency as well as total aerobic microbial, yeast, and mold counts are maintained within USP method specifications for at least 45 days. For purposes of this study, product must be used within 60 days of compounding. Dermaprazole cream is stable for at least one week at controlled temperature (36-46F) after it has been opened. However, in order to facilitate correct patient utilization of the product and to eliminate oxidation, we plan to utilize single-use syringes.

6.3. Packing, Shipping and Labeling by Compounding Pharmacy

Once the subject is registered onto the study, the study PI will notify the study biostatistician to ascertain the dose level needed and to verify the order. The compounding pharmacy will be notified of the dose level by the study PI and will then compound the cream at either 1% or 2% strength. Once compounded, Dermaprazole will be packaged into prefilled 5 mL single use syringes by the Compounding pharmacy. Each syringe will be labeled with the date it was compounded and the strength. The Compounding pharmacy will ship the Dermaprazole cream in syringes to the Investigational Pharmacy for dispensation to the study subject. Orders can only be shipped on a Tuesday from the compounding pharmacy and will be received by the Investigational pharmacy on a Wednesday.

6.4. Drug Storage, Disposal, Dispensation and use

The study drug should be stored under refrigerated conditions (36-46℉).

Prescription paper orders with patient instructions have been created for the main site and the affiliate site. After the order is signed by the ordering physician, it will be sent via fax and/or email to the Investigational Pharmacy.

The Investigational Pharmacy will label the syringes received from the Compounding pharmacy for the subjects. Study participants will be given syringes in a cold bag or on ice. Subjects will be instructed to store the cream under refrigerated conditions (36-46℉) and will be instructed to return all used and unused syringes at each visit. All syringes will be disposed of in the medical waste bins at either Baylor St Luke's or Smith Clinic after accountability is done. For any unused syringes that are not dispensed to the subject, the investigational pharmacist will perform IP accountability, generate certificates of disposal, and dispose of the syringes in the pharmacy biohazard waste bin. Dermaprazole syringes will be dispensed at the CT simulation visit for use until first radiation treatment, again at the beginning of external beam, and at the end of treatment for two additional weeks of Dermaprazole application after radiation treatment is over. One syringe is enough for one application and subjects will need to apply dermaprazole twice a day. Since two syringes will be used in a day, sufficient number syringes will be dispensed at the first weekly visit for use during radiation treatment (depending on the number of planned radiation treatments), and twenty eight syringes will be dispensed on the last day/week of radiation treatment for the additional two weeks of Dermaprazole application post radiation treatment.

7. TREATMENT/INTERVENTION PLAN

7.1. Radiotherapy Administration

Radiation treatment will be given per standard of care. The treatments outlined below reflect current clinic/hospital practices. Deviations from these treatments should be minimized but are at the discretion of the treating investigator, and do not constitute a protocol violation. Any delay in radiotherapy after simulation past 16 days will lead to removal from the study and discontinuation of the cream.

Dose, Prescription, and Planning: Breast radiation will be given as per standard of care. Ipsilateral chest wall radiation of 40- 50 Gy will be permitted with or without boost up to 66 Gy. Radiation is to be delivered at 1.8-3Gy per day, 5 days per week, for 3 to 7 weeks using three-dimensional technique. Intensity modulated radiotherapy (IMRT) or other experimental skin-sparing techniques are not permitted. Chest wall radiation must be delivered using medial and lateral tangential fields. Separate posterior axillary boost, supraclavicular field, and internal mammary field are permitted as long as all "hot spots" on skin are as per standard guidelines. All beams must be matched exactly at field edge.

Definition of "Chest Wall": Per RTOG Breast Atlas, the chest wall or breast to be covered by tangential fields is defined cranially as the caudal border of the clavicular head, caudally as loss of radiographically apparent contralateral breast, anteriorly by the skin, posteriorly by the rib-pleural surface, laterally by the mid axillary line, and medially as the sternal-rib junction.

Simulation and Treatment: CT-based simulation and planning must precede treatment. Tissue-equivalent bolus is permitted on protocol per discretion of consulting radiation oncologist. CT-based simulation must be used for treatment planning and weekly x-ray portal images are required to confirm accurate delivery.

7.2. Study Intervention

The sole intervention for this study is prophylactic Dermaprazole cream with monitoring as described below. The radiation and chemotherapy are standard of care. Additional research related components for the study include Quality of Life Survey, and treatment compliance survey which is done during routine visits.

7.2.1. Application prior to Radiation (Patch Test)

At consultation and prior to radiation therapy, patients will be screened for allergy and/or contact reactions using repeat open application ("patch") testing in the contralateral infraclavicular area. The patch test will be outside of the area to be irradiated. A 2x2 cm "patch" area will be marked by the treating physician at the time of CT simulation. The patient will be advised to apply a thin layer of Dermaprazole in the patch area at the time of CT simulation and assessed for immediate allergic reactions. If no allergic reactions occur upon this initial application, the subject will continue to apply the cream for 2 – 4 days in the patch area. The coordinator or treating physician will then call the patient to ask if any itching/rash in the patch area, and if not then the patient will be advised to begin the cream in the patch area and in the planned radiation field until the start of their radiation therapy. Patients will be instructed to discontinue use immediately if any local skin reactions occur.

If a patient experiences a local skin reaction to the initial application of dermaprazole, the agent will be applied a second time to the contralateral chest wall followed by assessment of the skin at 30 mins (to assess for immediate/anaphylactic reactions), and 2-4 days after application (for delayed hypersensitivity reactions). The first assessment will be conducted at the time of clinic visit, the latter assessment will be conducted via phone call. Patients will be questioned regarding any visible skin changes or irritation (itching, peeling, scaling), and patients responding in the affirmative will be asked to present for clinic visit or send photographs for visual classification according to the scale outlines in table 1 below. Skin reactions matching a score of 3 will be evaluated with a second clinic visit between 2 to 7 days after initial application. Any skin reactions of score 4 or 5 at final assessment will be deemed to be positive for allergic contact dermatitis, and patients will be deemed positive for allergic contact dermatitis.

Table 1: Grading System for Patch Test Reactions (immediate allergic reactions and delayed contact dermatitis)

Score	Description
1	Negative reaction
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4	Strong vesicular reaction with erythema, infiltration, and papules
5	Spreading bullous reaction

For the subset of patients determined to have allergic reactions or contact dermatitis, a second patch test will be conducted to determine whether the allergy is to dermaprazole itself or the vehicle used in the topical formulation. A topical application of the vehicle without the active ingredient (dermaprazole) will be applied to the patient's forearm. Similar to the above protocol, patients will be assessed at 30 minutes and 2-4 days after topical application (in clinic for first assessment, phone call for second). Patients with skin reactions will send photos or present for clinic follow up and reactions greater than 3 in the scale above will be interpreted to mean the patient has an allergic reaction to the vehicle rather than dermaprazole. Alternative formulations with different carrier vehicles will be considered in the future, but for the purposes of this phase I/II study, such patients will be excluded.

During the entire time while using the Dermaprazole, study participants will be evaluated for adverse events such as contact dermatitis in the patch test area as well as radiation dermatitis within the treatment field. All participants will be followed for 1 month after the final Dermaprazole application.

The study PI or co-Investigator (radiation oncologist) will document the patch area at CT simulation. Subjects will be evaluated weekly for adverse events by the study PI or Co-I (radiation oncologist) who will determine if the subject can continue to receive the Dermaprazole cream. Subjects found to have an AE in the radiation field prior to starting treatment will cease dermaprazole and the start of radiation therapy will be delayed to allow for healing. See Section 15.4 for details.

7.2.2. Application During And after Radiation Treatment

All radiation will follow standard practice. Variations (dose adjustments, delays, etc.) that follow standard clinical practice are allowed and are not considered deviations, though these will be recorded to assess for interference. Radiation details such as dose modality, fractionation, as well as total treatment time in days will be recorded in the electronic medical record as per routine practice.

Patients will apply Dermaprazole twice daily to assess the effect on radiation dermatitis. Patients will be instructed to apply a thin layer of the cream along the area exposed to chest wall irradiation (i.e., borders as specified above, plus a one to two inch margin around the irradiated area), starting from the day of simulation, throughout the radiation treatment period, and for two weeks after completion of radiation. Patients will also continue to apply Dermaprazole cream to the contralateral patch test area (for control) during the radiation treatment (RT) period and for the 2 weeks after radiation. Patients who develop open wounds may be prescribed topical or oral antibiotic if indicated per usual practices.

During adjuvant radiation, patients are assessed once every 5 treatments (i.e. weekly, for the duration of radiation treatment [up to 7 weeks]). Using CTCAE v5 criteria, the grade of radiation dermatitis is recorded in the area of radiation treatment by a radiation oncologist. Patients will continue to be clinically monitored in the control area of patch testing for contact/irritant reactions. If severe radiation dermatitis develops, it will be managed per usual care (sterile wound dressings, antibiotics) as per treating physician's discretion.

7.3. Prohibited Medications or Therapies

Prior to entry into the study, subjects must not use the medications and/or procedures specified in Section 5.2.

During the study, subjects must not use the following products:

- clopidrogrel
- St. John's Wort
- rifampin
- methotrexate

7.4. Assessments and Procedures

7.4.1 Baseline and Screening Evaluations

- Written Informed consent
- Review of inclusion/exclusion criteria
- Comprehensive History and Physical Exam
- ECOG Performance Status
- Outside Radiation Field Dermatitis form
- SkinDex16 questionnaire at consultation
- Other tests may be obtained at the investigator's discretion. Invasive interventions or procedures will be minimized and will only be performed with the approval of the principal investigator.

7.4.2 CT Simulation

- Radiation Oncologist will mark the patch test area, area of radiation field, and provide instructions to study participant about applying Dermaprazole to these areas prior to radiation treatment.
- Patient will apply Dermaprazole cream to the patch test area at CT simulation and the Radiation Oncologist will check for immediate allergic reactions (development of prutitis, urticarial, or rash after application) at the time of first application.
- Distribution of Dermaprazole syringes for two weeks

Application of Dermaprazole to patch test area (BID) by study participant for 2-4 days. Patient will be called by study coordinator or treating physician to ask if any itching or rash in the patch test area. If not, patient will be advised to begin the application of Dermaprazole to irradiated area (BID) by study participant until the start of radiation.

7.4.3 On Treatment: weekly during radiation treatment (i.e. one visit per 5 treatments), up to 7 weeks

- Evaluation for delayed type hypersensitivity reaction prior to start of radiation
- Focused exam by Radiation Oncologist
- Outside Radiation Field Dermatitis Form
- Weekly Evaluation questionnaire
- SkinDex 16 questionnaire
- Adverse event evaluation and DLT evaluation, including evaluation of radiation dermatitis with note of components (erythema, epilation, fibrosis, etc.,)
- Radiation dermatitis assessment done weekly by Radiation Oncologist
- Distribution of Dermaprazole syringes (Week 1)
- Application of Dermaprazole to patch test area (BID) by study participant
- Application of Dermaprazole to irradiated area (BID) by study participant

7.4.4 Two weeks post radiation treatment

- Application of Dermaprazole to patch test area (BID) by study participant
- Application of Dermaprazole to irradiated area (BID) by study participant
- Distribution of Dermaprazole syringes (on last day of radiation)

7.4.5 Post-Treatment follow-up

Subjects will be followed for a total of 6 weeks after completion of radiation to assess intervention-related safety.

Follow up Visit (6 weeks after completion of all radiation therapy, +/- 7 days)

- Focused exam
- Outside Radiation Field Dermatitis Form
- Weekly Evaluation questionnaire
- SkinDex 16 questionnaire
- Adverse event and DLT evaluation, including evaluation of radiation dermatitis with note of components (erythema, epilation, fibrosis, etc.,)
- Radiation dermatitis assessment by Radiation Oncologist

7.4.6 Table 1: Calendar of Study Assessments & Testing

	Screening/ Baseline	CT simulation	Phone Call to document no delayed type allergic reaction	Before First Radiation Treatment (can be on start day of radiation)	Weekly During radiation treatment	Follow/ up 6 weeks after radiation treatment [b]
SCREENING						
Written Informed Consent	X					
Eligibility (Inclusion/Exclusion Criteria)	X					
CLINICAL						
Comprehensive History and Physical Exam [c]	X					
Focused Exam (Radiation Oncologist)				X	X	X
ECOG Performance Status	X					
Pregnancy test	X					
ASSESSMENTS						
Outside Radiation Field Dermatitis Form	X			X	X	X
Allergic reaction evaluation		X	X	X	X	
Weekly evaluation questionnaire				X	X	X
SkinDex16 questionnaire	X			X	X	X
Adverse Events [d]				X	X	X
DLT assessment [d]				X	X	X
CTCAE Version 5 Dermatitis (Radiation Oncologist)				X	X	X
CTCAE Version 5						X
EXPERIMENTAL TREATMENT						
Distribution of Dermaprazole syringes [e]		X		X		
Dermaprazole Patch Test (applied BID)		X		X	X	

Dermaprazole in Irradiated Area (applied BID)		X		X	X	

(a) Radiation treatment may be anywhere from 3 to 7 weeks for a study participant. Weekly assessments to be performed within +/- 3 days.

(b) Weekly assessments to be completed within +/- 7 days during the 1 month follow-up period.

(c) Comprehensive history and physical exam to be completed within 12 weeks of enrollment.

(d) Adverse events will be assessed by the Radiation Oncologist. If a DLT occurs, the DLT form will be filled out.

(e) Dermaprazole syringes will be dispensed at the CT simulation visit to be applied during radiation treatment, and at the end of treatment for two additional weeks of Dermaprazole application after radiation treatment is over. One syringe is enough for one application and subjects would need to apply dermaprazole twice a day. Two syringes will be used in a day, so sufficient syringes will be dispensed at the CT simulation for two weeks, then at the beginning of radiation for the duration of radiation treatment, and twenty eight syringes will be dispensed on the last day/week of radiation treatment for the additional two weeks of Dermaprazole application post radiation treatment.

7.4.7. Criteria for Removal from Study Intervention (Dermaprazole)

Intervention is defined as Dermaprazole cream but not the radiotherapy itself. Subjects may be removed from study treatment (Dermaprazole) for any of the following:

a. Inter-current illness that prevents further administration of treatment,
b. Unacceptable adverse event(s), DLT, or suspected allergy,
c. Patient's decision to withdraw from the study treatment,
d. Deterioration in the patient's condition rendering the patient unacceptable for further treatment in the judgment of the investigator. This may include, but is not limited to: progression in comorbid diseases that become more life threatening, deterioration of performance status unrelated to the trial, or any other situation in which continuation of treatment on this study would be detrimental to the health of the patient at the discretion of the treating physician.
e. Any delay in radiotherapy after simulation past 16 days

Subjects should complete the post-treatment visits if they are removed from study treatment before completion.

8. TREATMENT EVALUATION

A general history and physical examination must be done within 12 weeks prior to registration. Pathologic diagnosis of the tumor must be within 2 years prior to registration.

After completion of adjuvant radiation, patients will be seen at one month for a toxicity check and clinical evaluation of skin by a radiation oncologist.

9. MEASUREMENT OF EFFECT

Rates and severity of radiation dermatitis will be determined by the radiation oncologist and defined using NCI Common Terminology Criteria for Adverse Events (CTCAE version 5) for dermatitis radiation. In particular, the individual components of radiation dermatitis will be recorded: erythema, desquamation, edema, bleeding, skin necrosis and skin ulceration. These will be used in assessment weekly by the treating radiation oncologist as well as during review by the dermatologist after completion of treatment (i.e. the dermatologist will not know where the patient is in their treatment course).

Compliance to intervention and use of other topical agents will be documented qualitatively during weekly assessments. The effect of the intervention on quality of life will be evaluated using SkinDex 16 (Appendix 1).

10. STATISTICAL CONSIDERATIONS

10.1. Study Design

This is a combination Phase I/II trial of Dermaprazole to determine the maximum feasible dose (MFD) among two dose levels (topical intervention at 1% and 2%), and to evaluate the disease

response rate at the MFD. Dose-limiting toxicity will be ascertained using the Common Terminology Criteria for Adverse Events v5.0 (See Appendix 2). The primary outcome for the phase II component will be the rate of clinically bothersome radiation dermatitis. No individual dose modifications will be made. If a patient develops toxicity, the study drug will be discontinued.

This study will use Bayesian Optimal Interval (BOIN) design to provide monitoring of toxicity beyond the Phase I cohort. BOIN design has algorithmic escalation/de-escalation rules easy to implement like a traditional 3+3 design but allows for specification of the target DLT rate, different size cohorts, is more likely to correctly select the MFD and allocate more patients to the MFD and expands consistent toxicity monitoring to the entire cohort. BOIN design with a target DLT rate of 0.3 and cohort size of 3 begins exactly in the same fashion as the "3+3" allowing for the implemented design change in early stages. Calculations were done using R package BOIN.[xxv]

10.2. Sample Size/Accrual Rate

Phase I component considerations.

The study is designed to escalate the dose if the observed toxicity rate at the current dose is <= 0.2365, and de-escalate the dose if the observed toxicity rate at the current dose is >= 0.3585. If the observed toxicity rate is between 0.2365 and 0.3585, additional patients will be treated at the current dose. For cohorts of size 3, the decision boundaries are shown in Tables 2a and 2b. Two doses levels of Dermaprazole (1% and 2%) are evaluated, beginning with the lower dose for each disease site.*

Table 2a: DLT Regulation of Dose Escalation and De-Escalation:

Number of patients treated	3	6	9	12	15	18	21	24	27	30	33	36+1
Escalate*** if number of DLT <=	0	1	2	2	3	4	4	5	6	7	8	9
Treat additional 3 pts on current dose if number of DLT=	1	2	3	3,4	4,5	5,6	5-7	6-8	7-9	8-10	9-11	10-12
Deescalate* if number of DLT >=	2	3	4	5	6	7	8	9	10	11	12	13
Eliminate** if number of DLT >=	3	4	5	7	8	9	10	11	12	13	14	15

* At the lowest dose level, if the recommendation is to de-escalate AND the dose level has not been eliminated from consideration, 3 additional pts will be accrued at the same dose level; otherwise, the trial will stop. Last cohorts have 5 and 4 patients to reach the required sample sizes.

** Eliminate dose level and all higher doses from further use.
*** At the time of the design change the study escalated to the highest dose and will continue enrolling additional patients at this dose unless de-escalation is recommended.

Phase II component considerations.
Sample size was estimated using historical rates of radiation dermatitis which are well established in the literature based on dose and target. Relevant to our study, the rate of clinically bothersome radiation dermatitis in our historical breast cancer patients is 65%. Based on our preclinical study with animal and human skin models, we expect a 20% absolute reduction in the proportion of patients with clinically meaningful radiation dermatitis from historical controls (i.e. we expect to see 45% of the patients in the breast cancer arm with clinically meaningful radiation dermatitis To attain the power of 80%, with a one-sided test, alpha (α) of 0.05, and assuming no attrition, our final sample size has to be 37 patients in the breast cancer cohort. The treatment is considered effective if 25 or more of breast cancer patients are responding to therapy as defined as not having grade 2 or greater radiation dermatitis (i.e <25 of 37 breast cancer patients having grade 2 or higher skin toxicity).

Total study sample size.
This study will enroll at least 3 patients at each dose level and 37 breast cancer patients at the MFD level. Each time a cohort of 3 DLT evaluable subjects in the Breast group (or sooner if there are safety concerns) is complete, the study statistician will be notified and will review the data and make a recommendation as to whether to escalate, de-escalate or keep them at the same dose level. Participants will continue to be enrolled and monitored for toxicity according to the rules specified above until all efficacy evaluable participants have been enrolled to any single dose level. For the purposes of this intent-to-treat analysis, a subject is considered evaluable for the primary endpoint after completing at least one day of Dermaprazole treatment with radiotherapy. It is expected that all dose levels will be safe and assuming that even the highest dose level has a DLT rate substantially lower than the target (i.e. <10%), which is what we expect. We will have more than 99% chance of selecting the top dose level at the end of the trial. In this case the total number of patients enrolled would be 40 (3+37). Per our current database, the clinic is treating approximately 40 eligible patients per year. As such, accrual should take no longer than 12 months with planned completion of follow up within 6 months of completion. This is a conservative estimate given that some patients may decline to partake in a study for an investigational drug. These calculations are based on assumption that clinic is treating 40 eligible patients per year. Assuming this is overestimating true availability by 20% and this study would require an additional 6 months to complete enrollment for a total study duration of 24 months.

10.3. Statistical Analysis

Primary Analysis: The primary objective is to determine the safety and MFD of topical Dermaprazole cream in preventing radiation dermatitis. This will be evaluated in two ways: by assessment of baseline irritant (as described in section 15.1) or contact dermatitis as part of the patch test (outside of the irradiated field) to before/during radiation.

Evaluation of DLT (as described in section 15.1.4) of Dermaprazole when in the field of radiotherapy. The dose enrolling according to rules described in Table 2b will be determined to be the MFD. The posterior DLT rate and 95% confidence interval will be estimated using all toxicity evaluable cases.

The rates of clinically bothersome radiation dermatitis in our historical breast cancer patients will be calculated along with 95% confidence intervals and compared with historical rates using One Sample Test of Proportions.

Secondary Analysis: The proportion of patients with maximum observed acute grade 2, 3, and 4 skin reactions (as described in Section 9) will be expressed in percentage. Time to develop grade 2, 3, and 4 radiation reactions and time to healing if grade 2 or higher acute radiation dermatitis develops will be described using Kaplan Meier curves. The median of the peak score of each QOL component will be reported. Radiation compliance will be reported in terms of number of missed treatments due to skin toxicity. Descriptive and summary statistics will be computed for demographic and clinical data of all subjects enrolled in the study considering other factors that could potentially affect the severity of radiation dermatitis, such as age, radiation technique, concurrent chemotherapy, smoking or tobacco use, body mass index, comorbidities, and ECOG performance status, will be reported

11. DATA MANAGEMENT

All subject data will be abstracted from the electronic medical record available for each enrolled patient and documented in an electronic database created for this study using OnCore, the proprietary, HIPAA-compliant software used by Dan L Duncan Comprehensive Cancer Center for these purposes. Each subject will be assigned a study code to facilitate subsequent coding of the data set once complete. This number will be used to link any primary source data stored in the HIPAA-compliant electronic database used for this study.

12. QUALITY ASSURANCE

All Dan L Duncan Comprehensive Cancer Center treatment studies conducted at BCM-affiliated institutions are subject to a formal, comprehensive source document review through the Quality Assurance program. The primary purpose of Quality Assurance (QA) activity is to evaluate and ensure that the conduct of clinical trials complies with all federal regulations and International Conference on Harmonization Good Clinical Practices. A secondary purpose of QA activity is to ensure that standard operating procedures (SOPs) establishing the processes used for conduct of clinical trials, and data collection and management related to clinical trials are appropriately defined, implemented, and being followed, and to improve and refine the processes established in the SOPs when necessary. Adherence to protocol compliance, eligibility verification, informed consent verification, and data accuracy will be evaluated by the PI. The PI will provide radiation therapy quality control. All cases will be discussed and reviewed by a group of board certified radiation oncologists within the department.

All handling and storage once delivered from the compounding pharmacy will be shipped to the investigational pharmacies at Smith Clinic and Baylor St. Luke's respectively and will be dispensed by the investigational pharmacies. Airtight and light-protected syringes have been chosen to minimize product oxidation and contamination. Please note the compounding pharmacy will ship Dermaprazole on ice, and the investigational pharmacy will maintain the drug in a refrigerated environment. Additional information is provided in Section 6 of the protocol.

13. DATA AND SAFETY MONITORING

This study will be reviewed regularly by the Data Review Committee (DRC) of the Dan L Duncan Comprehensive Cancer Center. The DRC will monitor the study for progress and enrollment, toxicities, adverse events, and soundness of data, in accordance with the DDLCCC Data and Safety Monitoring Plan and the DRC SOP.
The frequency of data review by the DRC is determined by the Protocol Review and Monitoring Committee at the time of initial review and is based on the level of risk to the study subjects. Review will occur at a minimum of once each year after activation.

Data Quality Assurance

This study will be monitored by the DLDCCC Quality Assurance program for study conduct and quality of data, according to CTSU policy. Protocol compliance, eligibility verification, informed consent procedure verification, and data accuracy will be monitored.

14. PROTECTION OF HUMAN SUBJECTS

This study will protect the rights of human subjects. No additional financial cost will be incurred by the patients. Efforts will be made to protect patient confidentiality. The study is completely voluntary and patients will be able to withdraw at any time.

The study will be conducted in compliance with Food and Drug Administration (FDA) regulations, the ethical principles of the Declaration of Helsinki concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964 and amendments 2013), the International Council for Harmonization (ICH) – Good Clinical Practice (GCP) Guidelines as currently amended, and all applicable standard operating procedures (SOPs) of the Baylor College of Medicine.

15. ADVERSE EVENTS

15.1. Adverse Event (AE) Definition

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

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

15.2. Serious adverse event (SAE) Definition

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

- is fatal;
- is life-threatening (immediate risk of death);
- requires or prolongs inpatient hospitalization for ≥24 hours;
- results in persistent or significant disability/incapacity to conduct normal life functions;
- constitutes a congenital anomaly or birth defect; or

• Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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

• routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
• elective or pre-planned treatment for a pre-existing condition that did not worsen, or that is required per protocol
• emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
• respite care
• Death due to disease progression unless attributable to the study drug(s).

Events listed above may be reported to a participating site's local IRB, if required per local regulations.

15.3. Relationship of Adverse Events to the Study Intervention

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. The Investigator is to classify the drug relationship of an AE according to the definitions outlined below:

Definitely: The AE is *clearly* related to the study treatment.

Probably: The AE is *likely* related to the study treatment.

Possibly: The AE *may* be related to the study treatment.

Unlikely: The AE is *doubtfully* related to the study treatment.

Unrelated: The AE is clearly *NOT* related to the study treatment.

15.4. Adverse Event (AE) Grading scale

15.4.1. Rash Maculo-Papular outside the radiated field

- **Grade 1:** Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)
- **Grade 2:** Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL; rash covering > 30% BSA with or without mild symptoms
- **Grade 3:** Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self care ADL
- **Grade 4:** n/a

Any reaction outside the radiated field ≥Grade 2 at any point will lead to immediate halting of Dermaprazole use in that patient and reported as an adverse event and a dose limiting toxicity.

The patch test area will be used to assist in deciding the likelihood of Dermaprazole causing the adverse event.

15.4.2. Adverse events inside the Radiation Field:

Adverse events are at the discretion of the managing radiation oncologist. All adverse events must state if they are definitely, probably, possibly, unlikely, or unrelated to the Dermaprazole intervention. All adverse events are in terms of CTCAE V 5.0 .

The following definitions will be used for radiation dermatitis:

- **Grade 1**: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
  - Faint erythema or dry desquamation
- **Grade 2**: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
  - Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema
- **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
  - Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion
- **Grade 4**: Life-threatening consequences; urgent intervention indicated.
  - Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated
- **Grade 5**: Death related to radiation dermatitis.

AEs will be graded in accordance with the NCI Common Terminology Criteria for Adverse Events v 5. (CTCAE) http://ctep.cancer.gov/reporting/ctc.html. If not described in the NCI-CTCAE, AEs will be graded according to their severity using the following criteria (38).

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptoms or Signs	Asymptomatic or mild	Moderate limiting age appropriate instrumental ADLs	Severe, not immediately life threatening. Disabling, limiting self-care ADLs	Life threatening	Death related to AE

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Intervention	Observation	Local or non-invasive intervention	Hospitalization	Urgent/ emergent intervention	Death related to intervention

The AE collection/reporting period will begin with the first day of application of Dermaprazole and will end 30 days after radiation. AEs after study registration but prior to the first day of study treatment will be captured as baseline symptoms present at the start of study.

Acute and late designations will be defined by the timing of occurrence from treatment.

- Acute toxicity will be defined as events occurring during or within 30 days of treatment completion.
- Late toxicity will be defined as events occurring or persisting ≥30 days from treatment completion.

15.5. Dose Limiting Toxicity (DLT):

A DLT is defined as any of the following:

1. Any ≥Grade 2 skin toxicity events **outside** the radiation field.
2. Any >Grade 2 radiation dermatitis **inside** the radiation field that is *probably* or *definitely* related to Dermaprazole. (AE Attribution will be at the discretion of the study PI/Co-I).
3. Any Grade greater than or equal to 4 radiation dermatitis inside the radiation field.
4. A DLT will be detected from the first day of treatment to 1 month after the end of radiation. Any skin reaction ≥Grade 2 will lead to immediate halting of Dermaprazole use in that patient and reported as an adverse event and a dose limiting toxicity. The patch test area will be used to assist in deciding the likelihood of Dermaprazole causing the adverse event. Patients not completing the evaluation period for acute toxicity will be considered not evaluable and be replaced.

Note: All patients will be followed for safety until the end of the trial; in an unlikely event of detecting a late Grade 4 skin toxicity, the study will be halted to consider dose de-escalation or may be stopped.

15.6. Potential Risks/Discomforts

Dermaprazole: The interventional cream is not yet tested in humans and reactions *in* vivo (especially in patients experiencing radiation dermatitis) are not yet known. Possible side effects include allergy or infection. Given the efficacy and lack of toxicity in pre-clinical studies, it is unlikely that the interventional cream would lead to worsened rates of radiation dermatitis and skin integrity, though this is a possibility. Please also refer to the Investigator's Brochure for Dermaprazole.

Adverse events of Special Interest:

The systemic exposure of Dermaprazole is not yet known; therefore, weekly monitoring for clinical signs or symptoms that may be evident of systemic toxicity (e.g., acute interstitial nephritis, C. dificile associated diarrhea, bone fracture, new onset cutaneous and systemic lupus erythematosus) will be required.

15.7. Adverse Event Reporting Requirements:

The AE collection/reporting period will begin with the first day of treatment with Dermaprazole.

New AEs and SAEs that are ongoing at the end of the radiation will be followed for 30 days, unless they have resolved earlier.

All adverse events will be recorded on the appropriate study-specific case report form (CRFs).

15.7.1. The AE description will include the nature of the experience, the date of onset, the resolution date, the severity of each sign or symptom reported using the NCI-CTCAE (version 5.0), the seriousness of the event, the potential relationship to study treatment, the course of action taken, and the outcome of the experience.

15.7.2 If an adverse event meets all of the elements below, it should be reported to the IRB within 5 working days of the event:

a) suggests that the research places one or more participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized; and

b) is unexpected/unanticipated (in terms of nature, severity, or frequency); and

c) is possibly, probably or definitely related to the participation in the research procedures (an event is “related to the research procedures” if in the opinion of the principal investigator, it was more likely than not to be caused by the research procedures or if it is more likely than not that the event affects the rights and welfare of current participants).

15.7.3 Any Adverse event that is unexpected, serious, and possibly/probably/definitely related to the study should be reported to the review committee (DRC) within 15 calendar days of knowledge of event. Adverse events that are reported should be sent to the DLDCCC Patient Safety Officer (PSO) at dldcc-pso@bcm.edu by the PI and study team. The PSO will review and distribute the report to the DRC Chairs and members and send any correspondence back to the PI.

15.7.4 For studies in which the IND is held by a DLDCCC investigator, any event that is reported to the FDA should also be reported to the DRC at the same time.

15.7.5 All serious adverse events should be communicated to the principal investigator within 24-48 hours.

15.7.6 Unexpected serious adverse events believed to be definitely, probably, or possibly related to the medications will be reported to the Food and Drug Administration via MedWatch within 7 days of the Investigator becoming aware of the occurrence of the event.

15.7.7 Serious adverse events that are an unanticipated problem should be reported to the IRB within 5 days of knowledge

15.7.8 Follow up information pertaining to a previously submitted IND Safety Report will be submitted as soon as available and no later than 15 calendar days after sponsor's awareness of the information.

15.8. Management of AEs and Impact on Treatment

15.8.1 Expected mild/moderate Grade 1 adverse events inside or outside the radiation field that are either possibly related or unrelated to the investigational product will be managed conservatively by the treating physician.

15.8.2 Unexpected or serious adverse events will be managed on a case by case basis at the discretion of the treating Investigator in coordination with the study team. Emergent face-to-face evaluation within 48 hours will be sought for each suspected intervention-related serious adverse effect.

15.8.3 Adverse events possibly, probably, or definitely related to Dermaprazole will prompt result in discontinuation of the study treatment (Dermaprazole cream). If the AE occurs within the planned radiation field prior to the start of radiation, the start of radiation will be held until the AE resolves (~2 weeks). If the AE occurs after the start of radiation, the radiation will continue as scheduled unless Grade 4 toxicity occurs, in which case delay to allow for healing is permitted. Any changes to radiation treatment will be per routine clinical care. If severe (≥Grade 3) radiation dermatitis develops it will be managed per usual care (sterile wound dressings, antibiotics) as per treating physician's discretion.

16.0 Pregnancy

Pregnancy testing will be performed at screening/baseline prior to study enrollment for women of childbearing age as part of the standard of care procedure for receiving radiation therapy and to ensure the subject meets study eligibility. Pregnant patients will be excluded from the study since they will not be able to receive radiation and will meet one of the exclusion criterions.

APPENDIX 1. SKINDEX16 FORMS IN ENGLISH & SPANISH

THESE QUESTIONS CONCERN THE SKIN CONDITION WHICH HAS BOTHERED YOU THE MOST DURING THE PAST WEEK

During the past week, how often have you been bothered by:	Never Bothered ↓			•			Always Bothered ↓
1. Your skin condition **itching**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2. Your skin condition **burning** or **stinging**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3. Your skin condition **hurting**. . . .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4. Your skin condition **being irritated** .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5. The **persistence / reoccurrence** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6. **Worry** about your skin condition (For example: that it will spread, get worse, scar, be unpredictable, etc).	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7. The **appearance** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8. **Frustration** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9. **Embarrassment** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10. **Being annoyed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11. **Feeling depressed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12. The effects of your skin condition on your **interactions with others** ..... (For example: interactions with family, friends, close relationships, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13. The effects of your skin condition on your **desire to be with people**	☐0	☐1	☐2	☐3	☐4	☐5	☐6

14.	Your skin condition making it hard to **show affection**	☐$_0$	☐$_1$	☐$_2$	☐$_3$	☐$_4$	☐$_5$	☐$_6$
15.	The effects of your skin condition on your **daily activities**	☐$_0$	☐$_1$	☐$_2$	☐$_3$	☐$_4$	☐$_5$	☐$_6$
16.	Your skin condition making it hard to **work or do what you enjoy**	☐$_0$	☐$_1$	☐$_2$	☐$_3$	☐$_4$	☐$_5$	☐$_6$

Have you answered every item? **Yes ☐** **No ☐**

ESTAS PREGUNTAS SE RELACIONAN CON LA AFECCIÓN EN LA PIEL QUE MÁS LE HA MOLESTADO DURANTE LOS ÚLTIMOS 7 DÍAS

Durante los últimos 7 días, ¿con qué frecuencia le ha molestado…?	Nunca me molestó ↓			•			Siempre me molestó ↓
1. La **picazón** en la afección en la piel . .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2. El **ardor** o **escozor** en la afección en la piel	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3. El **dolor** en la afección en la piel . . .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4. La **irritación** en la afección en la piel .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5. La **persistencia / recurrencia** de la afección en la piel	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6. La **preocupación** por la afección en la piel (Por ejemplo: de que se extenderá, empeorará, dejará cicatriz, sea impredecible, etc.) . .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7. El **aspecto** de la afección en la piel . .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8. La **frustración** por la afección en la piel .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9. La **vergüenza** por la afección en la piel .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10. **Sentirse fastidiado** por la afección en la piel	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11. **Sentirse deprimido** por la afección en la piel	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12. Los efectos de la afección en la piel en sus **relaciones con los demás** (Por ejemplo: relaciones con su familia, amigos, relaciones cercanas, etc.)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13. Los efectos de la afección en la piel en su **deseo de estar con otras personas** .	☐0	☐1	☐2	☐3	☐4	☐5	☐6

14.	Que la afección en la piel le dificulte **demostrar afecto**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
15.	Los efectos de la afección en la piel en sus **actividades diarias**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
16.	Que la afección en la piel le dificulte **trabajar o hacer lo que disfruta** . . .	☐0	☐1	☐2	☐3	☐4	☐5	☐6

¿Ha respondido cada pregunta? **Sí ☐** **No ☐**

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