COVER PAGE

Official Study Title: A Phase II Clinical Trial of Dermaprazole Cream for Radiation Dermatitis in Head and Neck Cancer Patients (CTMS# 20-0147)

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Protocol Version 12 dated 5/15/24

Summary of Changes

Cover Page
Updated cover with current version change.
Reason: Administrative change
Principal Investigator
Change in PI from Timothy Wagner, MD to Shraddha Dalwadi, MD, MBA
Reason: current PI is leaving the institution

A PHASE II CLINICAL TRIAL OF DERMAPRAZOLE CREAM FOR RADIATION DERMATITIS IN HEAD AND NECK CANCER PATIENTS

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1 Protocol Summary and Schema

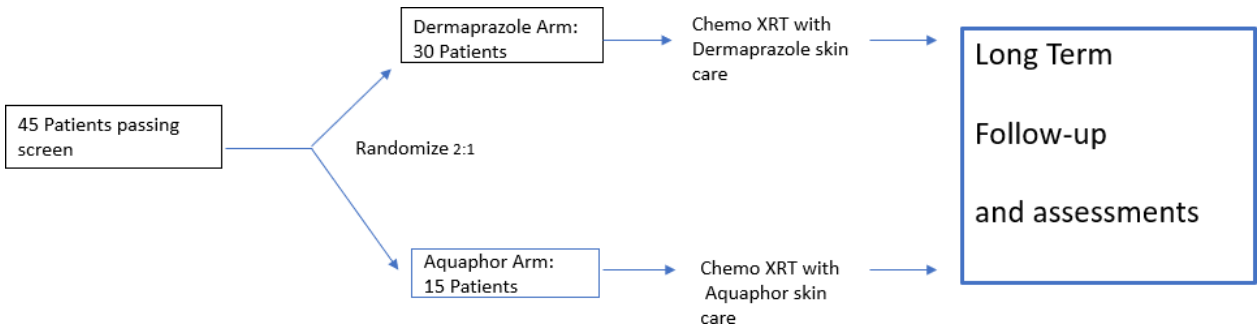
Quantitatively, up to 95% of patients receiving radiation therapy (RT) experience radiation dermatitis (RD) with 20-25% of patients developing severe skin reaction including moist desquamation, ulceration, necrosis, and scarring (R. J. Chan, 2014). There is no gold standard treatment for RD. In this study, we seek to conduct a pilot clinical study to evaluate the safety and efficacy of a reformulated proton pump inhibitor (PPI) cream (Dermaprazole) in head and neck cancer (HNC) patients.

This conviction stems from our extensive preclinical study that demonstrated pleiotropic beneficial effects of PPIs in regulating tissue inflammation and fibrosis induced by chemotherapy or ionizing radiation. Our most recent data in a mouse model of RD shows that PPIs have remarkable effect in protecting the skin from the harmful effects of ionizing radiation. Primarily, we aim to evaluate the safety and tolerability of Dermaprazole cream in HNC patients at risk of developing RD. This study will consist of 2 arms: arm 1 consists of 30 HNC patients who will be using Dermaprazole twice daily while arm 2 consists of 15 HNC patients using Aquaphor, the current clinical standard of care.

We will assess for treatment-related adverse effects including burning, itching, tenderness, rash, and any other local or systemic allergic reactions. In addition, we will collect patient- reported quality of life questionnaire (skindex16) throughout the treatment period and during the follow up period. Furthermore, inflammatory markers including CRP, TNFa, IL-1b, and IL-6 will be drawn, pre-treatment, in the last week of treatment, and post-treatment. If found safe and effective, our product has the potential to dramatically impact clinical practice by significantly decreasing treatment-related morbidity and allowing adherence to the prescribed dose of RT which may otherwise be interrupted because of severe dermatitis.

We will track the dose delivered to the skin in the treatment planning system and repeat a simulation in the last week of therapy to assess the accuracy of this tracking and possible RD correlation with updated dosimetry from the new scan.

STUDY SCHEMA



2 OBJECTIVES

2.1 Safety/Efficacy

2.1.1 Primary Objective

A. Determine if objectively lower rates of significant radiation dermatitis occur with Dermaprazole for HNC patients receiving radiation when compared to patients receiving Aquaphor. An objective measure will be tabulated: the rate of clinically significant (CTCAE version 5 grade 2 or higher) radiation dermatitis. This measure will be reported weekly during treatment by both the treating radiation oncologist and blinded review by a board-certified dermatologist via medical photography.

2.1.2 Secondary Objectives

2.2.2.1
To assess the highest grade of CTCAE version 5 radiation dermatitis during radiation treatment

2.2.2.2
To assess the time to occurrence of CTCAE version 5 grade 2 or higher acute radiation dermatitis.

2.2.2.3
To assess the time to healing if CTCAE version 5 grade 2 or higher acute radiation dermatitis develops.

2.2.2.4
To evaluate quality of life via acute and long-term symptoms and symptom scores utilizing the SkinDex16 scoring system.

2.2.2.5
To evaluate the threshold dose at which RD appears in either arm, utilizing skin dose tracking structures (V20 to V80 in 5 Gy increments reaching skin shell contours of “skin minus 3 millimeters” and “skin minus 5 millimeters”)

2.2.2.6
To evaluate the threshold dose at which RD appears in either arm, using the same metrics as in 2.2.2.5, but with a new simulation scan in the last week of radiotherapy

2.2.2.7

To evaluate the effect of dermaprazole on inflammatory markers: CRP, TNFa, IL-1b, IL-6, by measuring values before, during, and after treatment. We expect this to give further evidence for the mechanism of action of dermaprazole.

3 BACKGROUND AND RATIONALE

3.1 Study Disease

Radiation dermatitis is an expected complication of radiotherapy that can lead to worse patient-reported quality of life during treatment and worse cosmesis, particularly in obese patients. Patients within the Bexar County Health System are more likely to have risk factors associated with radiation dermatitis, including obesity and diabetes. While our mostly low socioeconomic status patients stand to benefit the most from upfront therapy in order to prevent later cancer-related morbidity and mortality, they are also more likely to suffer from acute treatment-related morbidity, including radiation dermatitis.

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 inhibitor (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 (Services, 2017) and RTOG (J. D. Cox, 1995) scoring systems, mild dermatitis (Grade I) is characterized by mild redness (erythema), epidermal thickening (hyperkeratosis) or dry desquamation and appears shortly after initiation of T. 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) (S. R. Hymes, 2006).

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. In addition, radiation upregulates inflammatory cytokines (M. A. Brach, 1993) (e.g., TNFα, IL1β, IL6, VCAM1 and ICAM1) that can exacerbate sustained injury and compromise skin integrity. Almost all head and neck cancer patients are profoundly affected by severe 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 chemotherapy regimen and presence of diabetes, autoimmune disorders, or genetic mutations (F. Meyer). Severe dermatitis can result in discontinuation of the radiotherapy before completion of the prescribed dose and threatens the relapse of underlying cancer (S. A. McCloskey, 2009), (Asa Bostrom, 2001).

3.2 Rationale for Dermaprazole

Several non-pharmacological and pharmacological approaches have been evaluated for the prevention, treatment or management of severe radiation dermatitis (P. Okunieff). 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 (Andrew Hindley, 2014).

While steroid use has been shown in clinical trials to decrease radiation dermatitis, some drawbacks have limited their widespread use including concern regarding: risk of cutaneous atrophy, stretch marks (striae), and secondary skin infection (e.g., cellulitis, candidiasis).

Proton pump inhibitors now have well described anti-inflammatory effects (R. R. Kedika, 2009). 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. 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.

We recently reformulated esomeprazole powder into a Lipoderm®-based cream (Dermaprazole) that retained the inherent biologic antioxidant, anti-inflammatory, and anti-fibrotic effects of esomeprazole. This was executed by weighing of >98.5% purity esomeprazole powder and placing in a mortar, wetting with propylene glycol, and mixing with a transdermal base (i.e., Lipoderm). 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.

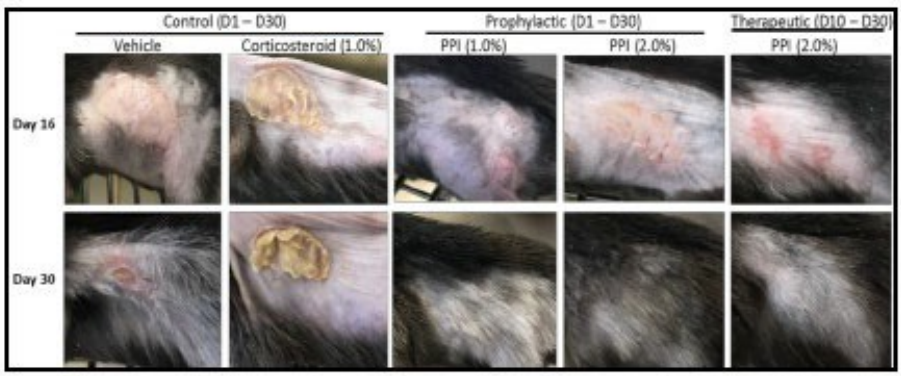


Figure 1: Topical application of Dermaprazole improves skin appearance in a model of radiation-induced dermal inflammation & fibrosis. Mice were irradiated (2 x 15 Gy) on Days 0 & 7. Dermaprazole, vehicle (base) cream, or the corticosteroid hydrocortisone were applied once a day on the indicated days (D1-D30 for prophylactic group & D10-D30 for therapeutic group). Representative images from the same animals are shown (n=10 animals/group).

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 also observed that Dermaprazole use led to significantly lower ulceration, necrosis, inflammation, and fibrosis (Figure 2 and Figure 3). Overall, most Dermaprazole treated animals showed complete or nearly complete closure of the wounds within 4 weeks following exposure to ionizing radiation (Pham, et al., 2019).

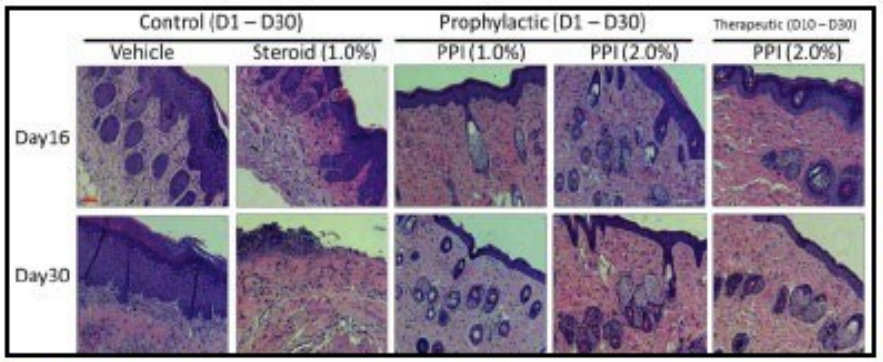


Figure 2: H&E stain showing that topical delivery of Dermaprazole improves skin histology in an animal model of radiation-induced dermal inflammation & fibrosis. Mice were irradiated (2 x 15 Gy) on Days 0 & 7. Dermaprazole, vehicle (base) cream, or the steroid hydrocortisone (1.0%) were applied once a day on the indicated days (D1-D30 for prophylactic group & D10-D30 for therapeutic group). Dermal thickening is observed in the Vehicle group and profound loss of skin integrity is seen by Day 30 in the steroid-treated group. Representative images are shown at 20X mag.

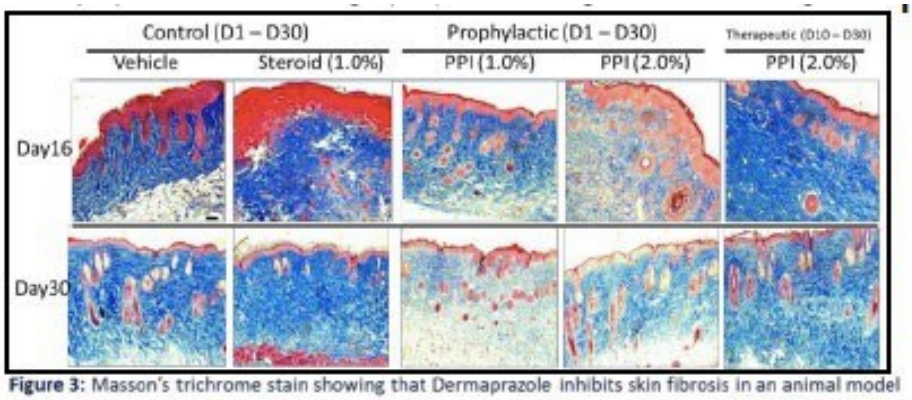


Figure 3: Masson's trichrome stain showing that Dermaprazole inhibits skin fibrosis in an animal model of radiation-induced dermal inflammation & fibrosis. Dermaprazole, vehicle (base) cream, or the steroid hydrocortisone (1.0%) were applied once a day on the indicated days (D1-D30 for prophylactic group & D10-D30 for therapeutic group). Increased collagen deposition (blue stain) & dermal thickening are observed in the vehicle and steroid groups. Representative images are shown at 20X mag.

4 Patient Selection

4.1 Inclusion Criteria

____ a) Patients with head and neck malignancy (including radiation therapy to primary head cancers of any histology and/or neck lymphatics, excluding brain malignancies)

____ b) Biopsy proven diagnosis of head and neck malignancy

____ c) Planned to receive chemoradiation of at least 60Gy

____ d) Age 18 years or older

____ e) Eastern Cooperative Oncology Group (ECOG) performance status 0 - 2

____ f) Written Informed Consent

____ g) History and Physical within 12 weeks of enrollment

____ h) Agree to not take proton pump inhibitors during treatment.

4.2 Exclusion Criteria

____ a) Prior head and neck radiotherapy

____ b) Neoadjuvant chemotherapy

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

____ d) Currently taking proton pump inhibitors. Eligible if discontinues with physician approval.

____ e) Lack of concurrent chemotherapy

____ f) Open wound at time of simulation

____ g) Known autoimmune, connective tissue, or skin disorder; or other theoretical radiosensitivity to include bullous pemphigoid, dermatomyositis, lupus of the skin and scleroderma

____ h) Pregnant or lactating patients

____ i) Concurrent chemotherapy with cetuximab

5 Treatment/intervention plan

5.1 Baseline and Screening Evaluations

- Informed consent
- Review of inclusion/exclusion criteria
- Comprehensive History and Physical Exam (within 12 weeks of registration)
- ECOG Performance Status
- Pregnancy test (for women of child-bearing potential)
- SkinDex16 questionnaire
- Photographic documentation of skin at baseline
- WBC, Hgb, ALT, AST, creatinine and calcium taken from standard care clinical labs drawn closest to consent
- Research Blood Draw to Central Labs: CRP, TNFa, IL-1b, IL-6

5.2 Randomization

Enrolled patients will be randomized in a 2:1 fashion to arm 1 (Dermaprazole) or arm 2 (Aquaphor). A randomization table will be generated by block randomization using a computer program (Sealed Envelope™). This table will be provided to the MCC Investigational Pharmacy prior to start of study enrollment. Each patient that has been enrolled into the study and consented will be allocated to arm 1 or arm 2 according to the sequence of the randomization table.

5.3 Radiotherapy Administration

Dose, Prescription, and Planning: Head and neck radiation of over 60Gy will be permitted with or without boost up to 70Gy (but not higher). Radiation is to be delivered 5 days per week (with exception of weeks with holidays), using intensity-modulated technique.

Simulation and Treatment: CT-based simulation with thermoplastic mask and volumetric planning must precede treatment. Tissue-equivalent bolus is permitted on protocol. Daily cone beam CT images are required to confirm accurate delivery.

Resimulation: Will be done in the last week of radiotherapy to allow for recalculation of beams.

5.4 Intervention

Head and neck radiation treatment 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.

Patients will be managed with twice daily prophylactic use of the proposed intervention (Dermaprazole) topical cream for radiation dermatitis or Aquaphor. The amount of cream or Aquaphor will be 2cc per application and will be measured in pre-filled capped syringes for every application.

The Dermaprazole topical cream will be manufactured by Village Pharmacy in Houston. After the product is compounded it will be overnight shipped to the Mays Cancer Center Pharmacy in insulated shipping containers with temperature monitors. The cream will be

stable for a minimum of 60 days in airtight containers under refrigerated conditions (2^{o} – 8^{o} C) and is stable at controlled room temperature for at least 1 week. Room temperature is 20°C – 25°C (excursions permitted between 15°C and 30°C). A one to three week supply of the cream will be dispensed to the subject during study participation, with the exception that a 2 - 3 week supply will be provided at the time of CT Simulation (determined by the anticipated radiation start date). The same method will be used for the dispensing of the Aquaphor except that refrigeration will not be done in the pharmacy.

Patients will be instructed to apply the cream/Aquaphor along the area exposed to radiation from the day of simulation to two weeks after completion, correlating with the acute phase of radiation dermatitis. If the time from CT Simulation to start of radiation is greater than 2 weeks then the patient may be instructed to start the cream/Aquaphor 2 weeks prior to the anticipated start of radiation rather than at the time of CT Simulation. In the event of a delay from the time of CT simulation to the start of XRT, if the patient has no more than 3 days of interruption of the cream, this will not be considered a violation of the protocol. An interruption longer than 3 days will be considered a minor deviation. Patients who develop moist desquamation in the radiation treatment area may be prescribed a topical antibiotic or other standard of care treatment if indicated. Subjects will be instructed to not use other lotions, creams or any other products in the radiation treatment area without the study doctor's approval.

Neither the Dermaprazole cream or the Aquaphor is expected to be irritating or sensitizing but, subjects will be instructed to inform study personnel if a skin irritation occurs. If eye contact occurs the subject will be instructed to flush the eyes with water while open and to inform study personnel.

5.5 Assessments & Labs During Treatment

Weekly on-treatment assessments are as follows:

- Focused skin exam
- Adverse event/toxicity evaluation, including CTCAE version 5 evaluation of radiation dermatitis with note of components (erythema, epilation, fibrosis, etc)
- SkinDex16 questionnaire
- Photographic documentation of skin reaction with dermatologist's evaluation of CTCAE version 5 from this photography (photography may be discontinued if dermatitis radiation has resolved, or does not occur, at the discretion of the treating investigator or Principal Investigator)
- Compliance diary
- WBC, Hgb, ALT, AST, creatinine and calcium taken from standard care clinical labs
- Research Blood Draw to Central Lab: CRP, TNFa, IL-1b, IL-6 (in the last week of radiation and at 2 weeks after end of radiation)

5.6 Post-Treament Follow-Up

Patients will be followed for up to 60 months after completion of radiation or until death to assess intervention-related tolerance. See study calendar.

1. Month 1 visit (30 days after completion of all radiation therapy, +/- 14 days)
2. Month 3 visit (90 days after completion of all radiation therapy, +/- 28 days)
3. Long Term Follow-Up Visits: Month 6 (M6), Month 9 (M9), Month 12 (M12), Month 18 (M18), Month 24 (M24), Month 36 (M36), Month 48 (M48), and Month 60 (M60) (calculated from completion of all radiation therapy, +/- 28 days)

Assessments include:

- Focused skin exam
- Adverse event/toxicity evaluation, including CTCAE version 5 evaluation of radiation dermatitis with note of components (erythema, epilation, fibrosis, etc)
- SkinDex16 questionnaire
- Photographic documentation of skin reaction with dermatologist's evaluation of CTCAE version 5 from this photography

5.7 Criteria for Removal from Study Treatment

Subjects may be removed from study treatment for any of the following:

- Intercurrent illness that prevents further administration of treatment,
- Patient's decision to withdraw from the study treatment,
- 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.

Early Study Treatment Discontinuation or Study Termination

In accordance with good medical practice, any ongoing study drug-related adverse event present at study termination, including a clinically significant laboratory test abnormality, will be followed until resolved or until the event stabilizes and the overall clinical outcome has been ascertained. Skin photographs will be continued for adverse events which take place in the radiation field until resolution. Adverse events starting up to 30 days after the last dose of study medication may be collected by telephone contact.

6 TREATMENT EVALUATION

6.1 Calendar of Study Assessments & Testing

		Head/Neck RT(Weekly) [a]								
	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7 If needed	Week 8	Week 9[h]
SCREENING										
Written Informed Consent	X									
Inclusion/Exclusion Criteria	X									
PHYSICAL										
Comprehensive History and Physical (ECOG only at Baseline)	X									
Focused Skin Exam (Radiation Oncologist)	X	X	X	X	X	X	X	X		
Medical Photography[d]	X	X	X	X	X	X	X	X		
ASSESSMENTS										
CTCAE Version 5 Radiation Dermatitis (Radiation Oncologist)		X	X	X	X	X	X	X		
CTCAE Version 5 Radiation Dermatitis (Blinded – Dermatologist)		X	X	X	X	X	X	X		
Adverse Events/Toxicity		X	X	X	X	X	X	X		
SkinDex16 Questionnaire	X	X	X	X	X	X	X	X		
TREATMENT										
CT Simulation	X							X[g]		
XRT		X	X	X	X	X	X	X		
Dermaprazole or Aquaphor[c]	X	X	X	X	X	X	X	X	X	X
Compliance Assessment	X[f]	X	X	X	X	X	X	X		X
LAB DRAW										
Serum Pregnancy Test if Woman of Child-Bearing Potential	X									
WBC, Hgb, ALT, AST, creatinine, calcium captured from clinical labs[e]	X	X	X	X	X	X	X	X	X	X
Research Blood Draw to Central Lab: CRP, TNFa, IL-1b, IL-6	X							X[b]		X

(a) Weekly assessments to be performed within +/- 3 days of the end of each week (defined by a period of 5 treatments).
(b) In the last week of radiotherapy, may be different than week 7
(c) See Section 5.3 for detailed instructions regarding Dermaprazole and Aquaphor
(d) Photos will be taken with a Canon EOS Rebel T7 DSLR Camera with 18-55mm Lens. Photos will be uploaded to a protected research folder directly from the camera and the dermatologist will have access to the folder. The photos will be de-identified and labeled with study case number.
(e) WBC, Hgb, ALT, AST, creatinine and calcium data will be obtained from standard care clinical labs during treatment. If labs are not being drawn then they will not be obtained for the study.
(f) Compliance assessment may be performed by telephone by research staff from Baseline to start of XRT
(g) CT Simulation to be done anytime during the last 7 days of radiation treatment
(h) Week 9 is defined as 2 weeks post last radiation treatment ± 5 day

	Post-Treatment Assessment		Long Term Follow-Up Up to 60 months post-tx	
	Month 1 30 days post-tx[i]	Month 3 90 days post-[txj]	Every 3 Months M6, M9, [M12j]	Every year M24, M36, M48, [M60j]
PHYSICAL				
Focused Skin Exam (Radiation Oncologist)	X	X	X	X
Medical Photography	X	X	X	X
ASSESSMENTS				
CTCAE Version 5 Radiation Dermatitis (Radiation Oncologist)	X	X	X	X
CTCAE Version 5 Radiation Dermatitis (Blinded – Dermatologist)	X	X	X	X
Adverse Events/Toxicity	X[k]	X[k]	X[k]	X[k]
SkinDex16	X	X	X	X

Note: Timing of post-treatment visits is from the completion of radiotherapy

(i) To be completed within +/- 14 days

(j) To be completed within +/- 28 days

(k) See Section 10.5.

6.2 Treatment Evaluation

A general history and physical must be done within 12 weeks prior to registration. Pathologic diagnosis of the tumor must be done within 6 months prior to registration.

After completion of chemoradiation, patients will be seen at one, three, six, nine, and twelve months for an adverse events/toxicity check and clinical evaluation of skin by a radiation oncologist during the first year. Subsequent evaluation at two, three, four and five years will be completed to assess for long-term adverse events/toxicities. Medical photographs will be obtained for review by a board-certified dermatologist. See study calendar.

7 MEASUREMENT OF EFFECT

Rates and severity of radiation-related toxicity will be defined using NCI Common Terminology Criteria for Adverse Events version 5. These will be used in assessment by the treating radiation oncologist as well as during blinded review by the dermatologist.

The following definitions will be used:

- 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 adverse event.

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

8 STATISTICAL CONSIDERATIONS

8.1. Study Design/Endpoints

This portion of the study is designed to evaluate toxicity profile and preliminary efficacy of prophylactic Dermaprazole cream for radiation dermatitis in head and neck cancer patients receiving chemoradiation.

The first primary outcome is rates of clinically significant radiation dermatitis as defined as NCI CTCAE version 5 grade 2 or higher. Although not expected, if half our expected enrollment in the Dermaprazole group, 50% or more of patients experience moderate intervention-related toxicity, this treatment regimen will not be considered safe. The trial will be monitored for SAEs and stopped early for safety if two treatment-related grade 3 SAEs are reported or if one treatment-related grade 4-5 SAE is reported at any point of the trial for the Dermaprazole group.

Another primary endpoint will be feasibility, which is defined as the consideration of whether the protocol implementation will be successful in terms of accrual within the expected timeframe, as well as whether patients would comply with the study protocol and necessary data collection is logistically feasible in the clinical setting. To evaluate feasibility, we will measure:

- Accrual rate and summary of causes for non-enrollment
- Percentage of patients compliant with therapy, defined as receiving at least 60Gy to the head and neck while using prophylactic Dermaprazole as directed
- Compliance rate and rate of completion of SkinDex16 forms

All endpoints will be evaluated when the last patient completes their 3 Month follow-up visit, although patients will continue with additional regular follow-up visits as described in the protocol schedule. Since by that point a patient would have completed all treatments, the data would provide accurate estimate of compliance and acute toxicity.

For the study to be considered feasible, all of the following must be true:

- No more than 5 patients fail to complete the treatment regimen due to study drug toxicity
- No more than 15 patients fail to comply to prophylactic Dermaprazole cream application of at least 80%
- Enrollment takes no longer than 24 months, and
- Proportions of analyzable questionnaires at baseline, while on-treatment, and off-treatment during follow-up, and within questionnaires completion rates are no worse than 80%, 80%, and 60% respectively.

8.2 Sample Size/Accrual Rate

Participants will continue to be enrolled and monitored for toxicity per the above criteria until 30 patients in arm 1 and 15 patients in arm 2 have completed the course of head and neck radiation as evaluable patients. Patients will be randomized by computer in a 2:1 fashion. Per our current database, the clinic is treating approximately 60 eligible patients per year. As such, accrual should take no longer than 12 months but will be allowed to extend to up to 24 months without closing the study.

Initial sample size for this pilot study was estimated as if this study was conducted as a phase II study. Sample size calculation was determined using significance/alpha (α) of 0.05, to at least detect a difference in incidence of 45% and power (β) of 80%. In general, rates of clinically bothersome grade II dermatitis in the literature appear to be approximately 65%. Based on our preclinical study with animal and human skin models, we expect 20% of the Dermaprazole arm to have CTCAE grade II or higher RD. Given these values, we calculated our final sample size to be approximately 39 and we aim to enroll 45 subjects.

8.3 Analysis of Primary and Secondary Endpoints

Descriptive and summary statistics will be computed for demographic and clinical data of all subjects enrolled in the study to describe the study sample.

Toxicity will be reported as the frequency of each adverse event according to the CTCAE version 5.0 as well as the grade of each recorded adverse event (38). Generally, adverse events in this system are graded from 1 to 5, with 1 corresponding to either mild or asymptomatic clinical manifestations of toxicity and 5 corresponding to death related to the

adverse event (see Appendix 2). Clinically relevant toxicity will be defined as grade 2 or higher, while severe toxicity will be defined as grade 3 or higher. Acute toxicity will be defined as adverse events that occur during or within 90 days after completing radiation therapy. We will consider this intervention safe if there is a grade 1 toxicity rate of <50%, a grade 2 or higher toxicity rate of <10% and no grade 3 or higher events.

Percentages of patients enrolled per month will be recorded. If the enrollment time exceeds 24 months, the study will be considered not feasible as written. Percentage of patients not enrolled will be summarized by cause.

Quality of life will be measured with the use of SkinDex16 questionnaires filled out by the patient at baseline, throughout treatment, at the completion of radiation treatment, and at each follow up visit subsequently. We will also consider the compliance to questionnaire completion and within questionnaires completion rates. This will be reported as the average proportion of questions within each form completed properly, without errors. As long as the rates are not below the minimum threshold defined above, the study will be considered feasible.

All analyses outside of the primary endpoint will be considered exploratory in nature. Chi square and t-test will be used to evaluate differences in categorical and numerical values between arms. Subgroup analyses for BMI, total dose, and comorbidity will be conducted. We will also evaluate the incidence of RD for specific radiation skin dose stratification by reviewing the V20 to V80 in 5 Gy increments reaching a skin shell representing the thickness between the skin and the “skin minus 3 millimeters” and the “skin minus 5 millimeters.” This will be done on both the original dosimetry as well as a recalculated plan from the resimulation scan.

We will also evaluate any statistically significant differences in both the absolute numbers and relative changes of the lab values: CRP, TNFa, IL-1b, IL-6 at each of the 3 time points in which they are drawn for each arm.

All statistical tests will be two-sided. We will report comparative data in good faith and emphasize that the primary intention of this study is to understand the safety and tolerability profile of Dermaprazole.

8.4 Reporting and Exclusions

All patients enrolled in this study who complete at least 60Gy of radiation and follow up at 30 days post treatment will be included in the analysis.

9 DATA MANAGEMENT

Patient information will be acquired from patient medical records within the clinical site Electronic Medical Record (EMR) system.

Patient characteristics including age, race/ethnicity, initial biopsy result, cancer stage, BMI and known comorbidities will be collected.

Patient data for analysis will be captured using REDCap. Paper forms including the skindex16 questionnaires will be kept in a locked cabinet in the Radiation Oncology offices and input into REDCap. Photos of patients' skin reaction will also be kept on this limited-access network drive. Patient information will be de-identified for final statistical analysis by removal of patient names and MRNs. Each patient will be assigned a study code at time of study registration.

Information gathered from the planning system will include the V20 to V80 in 5 Gy increments reaching skin shell contours of "skin minus 3 millimeters" and "skin minus 5 millimeters" as well as the total dose. This will be collected for both simulation scans.

10 DATA AND SAFETY MONITORING

10.1 Data and Safety Monitoring Oversight:

A Data and Safety Monitoring Plan (DSMP) is required for all protocols conducted at MAYS CANCER CENTER. All protocols conducted at MAYS CANCER CENTER are covered under the auspices of the MAYS CANCER CENTER Institutional Data Safety Monitoring Plan. The MAYS CANCER CENTER Institutional DSMP global policies provide individual trials with:

- institutional policies and procedures for institutional data safety and monitoring,
- an institutional guide to follow,
- monitoring of protocol accrual by the MAYS CANCER CENTER Protocol Review Committee,
- review of study forms and orders by the Forms Committee,
- tools for monitoring safety events,
- monitoring of UPIRSO's by the Director of Quality Assurance and DSMC,
- determining level of risk (Priority of Audit Level Score – PALS),
- oversight by the Data Safety Monitoring Committee (DSMC), and
- verification of protocol adherence via annual audit for all Investigator Initiated Studies by the MAYS CANCER CENTER Quality Assurance Division.

10.2 Monitoring Safety:

The PI or treating investigator will perform primary assessment of adverse events, adverse event trends and treatment effects on this study. The PI will conduct independent quarterly reviews and report findings to the MAYS CANCER CENTER Data Safety Monitoring Board (DSMB) and the UT HEALTH IRB. Baseline events and adverse events will be captured using the MAYS CANCER CENTER Master Adverse Events Document for each patient using CTCAE v5.0 for the grading and attribution of adverse events. Usage of the MAYS CANCER CENTER Master Adverse Events Document centrally documents:

- the event and grades the seriousness of it,
- if the event was a change from baseline,

- determines the relationship between the event and study intervention,
- if the event was part of the normal disease process, and
- what actions were taken as a result of the event.

	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
Intervention	Observation	Local or non-invasive intervention	Hospitalization	Urgent/ emergent intervention	-

10.3 Safety Definitions: For this study, the following safety definitions will be applicable:

Adverse Event Definition:

An adverse event (AE) is defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

The adverse event (AE) collection/reporting period will begin with the first day of treatment with radiation or chemotherapy. AEs after study registration but prior to the first day of study treatment will be captured as ongoing concurrent secondary diagnoses and symptoms present at the start of study.

Serious Adverse Event Definition: is any adverse event that:

1. results in death;
2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. results in inpatient hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity;
5. results in a congenital anomaly/birth defect; or
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Unanticipated Problems Involving Risks to Subjects or Others Definition:

Unanticipated problem involving risk to subjects or others includes any incident, experience or outcome that meets all of the following criteria:

A. unexpected (in terms of nature, severity, or frequency) given

(a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and

(b) the characteristics of the subject population being studied (note: the unfounded classification of a serious adverse event as "anticipated" constitutes serious non-compliance);

B. definitely related or probably related to participation in the research; and

C. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Expected adverse events are those that have been previously identified as resulting from administration of topical or radiation therapy.

For purposes of this study, an adverse event is considered expected when the events are those related to systems within the radiation treatment field and include: infection, allergy, or short & long-term (greater than 6 month) skin changes.

Radiation: The common side effects of radiation to the head and neck most commonly includes radiation dermatitis (i.e., erythema, blistering, pigmentation changes) and fibrosis/firmness of head and neck in the long-term. Commonly, patients develop dry mouth, changes in taste, pain when swallowing, and weight loss. Long term, some patients can continue to have changes in taste and lymphedema.

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 success 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.

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 90 days of treatment completion.
- Late toxicity will be defined as events occurring or persisting ≥90 days from treatment completion.

Attribution: An attribution scale which will be utilized to attribute relatedness of the adverse event to the radiation treatment or to the Dermaprazole/Aquaphor as determined by the treating investigator or Principal Investigator. Assignment of attribution is the responsibility of the treating investigator or Principal Investigator.

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – 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.

10.4 Management of Adverse Events and impact on treatment

- Expected mild/moderate toxicity (Grade 1-2) will be managed conservatively by the treating physician.

- Unexpected or severe adverse events will be managed on a case by case basis at the discretion of the treating physician in coordination with the study team. Emergent dermatology consult and face-to-face evaluation within 48 hours will be sought for each suspected intervention-related adverse effect. Every effort will be made to continue radiation treatments for the prescribed duration, as would be the standard of care. If the risks of continuation of any portion of the patients' treatment is felt to immediately outweigh the benefits or be detrimental to the patient, it may be temporarily withheld at the discretion of the treatment team.

- Adverse events directly related to Dermaprazole may prompt withdrawal from the study. Radiation will continue as scheduled unless Grade 4 toxicity occurs, in which case delay to allow for healing is permitted.

10.5 Reporting Requirements

The adverse event (AE) collection/reporting period for events related to Aquaphor or Dermaprazole will begin with the first day of application of the product. The adverse event (AE) collection/reporting period for all other events will begin with the first day of treatment with radiation or chemotherapy. AEs not related to Aquaphor or Dermaprazole that occur after study registration but prior to the first day of study treatment will be captured as ongoing concurrent secondary diagnoses and baseline symptoms present at the start of study.

The following adverse events, regardless of perceived relationship to study treatment, will be reported and recorded:

- Scarring, fibrosis, epilation, or pigmentation changes that extend beyond 6 months
- Anaphylaxis, hypotension, urticarial, or other reactions felt to be allergic
- All SAEs
- Adverse events (AEs) and serious adverse events (SAEs) that are ongoing at the end of the treatment and related to radiation treatment or investigational product application (but not chemotherapy) or lab abnormalities specified on the Study Calendar will be followed until resolution or the end of study follow-up.

For this study, all Master Adverse Events Documents collected on patients for this protocol will be reviewed by the Principal Investigator on a quarterly basis to determine if a serious safety problem has emerged that results in a change or early termination of a protocol such as:

- suspending enrollment due to safety or efficacy, or
- termination of the study due to a significant change in risks or benefits.

As per the MAYS CANCER CENTER DSMP, any protocol modifications, problematic safety reports, unanticipated problems, and suspension or early termination of a trial must be reported to all members of the research team. Suspension and early termination of a trial must also be reported immediately to the Director of Quality Assurance (DQA) who will promptly notify the sponsor and the UT HEALTH IRB. The PI will review the Master Adverse Events documents to determine the significance of the reported events and will file the Investigator Initiated Study Annual DSMB Report Form on an annual basis with the MAYS CANCER CENTER DSMB. The Investigator Initiated Study Annual DSMB Report Form includes information on adverse events, current dose levels, number of patients enrolled, significant toxicities per the protocol, patient status (morbidity and mortality), dose adjustments with observed response, and any interim findings. Any trend consisting of three or more of the same event will be reported to the MAYS CANCER CENTER DSMP for independent review outside of the annual reporting cycle, which begins three months following protocol start up. Conflict of interest is avoided by the independent review of the MAYS CANCER CENTER DSMB and by ongoing independent review of adverse events trends by the Director of Quality Assurance. All SAE and UPRISO's will be reported following MAYS CANCER CENTER and UT HEALTH institutional guidelines.

UT HEALTH SAE/UPRISO REPORTING REQUIREMENTS		
Type Event	Report to	Timeframe
All AE, SAE and UPIRSO	Regulatory Affairs and DQA	Same as other notification timeframes except for SAE/AE which should be reported on Monday for the prior week
SAE	Clinical Trial Sponsor	within 24 hours
AE/SAE	UT HEALTH IRB	Annually
UPIRSO – all	Clinical Trial Sponsor	within 24 hours of the PI determining a UPIRSO exists
UPIRSO - life threatening	UT HEALTH IRB	within 48 hours of the PI determining a UPIRSO exists
UPIRSO - non-life threatening	UT HEALTH IRB	within 7 days of the PI determining a UPIRSO exists

AE's and SAE events that occur during clinical trials with or without an Investigational New Drug (IND) application are mandatory reports submitted to FDA via Medwatch FDA F3500A within 15 days for events that have at least a possible relationship with the drug.

10.6 Quality Assurance

As with all studies conducted at MAYS CANCER CENTER, the PI has ultimate responsibility for ensuring protocol compliance, data accuracy/integrity and responding to recommendations that emanate from monitoring activities. Protocol compliance, data

accuracy and reporting of events is further ensured by an annual audit conducted by the Data Safety Officer, whose audit report is shared with the PI, the research team, and will be reviewed by the MAYS CANCER CENTER DSMC.

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.

Village compounding pharmacy in Houston, with prior experience compounding this product, will maintain stability & bio availability data. Presently, the product is believed to be stable for at least 1 week at room temperature and up to 60 days if refrigerated. Likewise, the compounding records will be kept with Village pharmacy. All handling and storage once delivered from the compounding pharmacy will be managed by the Mays Cancer Center pharmacy until delivered to the patient.

Likewise, Aquaphor will be provided to the patient to ensure all subjects use the same product.

11 PREGNANCY

Pregnancy testing will be performed at the discretion of the treating physician if there is any suspicion or possibility the patient is pregnant. Pregnant patients will be excluded from the study. The following procedures will be followed in the unlikely event of a pregnancy on study. A subject who is determined to be pregnant at any time after the first dose of investigational therapy will be immediately withdrawn from all participation in the study. All study conclusion/withdrawal assessments will be collected at the time of discontinuation. Pregnancy information is to be recorded in the Case Report Forms. While pregnancy itself is not considered to be an SAE, it may result in an SAE. Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an SAE and will be reported as such. A spontaneous abortion is always considered an SAE and will be reported as such.

12 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.

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