ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A221304

A PHASE III PLACEBO-CONTROLLED, RANDOMIZED THREE-ARM STUDY OF DOXEPIN AND A TOPICAL RINSE IN THE TREATMENT OF ACUTE ORAL MUCOSITIS PAIN IN PATIENTS RECEIVING RADIOTHERAPY WITH OR WITHOUT CHEMOTHERAPY

Doxepin solution, placebo solution, and DLA (diphenhydramine, lidocaine, antacid) provided and distributed by Alliance Research Base Pharmacy

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Study Resources

Expedited Adverse Event Reporting
https://eapps-ctep.nci.nih.gov/ctepaers/

Medidata Rave® iMedidata portal
https://login.imedidata.com

OPEN (Oncology Patient Enrollment Network)
https://open.ctsu.org

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Questions	Contact (via email)
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document:	Protocol Coordinator
Questions related to IRB issues and model consent revisions:	Regulatory Affairs Manager: *regulatory@alliancenctn.org*
Questions regarding CTEP AERS reporting:	*regulatory@alliancenctn.org*

Document History Effective Date:
Update ## Date

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead National Clinical Trial Network (NCTN) Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206	Please refer to the patient enrollment section for instructions on using the OPEN system.	All participating sites will submit study data via Medidata Rave System. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol. CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.		
For patient eligibility or treatment-related questions see the Protocol Contacts, Page 2.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org.		
The CTSU Web site is located at https://www.ctsu.org.		

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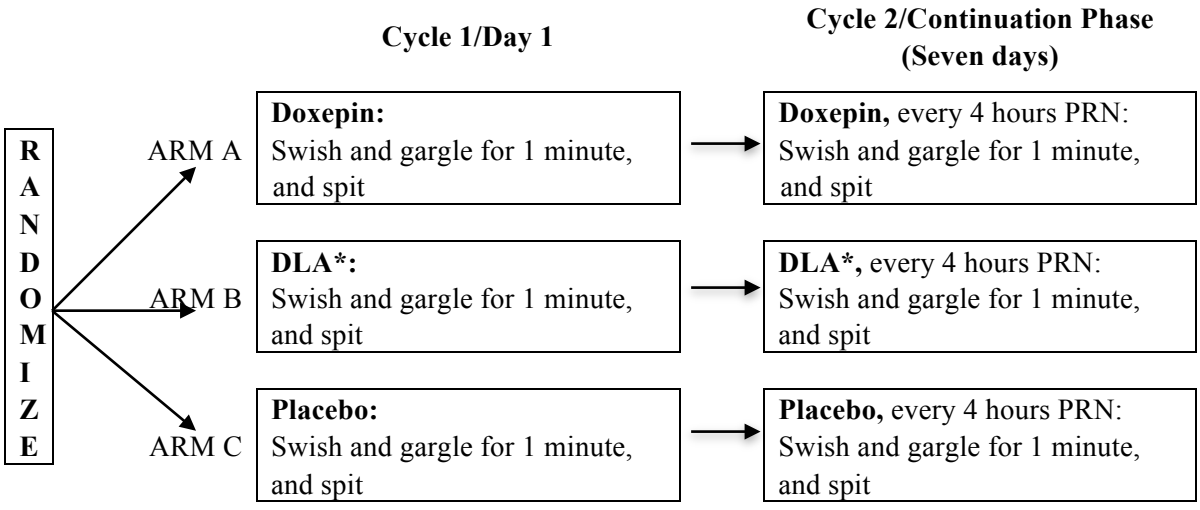
Eligibility Criteria

Histologic documentation of malignancy currently undergoing a course of RT including the oral cavity and/or oropharyngeal area to a dose of at least 4500 cGy using more than 5 fractions (See § 3.2.1)
Physical exam demonstrating evidence of radiotherapy-related mucositis in the visible oral cavity and/or oropharynx consistent with mucous membrane toxicity greater than 0 using the Acute Radiation Morbidity Scoring Criteria (See § 3.2.2)
At least 4 (out of 10) patient-reported oral pain related to oral mucositis secondary to RT for which the patient seeks relief (See § 3.2.3)
Ability to complete questionnaire(s) by themselves or with assistance.
No known allergy to diphenhydramine, lidocaine, antacid, doxepin, tricyclic antidepressants (See § 3.2.5)
No use of any anti-arrhythmic medication (See § 3.2.6)
No current diagnosed untreated or unresolved oral candidiasis or oral HSV infection.
No history of untreated narrow angle glaucoma within 6 weeks prior to registration.
No untreated urinary retention within 6 weeks prior to registration.
No current use of glutamine or sucralfate powders at the time of registration.
No cryotherapy for prophylactic mucosal protection within 6 weeks prior to registration.
Not pregnant (see § 3.2.12)
Age ≥ 18 years
ECOG Performance Status 0, 1, or 2.

Required Initial Lab Values

None

Schema



* Diphenhydramine HCl, Lidocaine HCl, and Antacid Suspension

Continuation Phase: Following Day 1, patients may begin the 7-day continuation phase and take doxepin/DLA/placebo up to every 4 hours as needed for pain. If desired, initiation of the Cycle 2/Continuation Phase may be delayed for up to one week after Cycle1/Day 1.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

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1.0 BACKGROUND

1.1 Definition and epidemiology of oral mucositis

Oral mucositis (OM) related pain is a significant problem in patients undergoing head and neck radiation therapy with or without chemotherapy. Acute OM refers to an inflammatory process of the mucosa of the oral cavity and oropharynx manifested as painful, erythematous, ulcerative lesions. These lesions typically develop within 7−14 days of the initiation of cytotoxic chemotherapy or radiotherapy (RT)[1-3]. The pain and associated dysgeusia caused by OM frequently require treatment with systemic analgesics. They also decrease patients' oral intake and nutrition leading to dehydration, weight loss, and declining performance status that may require intravenous fluid hydration, feeding tube placement, and hospitalization[4]. When severe, OM increases the risk of infection and may compromise clinical outcomes by necessitating treatment breaks, dosage reductions, and reduced compliance with therapy[2,5,6].

A majority of patients with head and neck cancer (HNC) treated with RT with or without chemotherapy experience painful OM. Standard fractionated head and neck RT can cause OM in doses as low as 10 Gy, but most patients experience ulcerative OM by the end of the third week of RT, after receiving 30 Gy[7-9]. In a systematic review of 33 studies reporting OM in 6181 such patients, Trotti and colleagues found that the mean overall incidence of OM was 80%[4]. Elting et al. reported that OM occurred in 91% of 204 consecutive patients with HNC treated with RT with or without chemotherapy at M.D. Anderson Cancer in 2002. OM was severe (grade 3−4) in 66%[7]. OM was more common among patients who received concomitant chemotherapy (98%), who had oral cavity or oropharyngeal primaries, or who were treated with altered RT fractionation schemes. OM typically developed after the second week of RT and persisted for an average of 5 weeks. Patients who developed OM were significantly more likely to have severe pain (54% vs. 6%; $p < 0.001$) and incurred incremental costs of $1700−$6000 depending on OM severity. Vera-Llonch et al. conducted a nationwide survey of 154 medical and radiation oncologists collecting OM data on 450 patients with HNC treated with RT with or without chemotherapy. They found that 83% of patients developed OM and in 29% it was severe[10]. Similarly, OM was more common when patients received concurrent chemotherapy or when they had nasopharyngeal or oropharyngeal primaries. In a series of in-depth interviews with 33 patients who had undergone RT with or without chemotherapy, painful OM was the single most debilitating reported side effect[11].

1.2 Pathophysiology, Prevention, and Treatment of OM

Historically, OM has been viewed as the consequence of cytotoxic therapy (either chemical or radiation) in which rapidly dividing cells are preferentially killed—be they cancer or normal mucosal epithelium[12]. When the mucosa is damaged, the epithelial cells are not replenished, resulting in ulcer formation that persists until treatment is stopped or reduced. Sonis has proposed a 5-phase model for the pathophysiology of OM that modifies this traditional linear view[8,13,14]. In this model, initiation (phase I) of OM occurs immediately following chemotherapy or RT which directly damage mucosal DNA, generate reactive oxygen species, damage lipids and connective tissue, and initiate apoptosis by stimulating sphingomyelinase and ceramide synthase pathways. All of this leads to upregulation and messenger generation (phase II) in which the cells' normal molecular damage response pathways are turned on, creating a positive feedback loop. This upregulation of transcription factors (most notably nuclear factor-κB) triggers release of pro-inflammatory cytokines (tissue necrosis factor [TNF]-α, interleukin [IL]-I, IL-2, and IL-6), that result in further signaling and amplification (phase III) of tissue injury. This leads to clinically and symptomatically significant ulceration (phase IV) in which the extracellular membrane swells weakening attachments between the submucosa and epithelium creating deep, broad-based, erosions. This exposes free nerve

endings causing pain[15]. Finally, healing (phase V) occurs as a pseudomembrane of fibrin and dead cells forms over the ulcer, COX-2 likely stimulates new angiogenesis, epithelial cells from the periphery migrate and multiply to close the wound, and submucosal cells regenerate usually over a 2−3 week period.

1.3 Prevention and Treatment of OM

Numerous prophylactic agents and interventions have been investigated but relatively few have demonstrated benefit in decreasing the incidence or severity of cancer therapy-related OM[16]. The authors of the current National Comprehensive Cancer Network guidelines for OM note that the only effective preventive strategies are oral cryotherapy used in conjunction with bolus 5-FU, melphalan, or edatrexate and palifermin used to prevent HSCT-related OM[17]. Palifermin (Kepivance®, recombinant human keratinocyte growth factor) is the only FDA-approved preventive therapy for OM. This approval was based largely on a phase III trial in 212 patients undergoing conditioning with high-dose chemotherapy and TBI followed by autologous HSCT for hematologic malignancies[18]. Compared to placebo, palifermin decreased both the incidence of World Health Organization (WHO) grade 3−4 OM (63% vs. 98%, $p < 0.001$) and median duration of grade 3−4 OM (3 days vs. 9 days, $p < 0.001$). A report of a phase III trial involving 188 patients with locally advanced HNC treated with chemoradiotherapy demonstrated that palifermin again reduced both the incidence of WHO grade 3−4 OM (54% vs. 69%, $p = 0.041$) and median duration of grade 3−4 OM (5 days vs. 26 days, p = NS)[19].

Many cancer patients experience significant therapy-related OM pain. Management strategies include bland rinses (e.g., 0.9% normal saline or a solution with a ½ teaspoon baking soda in 1 cup warm water), topical anesthetics/analgesics, mucosal coating agents (e.g., benzydamine) and systemic analgesics[2,17,20]. Consistent with the WHO pain management ladder, most patients require opioid analgesia as OM severity increases. Topical anesthetics/analgesics can be used for mild to moderate OM pain and as adjuncts for more severe pain. Commonly utilized agents include lidocaine, benzocaine, dyclonine, and diphenhydramine[2,17,20]. There are several concerns with the use of topical anesthetics[21-23]. The duration of pain relief is typically less than 90 minutes. They can cause burning or stinging pain on first contact with damaged mucosa and then temporarily diminish or abolish taste and the gag reflex. Finally, there is the possibility of increased systemic absorption through a breached mucosal barrier. The latter concern was addressed in a small prospective study comparing plasma lidocaine levels after an oral rinse with 5 mL of 2% lidocaine solution for 1 minute in 5 patients with severe OM related to HSCT and five healthy control subjects[21]. Plasma lidocaine levels, while lower than the therapeutic range (0.2 μg/mL vs. 1.5−5.5 μg/mL), were measurable in the cancer patients; whereas, in the controls lidocaine was undetectable, indicative of minor systemic absorption resulting from lack of mucosal integrity.

1.4 Doxepin as an Analgesic Agent for OM-related Pain

Clinical pharmacology of doxepin: Doxepin is a dibenzoxepin tricyclic compound ($C_{19}H_{21}NO$•HCl or N,N-dimethyldibenz(b,e)oxepin-propylamine hydrochloride) with a molecular weight of 316 belonging to the tricyclic antidepressant (TCA) class of medications[23]. TCAs have been used since the early 1960s to treat patients with major depression[24]. Doxepin is FDA-approved in the United States for treatment of depression and anxiety with or without associated alcoholism or psychoneurosis and topically for short-term management of moderate pruritus. It is recommended for off-label prevention of migraine headaches and as an adjunctive therapy in chronic pain syndromes[25-28].

Mechanism of Action: Doxepin has effects on both the central and peripheral nervous system. With respect to topical OM pain relief, the main mechanism of action is peripheral. Though

the exact mechanism of doxepin's efficacy in neuropathic pain is not entirely clear, doxepin's anesthetic and analgesic effects may be due to the fact that it is a potent Na^+ channel blocker thereby limiting conduction of noxious stimuli in cutaneous nociceptors[24]. Doxepin also has potent peripheral H_1 and H_2 receptor blocker activity making it an effective topical anti-pruritic agent[23,25]. Also, doxepin likely has a synergistic effect with endogenous and exogenous opioids. Systemic administration resulted in a significant increase in plasma enkephalin-like activity compared to placebo, in patients with chronic cervical or low back pain[27]. Rat models have demonstrated that doxepin potentiates opioid analgesia and is a strong local anesthetic when administered via sciatic nerve injection, intraperitoneally, intrathecally, or topically[24,26,28,29]. In the CNS, doxepin increases synaptic concentration of serotonin (5HT) and norepinephrine (NE) by inhibiting receptor reuptake at the presynaptic neuronal membrane, the therapeutic site of its antidepressive action[23,24,30]. 5HT and NE re-uptake inhibition is also believed to activate the descending anti-nociceptive system[23,29]. Doxepin may also act as a modulator of N-methyl-D-aspartate (NMDA) receptors, involved in spinal nociception, decreasing afferent input through the spinothalamic tract[23,30,31]. A few TCAs, including doxepin and amitriptyline, are tertiary amines making them more lipophilic than other antidepressants and therefore better able to penetrate nerve fibers[24].

Epstein and colleagues conducted two non-randomized, open-label, prospective trials of an oral doxepin rinse that reported a significant short duration of anesthesia followed by more extended analgesia for patients with OM[22,23,32,33]. In the first trial, 41 patients with OM pain (37 from cancer therapy and 4 from other causes) were given a single dose of 5 mL of a doxepin (5 mg/mL) suspension containing 0.1% alcohol and sorbitol[23]. Baseline assessment of OM included evaluation of 9 oral sites for erythema and ulceration using the Oral Mucositis Assessment Scale (OMAS) and the patients rated their oral pain at rest and with most recent food intake. Patients swished for 1 minute and then spit out the rinse. At 5, 15, 30 minutes, 1 hour and then at 30 minute increments through 4 hours, patients utilized a Visual Analogue Scale (VAS) to grade their pain (0 = none, 10 = severe), stinging or burning (0 = none, 10 = severe), taste (0 = terrible, 5 = acceptable, 10 = excellent), and drowsiness (0 = none, 10 = severe, leading to sleep). Pain was again assessed 24 hours after the single dose of doxepin rinse. 34 patients had oral ulcerations and erythema was seen in 38. Maximum pain reduction was seen at 15 minutes with a mean decrease of 2.79 units (1.89 vs. 4.68 at baseline). Significant pain relief persisted for 3 hours, with a mean reduction of 1.21 units (3.50 vs. 4.68). Only one patient (2%) found the taste unacceptable, and only four patients (9%) reported stinging or burning discomfort. Drowsiness attributable to doxepin rinse was unable to be adequately evaluated due to lack of baseline assessment.

Epstein and his co-investigators enrolled 14 more patients with painful OM from cancer therapy (excluding the four non-cancer therapy related patients) for a total of 51 patients treated in the same manner with a single dose doxepin rinse[32]. In the subsequent report of this more homogenous cohort, they found a 56% maximum pain reduction from baseline that occurred 15 minutes after rinsing (mean decrease = 3.0 units, range 2.0−5.0). The median duration of pain reduction lasted 145 minutes (range 25−235). Pain recurrence was slow, with 19 patients (37%) continuing to report pain reduction at 4 hours when the study ended. Mild burning or stinging discomfort from the rinse was reported by 16 patients (31%) with a median score of 2 out of 10.

In a second separate study, Epstein et al. treated nine patients with OM due to cancer therapy with the same doxepin rinse, used three to six times daily, for one week[22,33]. Patients were evaluated in a similar manner to the previous study with baseline OMAS and VAS assessments. Oral pain following doxepin rinse was assessed with a VAS at the first visit and again one week later at the same time intervals as in the previous study. Patients kept diaries of systemic analgesic and doxepin rinse usage during the week between visits. After the first

doxepin dose, pain decreased significantly from a median baseline score of 5, to 3 units at 5 minutes after rinsing, down to a median score of 1 unit at 15 minutes, and persisted for a median of 2 hours. Patients reported similar reductions in pain scores at 5 and 15 minutes after doxepin rinse in their inter-visit diaries. They also reported decreased pain with eating and at rest. At the 1-week follow-up visit, median baseline pain scores had decreased from 5 to 3 units, and patients reported continued immediate and durable reduction of pain scores. Side effects of bad taste, burning or stinging discomfort, and drowsiness did not change over the one-week trial period.

1.5 Emerging Data Supporting the Clinical Efficacy of Doxepin in the Alliance

Recently, Miller and colleagues[34,38] reported the final results of N09C6, a phase III randomized, double-blind trial comparing doxepin to placebo for treatment of oral mucositis pain in patients undergoing high-dose, curative head and neck radiotherapy treatment. One hundred and fifty-five (155) patients were randomized to receive either a single dose of doxepin or placebo on Day 1, and then cross over to receive the other agent on a subsequent day. A pain questionnaire was administered at baseline and 6 scheduled time points after drug administration. The primary endpoint was met, showing a significant reduction in mouth and throat pain by doxepin (AUC, -9.1) compared to a placebo (AUC, -4.7, p=0.0003, Figure 1). Crossover analysis also confirmed the superiority of the doxepin arm compared to placebo (p<0.001). Doxepin was well tolerated, but did have more stinging/burning sensation, unpleasant taste, and greater drowsiness, compared to placebo. A majority of patients expressed a desire to continue doxepin treatment after initial testing of doses.

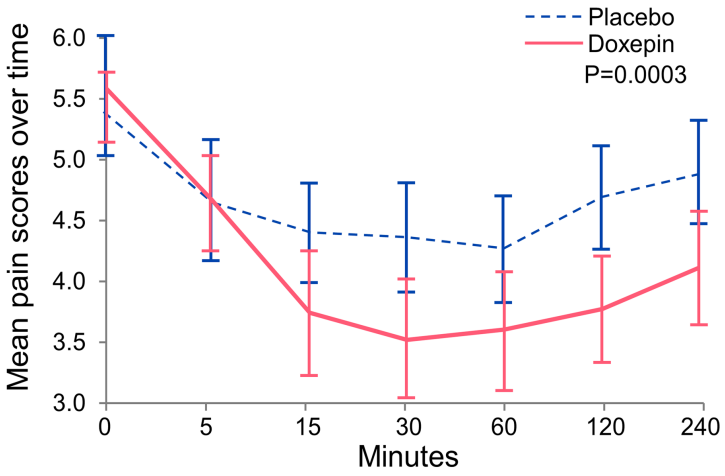

Figure 1. Mean pain scores of mouth and throat vs. time (N=140). The clinical effect of doxepin is shown in this graph. The blue dashed line shows a good example of the placebo effect, with a mean reduction in pain score of 1.0. The dark red line shows an average reduction in mean pain score of approximately 2.0 (on a scale of 0 to 10), following doxepin administration. This represented the primary end point of the doxepin study, which was met statistically ($AUC_{Doxepin}$=-9.1, $AUC_{Placebo}$=-4.7, P=0.0003, Miller *et al.*, ASTRO 2012, plenary session).

1.6 Diphenhydramine, Lidocaine, and Antacid (DLA) rinse

A number of "Magic" mouth rinse preparations exist for patients with treatment-related oral mucositis pain. They all require prescription from a medical practitioner. A common preparation contains 3 active ingredients including diphenhydramine hydrochloride, lidocaine hydrochloride, and antacid (such as Maalox®) for oral care. Diphenhydramine (2-(diphenylmethoxy)-N,N-dimethylethanamine) is an over-the-counter medication, which belongs to the first-generation antihistamine family. It has a number of pharmacologic properties including anticholinergic, antitussive, sedative, and most commonly, anti-allergic. It is used for a variety of common medical conditions such as seasonal allegories, cold, insomnia, pruritus, and Parkinsonian's extrapyramidal symptoms. Lidocaine (2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide) is commonly used as a local anesthetic, which is also well known for its antiarrhythmic properties when consumed systemically. When applied topically, lidocaine can relieve itching, pain and burning symptoms caused by local irritation or inflammation, making it a popular choice for dentistry and general surgery. The onset of its pharmacological action is immediate. For the antacid component (trade name: Maalox®) of a topical rinse mouthwash, it usually contains a number of components including aluminum hydroxide ($Al(OH)_3$), magnesium hydroxide ($Mg(OH)_2$), and a small amount of simethicone ($(C_2H_6OSi)_n \bullet (SiO_2)_m$). Aluminum hydroxide is a common antacid itself: it works as a base by interacting with excess acid in the stomach, therefore, neutralizing the acidity in the physiologic environment and provide symptoms relief. By itself, magnesium hydroxide is also known as Milk of Magnesia® due to its milk-like appearance; it is an aqueous, mildly alkaline solution, which has the dual action of being an antacid for neutralizing stomach acid and also as a laxative. Simethicone is anti-foaming, which acts as a stabilizer and helps reduce bloating and discomfort in the abdomen. When the three compounds (diphendydramine, lidocaine, and antacid) are mixed with other solvent components, a homogeneous suspension is produced ready for clinical use (suitable for rinse, spit or swallow).

Mechanism of Action: DLA mouthwash, or other similar preparations, is commonly prescribed for radiation- or chemotherapy-induced oral mucositis. Its mechanism of action, due to its various components, is multi-faceted. Depending on formulation, it has the pharmacologic properties of an antihistaminic for local anesthesia (diphenhydramine), analgesic/pain relieving (lidocaine), and anti-acidic (aluminum/magnesium hydroxide, Maalox). Other components may include nystatin, sucralfate, tetracycline and erythromycin. The most popular components of anti-mucositic mouthwash, however, are diphenhydramine, lidocaine and antacid (DLA).

The commonly prescribed mouthwash preparations can be used every four to six hours, as needed for pain. Patients are generally instructed to hold the mixture in the mouth for 1 to 2 minutes, then either split it out or slowly swallow. It is also recommended not to drink or eat 15 minutes after mouthwash use, so the medication can have a chance to work.

1.7 Limited Evidence for the DLA Mouthwash Being Analgesic for OM

Even though many preparations for DLA or "Magic" mouthwash rinsing are used clinically[35], a paucity of controlled data exist regarding this topic. Large-scale, randomized studies with positive results are lacking. In the largest published randomized clinical trial, Dodd et al.,[36] tested the effectiveness of three commonly used mouthwashes ("magic" mouthwash with lidocaine, diphenhydramine and Maalox®; chlorhexidine; and salt with soda) in 200 patients undergoing chemotherapy and experiencing mucositis. There were no significant differences among the three arms. Over 70% of the patients stopped having mucositis symptoms in less than 12 days, although it is not clear if this would have been any different from a placebo arm. No placebo-controlled trials are published.

Currently, due to the lack of high-quality evidence regarding the use of "magic mouthwash" preparations, multiple clinical practice guidelines[37-39] agree that this area represents a gap in our knowledge about whether these mouthwash preparations are truly useful (although very commonly used by many oncologists). Correspondingly, the Cochrane review[37] found inconclusive evidence regarding whether these "magic mouthwashes" truly decrease the severity and/or duration of oral mucositis pain.

1.8 Significance of the Positive Randomized, Placebo-controlled Doxepin Data

Do the above-described pilot data and the results of the recently completed randomized, double blinded, cross-over clinical trial, establish that doxepin should be preferentially used for patients with radiation therapy-induced oral mucosal pain? The positive nature of these data supports that doxepin is a reasonable treatment to utilize in this situation. ASTRO chose the abstract for a plenary session, something that they only do for abstracts that they believe are practice-changing. The manuscript from this abstract has been accepted for publication by a prominent clinical oncology journal, also supporting that the results are quite intriguing.

Further research is indicated at this time. Dr. Robert Dworkin, a noted expert with regard to pain studies, was a discussant for an abstract presentation regarding the completed Alliance doxepin trial at a recent Symptom Management and Health-related Quality of Life Steering Committee meeting. He felt that further research was indicated to further delineate the efficacy of doxepin in patients with oral mucosal pain related to radiation therapy. He noted that in pain research, experts believe that a positive study should be replicated before general acceptance into clinical practice. In addition, he raised the question as to whether doxepin was better than any other standard therapy (such as the number of "magic mouthwashes" that are commonly used for this condition). He recommended that a follow-up clinical trial be conducted to compare doxepin to another common clinically used mouthwash. Pending the results of such a trial, the question of whether doxepin added anything to the use of a "magic mouthwash" remained open. Pursuant to this, the current proposal has been developed.

1.9 Study design

This 3-arm study is designed to evaluate the effect of doxepin rinse or DLA versus a placebo on OM-induced pain in patients with head and neck cancer undergoing RT to the oral cavity.

This trial will utilize the same dose of 25 mg doxepin rinse used in the phase I-II trials by Epstein et al. [22,23,32,33] and the phase III trial by Miller et al.[34] This dose was reported to be effective and resulted in minimal side effects, and was well tolerated in the phase III study[34]. The doxepin oral concentrate is available in a 10 mg/mL formulation (desired test dose is 25 mg in 5 mL). It is expected that minimal systemic absorption of doxepin will occur despite compromise of the mucosal barrier by mucositis because patients will swish the oral cavity for one minute, then expectorate the solution. Should complete transmucosal absorption occur, this oral rinse dose would be less than the usual starting oral daily dose of 75−150 mg prescribed for depression or anxiety[23,24,27]. During radiation therapy treatments, the patient will be invited to participate in the study when s/he develops at least 4 (out of 10) oral pain thought to be related to oral mucositis secondary to radiation treatment, for which the patient would like to seek relief. After consent, the patient will then be registered/randomized to this study.

In addition to the initial dose evaluation (for the primary endpoint), a one-week continuation phase will be allowed in the current study. Within one week after the first dose of their study drug, patients will be allowed to initiate a 1-week continuation phase, where patients may repeat dosing every 4 hours PRN (as needed for pain). On each treatment day of the continuation phase, a patient-reported outcome (PRO) measure will be completed. The patient will be allowed to continue the study drug for up to one week for relief of OM-related pain. During the planned continuation phase, patients may opt out if/when they believe that the

treatment is no longer beneficial. Should that be the case, the patient's treatment will be unblinded and s/he will be treated per clinical practice recommendations off study.

1.10 Registration fatigue/uniscale assessment

QOL measurements of fatigue and overall perception of QOL are routinely included in Alliance studies and will be assessed upon registration in this study. Evidence has arisen indicating that baseline single-item assessments of fatigue and overall QOL are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses recently presented at ASCO, the first involving 23 NCCTG and Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates.[40]

2.0 OBJECTIVES

2.1 Primary objective

Determine whether the doxepin rinse or DLA rinse is more effective than placebo in reducing OM-related pain in patients undergoing RT to the oral cavity, as measured by a patient-reported questionnaire at baseline, 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours.

2.2 Secondary objectives

2.2.1 Assess the adverse event profile of the doxepin rinse, the DLA rinse agent, and the placebo using a patient-reported questionnaire at 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours for domains of unpleasant taste, burning or stinging discomfort, and drowsiness.

2.2.2 Compare the incidence of using additional analgesics between 1 and 4 hours after the initial mouthwash, between the doxepin oral rinse, the DLA rinse agent, and the placebo arms.

2.2.3 Compare the length of time that each study product is used by patients in the one-week continuation phase.

2.2.4 Compare the daily pain scores in the one-week continuation phase for the three study arms.

2.2.5 Compare the 24-hour morphine equivalent dose used in the continuation phase for the three study arms.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Contact Information page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness, which would prevent the patient from giving informed consent.

In addition:

- Women and men of reproductive potential must agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of radiation therapy and potential side effects of study rinses. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

___ **3.2.1 Documentation of Disease:**

Histologic documentation of malignancy currently undergoing a course of RT (with or without chemotherapy) including the oral cavity and/or oropharyngeal area to a dose of at least 4500 cGy using more than 5 fractions (i.e., stereotactic body radiation therapy [SBRT] is not allowed).

___ **3.2.2 Physical exam demonstrating evidence of radiotherapy-related mucositis** in the visible oral cavity and/or oropharynx consistent with mucous membrane toxicity greater than 0 using the Acute Radiation Morbidity Scoring Criteria (see Appendix VI or www.rtog.org/ researchassociates/adverseeventreporting/ acuteradiationmorbidityscoringcriteria.aspx).

___ **3.2.3 At least 4 (out of 10) patient-reported oral pain** related to oral mucositis secondary to RT for which the patient seeks relief, as measured on the Oral Pain Assessment (see Appendix I). Note: The pain score must be at least 4 at the time that the patient starts the first dose of study medication. The patient may be enrolled to the study if s/he, at times, has a pain score of at least 4, so long as initiation of study treatment begins when the pain score is at least 4.

___ **3.2.4 Ability to complete questionnaire(s) by themselves or with assistance.**

___ **3.2.5 No known allergy** to diphenhydramine, lidocaine, antacid (aluminum hydroxide, magnesium hydroxide, and simethicone), doxepin, tricyclic antidepressants, or any known component of the drug formulation in the testing arms.

___ **3.2.6 No use of any anti-arrhythmic medication** (except for beta-blockers) including lidocaine, linezolid, ipratropium, or medications with strong cholinergic properties (including neostigmine, a tricyclic antidepressant or a monoamine oxidase inhibitor) within 2 weeks prior to registration.

___ **3.2.7 No current diagnosed untreated or unresolved oral candidiasis or oral HSV infection.**

___ **3.2.8 No history of untreated narrow angle glaucoma** within 6 weeks prior to registration.

___ **3.2.9 No untreated urinary retention** within 6 weeks prior to registration.

___ **3.2.10 No current use of glutamine or sucralfate powders** at the time of registration (no washout required).

___ **3.2.11 No cryotherapy for prophylactic mucosal protection** within 6 weeks prior to registration.

___ **3.2.12 Not pregnant,** because patients eligible for this study will be receiving radiotherapy, which has known genotoxic, mutagenic and teratogenic effects.

Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 28 days prior to registration is required.

___ **3.2.13 Age ≥ 18 years**

___ **3.2.14 ECOG Performance Status 0, 1, or 2.**

4.0 PATIENT REGISTRATION

4.1 Registration Requirements

- **Informed consent:** The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.
- **Patient completed booklets:** Patient questionnaire booklets are to be ordered prior to the registration of any patients. Patient completed booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the A221304 web page) and faxing the form to the CTSU data operations center at 1-888-691-8039. Samples of the booklets are found in Appendices III-V, which are to be used for reference and IRB submission only. They are not to be used for patient completion.

4.2 Registration Requirements

4.2.1 CTSU registration requirements

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a National Clinical Trials Network (NCTN) Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical

Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for Alliance A221304 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

4.2.2 Patient Enrollment through OPEN

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

All site staff (Lead Group and CTSU Sites) will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the OPEN Enrollment forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.3 Stratification Factors

4.3.1 Patient Sex: Male vs. Female

4.3.2 Concurrent use of chemotherapy: No vs. Yes

4.3.3 Patient age at registration: < 60 years old vs. ≥ 60 years old

4.3.4 RTOG Acute Radiation Morbidity Criteria: 1 vs. 2 vs. 3 or more

4.4 Treatment assignments and blinding

4.4.1 The factors defined in Section 4.3 will be used as stratification factors.

4.4.2 After the patient has been registered to the study, the values of the stratification factors will be recorded and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure, which balances the marginal distributions of the stratification factors between the treatment groups.[38]

- Doxepin
- Diphenhydramine HCl, Lidocaine HCl, and Antacid Suspension
- Placebo

4.4.3 Procedures for blinding the treatment assignment: At the time that the site has registered/randomized the patient in OPEN and received an Alliance patient ID number, the Alliance Registration Office will also be notified. The Registration Office will contact the designated site contact person with the assigned treatment, "Doxepin, DLA, or Placebo." The name of this person and his/her contact information will be entered in OPEN on the Enrollment Form. This contact person may not be involved in assessing adverse events or any other outcome measure. The institutional pharmacist or designated contact person will maintain records that identify the patient and his/her corresponding treatment assignment.

5.0 STUDY CALENDAR

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Pre-Study Testing Intervals

- To be completed within 7 DAYS before registration: history and physical, oral pain assessment, pregnancy test

	Prior to Registration	**Day 1 Baseline** before oral rinse	**Day 1** In clinic*	**Day 1** At home**	**Continuation Phase*** **
Tests & Observations					
History and physical, PS	X				
Oral Pain Assessment	X(1)	X(1)			
Adverse Event Assessment (for CTCAE)			X		A
Oral Symptoms Booklet		X (2)	X (2)	X (3)	
Daily Questionnaire					X (4)
Fatigue/Uniscale Assessment	B				
Laboratory Studies Serum or urine HCG	C				

* To be completed by the patient in clinic at 5, 15, 30, and 60 minutes after oral rinse

** To be completed by the patient at 2 and 4 hours after oral rinse (may be completed at home). It is recommended that site staff give the patient a reminder by telephone at two and four hours post-administration to complete the questionnaires.

*** Daily for up to 7 days, beginning within 1 week of Day 1.

A As clinically indicated during Continuation Phase RT assessment(s).

B Within 21 days prior to registration (see Appendix II).

C For women of childbearing potential. Must be done within 28 days prior to registration.

1 See Appendix I

2 See Appendix III

3 See Appendix IV

4 See Appendix V. Also, note that patients should be instructed to complete the daily questionnaire at the time every day, preferably in the evening.

6.0 DATA SUBMISSION

This study will use Medidata Rave® for remote data capture (RDC) of all study data. The Rave system can be accessed through the iMedidata portal at https://login.imedidata.com. For additional information regarding account setup or training, please visit the training section of the Alliance web site. Copies of forms and a data submission schedule are also available for download on the CTSU web site.

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients (see Section 4.1). Samples of questionnaire booklets are available in Appendices III-V for reference and IRB submission only. They are not to be used for patient completion. Booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff either in person or by mail and site staff will enter patient and caregiver responses into the Rave database.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin within 14 days of registration. For questions regarding treatment, please see the Study Resources page.

Protocol therapy will consist of 2 cycles. Cycle One will consist of one day. Cycle Two will consist of an optional continuation phase lasting up to 7 days. Initiation of the Cycle 2/Continuation Phase may be delayed up to one week after Cycle 1/Day1.

Agent	Dose	Route	Cycle 1	Cycle 2: Optional Continuation Phase
			1 Day	7 Days
Arm A: Doxepin rinse	2.5 mL (25 mg) doxepin and 2.5 mL water**	Oral swish and gargle for 1 minute then spit	Taken in clinic	Taken at home every 4 hours, PRN, for OM pain
Arm B: DLA*	5.0 mL DLA	Oral swish and gargle for 1 minute then spit	Taken in clinic	Taken at home every 4 hours, PRN, for OM pain
Arm C: Placebo rinse	2.5 mL placebo and 2.5 mL water**	Oral swish and gargle for 1 minute then spit	Taken in clinic	Taken at home every 4 hours, PRN, for OM pain

* Diphenhydramine HCl, Lidocaine HCl, and Antacid Suspension (see Section 10.2)

** For Cycle 1, study agent will be diluted with sterile water for irrigation, sterile water for injection, and/or distilled water by site staff. For Cycle 2, the patient will use distilled water or tap water to dilute the oral rinse at home.

7.1 Day 1 of study intervention

Prior to the first dose of doxepin/DLA/placebo, the care provider or nurse will confirm that oral pain is at least 4 out of 10 severity level at the time of the rinse on the first day of the study (Appendix I). Patients will then be asked to complete the baseline evaluation in the Oral Symptoms booklet (Appendix III). If the pain score is less than 4 prior to administration of doxepin/placebo, administration should be delayed until pain is at least 4.

Doxepin/DLA/placebo 5 mL (doxepin/placebo) or 5.1 mL (DLA) will be given to patients to swish and gargle and then expectorate. The study dose should be prepared in the clinic just prior to administration.

Oral symptoms booklet: The patient will remain at the treating location for the first hour and complete the questionnaires in the Oral Symptoms booklet (Appendix III) at time zero (prior to the oral swish, gargle and spit), and at 5, 15, 30 and 60 minutes post-administration.

After completing the booklet at 60 minutes, patients may then leave the clinic and complete the 2- and 4-hour assessments at home (Appendix IV). The patient will be instructed on timing of questionnaire completion at two and four hours post-administration. It is recommended that site staff give the patient a reminder by telephone at two and four hours post-administration to complete the questionnaires.

7.2 Optional continuation phase

Within 7 days following Day 1 (ideally, on the first clinic day following Day 1), patients will be encouraged to continue treatment with the study agent for an additional week.

Patients randomized to Arms A or C who elect to continue with study treatment during the Continuation Phase (Cycle 2), will be provided with one 120 mL amber bottle of blinded study agent and a syringe for measurement. This should supply at least 42 doses after dilution. Patients will be instructed on preparation of the appropriate dose by dilution of the agent.

Patients randomized to Arm B who elect to continue with study treatment during the Continuation Phase (Cycle 2), will be provided with one 240 mL amber bottle containing 80 mL each of diphenhydramine HCl, lidocaine HCl, and antacid suspension and a syringe for measurement. This should supply at least 42 doses. Patients will be instructed to measure 5 mL of DLA.

All patients may repeat dosing every 4 hours PRN (as needed for pain) during the seven days of Cycle 2. On each day of that week at approximately the same time each day, preferably in the evening, a patient-reported outcome (PRO) measure will be completed (Appendix V). The patient will be asked by study staff on radiation treatment days in clinic if they feel that they are receiving enough benefit from the therapy to continue using it. If so, they will be allowed to continue for up to a week. Adverse event evaluations (for CTCAE events) should be done as clinically indicated during weekly RT assessments.

During the Continuation Phase, the patient can opt out at any time if/when they believe that the treatment is no longer beneficial. If the patient does not feel that they are receiving benefit from the therapy, s/he may be unblinded and the patient can be treated for OM at the treating physician's discretion.

8.0 ANCILLARY THERAPY, UNBLINDING

8.1 Ancillary therapy, concomitant medications, and supportive care

8.1.1 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions.

8.1.2 No analgesics or crushed ice should be given for mucositis pain for 60 minutes prior to and after the Day 1 dose. Patients will be allowed to take analgesics after 60 minutes if they feel the need for pain relief. They will be asked to record such usage on the timed questionnaires. If they utilize any other agents, aside from the test rinse, their data will be censored at the time of such use.

8.1.3 No viscous lidocaine, 'magic mouthwash', benzocaine, diphenhydramine or other rinses for mucositis on Day 1 of treatment, with the exception of 0.9 normal saline or baking soda rinse.

8.2 Unblinding Procedures

Emergency unblinding will be available 24 hours a day, every day, according to the criteria below.

Unblinding can be done in the event of an emergency or when the patient feels s/he is no longer receiving benefit from the study agent during the Continuation Phase. Please note that, if treatment is unblinded due to an emergency, the patient must permanently discontinue all protocol therapy.

Emergency Unblinding Procedures:

Examples of emergencies include 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose. Expected adverse events are listed in the "Toxicities" section below.

Contact the Alliance Executive Officer on call by calling 773-702-6800, pressing 1 to speak with an operator, and then asking for pager ID 8625 to return the call.

The institution must provide the following information to the Alliance Executive Officer:

- Alliance study ID (i.e., "A221304")
- Alliance patient ID number (e.g., "999999")
- Patient initials (e.g., "L, FM")
- Institution name
- Name and telephone number of treating physician
- Name and contact information of person requesting the unblinding procedure
- Name and contact information of person to inform of treatment assignment
- Reason for emergency unblinding

Please remember that an emergency unblinding request may be authorized only by an Alliance Executive Officer, and emergency unblinding applies only if unblinding would influence management of the medical situation.

After the Executive Officer deems unblinding is warranted, the treatment assignment will be provided to the contact person at the treating site.

Procedures for unblinding upon patient choice

Study participants can be unblinded when the patient feels s/he is no longer receiving benefit from the study agent during the Continuation Phase and all appropriate study forms have been completed. To receive patient treatment assignment, contact the Alliance Registration Office at 507-284-4130 during regular business hours

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. The CTCAE is available at http://ctep.cancer.gov/reporting/ctc.html. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

9.1 Routine adverse event reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, the Adverse Events form is used for routine AE reporting in Rave.

9.2 Expedited adverse event reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined below. Alliance investigators are required to notify the Alliance Central Protocol Operations Program Office, the Study Chair, and their Institutional Review Board if a patient has an adverse event requiring expedited reporting. All such events must be reported in an expedited manner using the CTEP Adverse Event Reporting System (CTEP-AERS). In the rare occurrence when internet connectivity is lost, a 24-hour notification is to be made to the Alliance Central Protocol Operations Office. Once internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

The Alliance requires investigators to route all expedited adverse event reports through the Alliance Central Protocol Operations Program Office for Alliance coordinated studies.

Be sure to read this entire protocol section, as requirements are described in both the table and bullet points following the table. Note that the additional instructions or exclusions are protocol specific, and in the case of a conflict, the additional instructions or exclusions supersede the table.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.2.1 Alliance A221304 reporting requirements

Expedited reporting requirements for adverse events that occur within 30 Days of the last dose of treatment [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour; 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

NOTE: Deaths clearly due to progressive disease should NOT be reported via CTEP-AERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exclusions:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- Treatment expected adverse events include those listed in Section 10.0 and in the package insert.
- All new malignancies must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e., solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), and in situ tumors. In CTCAE version 4.0, the new malignancies (both second and secondary) may be reported as one of the following: (1) Leukemia secondary to oncology chemotherapy, (2) Myelodysplastic syndrome, (3) Treatment-related secondary malignancy, or (4) Neoplasms benign, malignant and unspecified—other. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how it was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.
- All pregnancies and suspected pregnancies occurring in female patients or in the partner of a male patient during therapy or within 28 days after completion of treatment on A221304 must be reporting via CTEP-AERS. In CTCAE version 4.0, use the event term, *"pregnancy, puerperium, and perinatal condition-other, fetal exposure (grade 4)"*.
  - CTEP-AERS reports should be amended upon completion of the pregnancy to report pregnancy outcome (e.g. normal, spontaneous abortion, therapeutic abortion, fetal death, congenital abnormalities).
  - The CTEP-AERS report should be amended for any neonatal deaths or complications occurring within 28 days of birth independent of attribution. Infant deaths occurring after 28 days considered to be related to in utero exposure to the agents used in this trial should be reported via CTEP-AERS.
- The reporting of adverse events described above is in addition to, and does not supplant, the reporting of adverse events as part of the reporting of the results of the clinical trial, e.g. routine reporting.

10.0 DRUG INFORMATION

10.1 **Doxepin (Supplied)** IND Exempt

Procurement

Doxepin hydrochloride oral solution will be purchased and distributed in 4 oz. (120 mL) stock bottles by the Alliance Research Base Pharmacy. Participating institutions will order a starter supply of two bottles of doxepin HCl solution from the Alliance Research Base Pharmacy. Complete the Clinical Drug Order/Return Form, which is available on the A221304 page of the Alliance (www.allianceforclinicaltrialsinononcology.org) and CTSU (www.ctsu.org) web sites. Fax or mail the completed form to:

Medical Oncology Pharmacist
Mayo Clinic
Gonda 10-178
Rochester, MN 55905
Fax (507) 284-3464

Each site is responsible to monitor their supplies and order additional bottles as required. One bottle of doxepin HCl solution is considered to be a "bulk supply" and is to be reserved for the preparation of doses taken in the clinic. A site may order additional bottles of doxepin HCl solution in advance of patient participation in the optional continuation phase. Each site will provide their own Sterile Water for Irrigation, Sterile Water for Injection, or distilled water, oral syringes, and 4 oz. amber bottles.

At the end of the trial, any expired or remaining supplies should be destroyed according to institutional procedure.

Formulation

Each mL of solution contains doxepin hydrochloride equivalent to 10 mg doxepin. Inactive ingredients are glycerin, methlyparaben, propylparaben, flavoring agent and purified water.

Storage and Stability

Store at 20º to 25º C (68º to 77º F). A 4 oz. (120 mL) bottle is to be retained for the preparation of multiple doses. After the bottle has been opened for the first time, the site will assign an expiration date of one year, if this expiration date is shorter than the expiration date listed on the bottle.

Preparation

Cycle 1: The designated unblinded person at each institution will add 2.5 mL of doxepin HCl oral solution to 2.5 mL of Sterile Water for Irrigation, Sterile Water for Injection, or distilled water just prior to administration. This yields a dose of 25 mg doxepin in 5 mL.

Cycle 2/Continuation Phase: Sites will package doxepin 120 mL in a 4 oz. amber bottle. The prescription label will state "doxepin 10 mg/mL or placebo solution," with directions to dilute 2.5 mL with 2.5 mL of water. Assign an expiration date of one year, if this expiration date is shorter than the expiration date listed on the bottle. Patients continuing treatment at home during the continuation phase will be provided with a blinded bottle containing 120 mL of doxepin and should be instructed to use distilled water or tap water to dilute the doxepin solution.

Administration

Cycle 1: Patients will use the doxepin HCl solution as an oral rinse for one minute, then will expectorate the rinse. Patients should not eat or drink anything for 15 minutes before and after taking the medication.

Cycle 2/Continuation Phase: Patients will measure 2.5 mL of doxepin HCl 10 mg/mL solution and mix with 2.5 mL of distilled or tap water. Swish and gargle 25 mg/5 mL oral rinse for one minute, then expectorate the rinse. Patients should not eat or drink anything for 15 minutes before and after taking the medication.

Drug Interactions

Doxepin solution is not physically compatible with a number of carbonated beverages.

Pharmacokinetics

Doxepin is being used as an oral rinse for this study and no pharmacokinetics are available for this route of administration.

Adverse Events

Side effects are expected to be minimal. Based on experience in previous clinical trials, mild burning or stinging discomfort, unpleasant taste, and fatigue have been reported when the solution was used as an oral rinse.

At least minimal absorption through the oral mucosa is expected. Side effects reported when therapeutic oral doses are administered include weight gain, constipation, nausea, xerostomia, dizziness, somnolence, blurred vision, urinary retention, upper respiratory infection, low blood pressure, decreased production of blood cells, and suicidal thoughts.

Nursing Guidelines

- If solution needs to be diluted, use only water. Doxepin is not compatible with numerous carbonated beverages.
- Patients may experience a mild burning or stinging sensation after use.
- Patients may experience taste alterations.
- Because this agent is being used as an oral rinse, the normal systemic side effects of this agent are not expected. However a minimal amount of absorption through the oral mucosa is expected. Normal side effects when Doxepin is administered at full oral doses are: weight gain, constipation, nausea, xerostomia, dizziness, somnolence, blurred vision, urinary retention, and upper respiratory infection. Patients should be instructed to report any of these side effects to the study team.

10.2 DLA (diphenhydramine hydrochloride, lidocaine hydrochloride, and antacid) (Supplied)

Procurement

DLA will be provided by the Alliance Research Base Pharmacy in separate stock bottles of diphenhydramine hydrochloride, lidocaine hydrochloride, and antacid. Participating institutions will order a starter supply of two bottles of diphenhydramine hydrochloride, two bottles of viscous lidocaine hydrochloride, and two bottles of antacid from the Alliance Research Base Pharmacy. Fax or mail the Clinical Drug Order/Return Form request to the address listed in Section 10.1.

Each site is responsible to monitor their supplies and order additional bottles as required. A "bulk supply" is to be reserved for the preparation of doses taken in the clinic. A site may order additional bottles of diphenhydramine hydrochloride, lidocaine hydrochloride, and antacid in advance of patient participation in the optional continuation phase. Each site will provide its own syringes and 8 oz. amber bottles.

At the end of the trial, any expired or remaining supplies should be destroyed according to institutional procedure.

Formulation

Diphenhydramine hydrochloride 12.5 mg/5 mL alcohol free liquid is available in 120 mL bottles. Inactive ingredients are anhydrous citric acid, flavor, purified water, sodium benzoate, sodium chloride, sodium citrate, and sorbitol solution.

Lidocaine 2% viscous solution is available in 100 mL bottles. Inactive ingredients are flavoring, methylparaben, propylparaben, sodium carboxymethylcellulose, and sodium saccharin.

Antacid suspension (aluminum hydroxide 200 mg/magnesium hydroxide 200 mg/simethicone 20 mg) is available as 355 mL bottles. Inactive ingredients are butylparaben, carboxymethylcellulose sodium, flavor, hypromellose, microcrystalline cellulose, propylparaben, purified water, saccharin sodium, simethicone emulsion, and sorbitol.

Storage and Stability

Store at controlled room temperature (20° to 25° C, 68° to 77° F). Each bottle of diphenhydramine, lidocaine, and antacid will be used for the preparation of multiple doses. After the bottles have been opened for the first time, the site will assign an expiration date of one year, if this expiration date is shorter than the expiration date listed on the bottles.

Preparation

Cycle 1: The designated person at each institution will mix 1.7 mL of each of diphenhydramine hydrochloride, lidocaine hydrochloride, and antacid from each of the bulk bottles for a total dose of 5 mL.

Cycle 2/Continuation Phase: Sites will package 240 mL of DLA by mixing 80 mL each of diphenhydramine hydrochloride, lidocaine hydrochloride, and antacid in an 8 oz. Amber bottle immediately prior to dispensing to the patient. No tap or distilled water for dilution will be required. The prescription label will state DLA (diphenhydramine hydrochloride, lidocaine hydrochloride, antacid 1:1:1) with directions to take 5 mL (please note approval to round dose from 5.1 mL). Assign an expiration date of 14 days under refrigeration.

Administration

Cycle 1: Patients will use the DLA solution as an oral rinse for one minute, then will expectorate the rinse. Patients should not eat or drink anything for 15 minutes before and after taking the medication.

Cycle 2/Continuation Phase: Patients will shake the suspension well, then measure 5 mL (please note approval to round dose from 5.1 mL) of DLA solution. Swish and gargle 5 mL oral rinse for one minute, then expectorate the rinse. Patients should not eat or drink anything for 15 minutes before and after taking the medication

Drug Interactions

Not applicable.

Pharmacokinetics

Not applicable.

Adverse Events

As an oral rinse the patient may experience taste disturbances and burning/tingling in the oral cavity. Minimal systemic absorption through the oral mucosa is expected. Side effects with therapeutic oral doses are drowsiness or any CNS adverse effects, constipation, diarrhea, nausea and dry mouth.

Nursing Guidelines

- Patients should be instructed to rinse with the DLA solution for 1 minute and then expectorate the rinse. Patients should avoid food or drink for 15 minutes before and after administration.
- Warn patients of the possibility of loss of sensation to the mouth and tongue and to use caution when eating.
- As the rinse is not swallowed expected systemic side effects from the ingredients would not be expected. Instruct patient to report any unexpected side effects to the study team.

10.3 Placebo (Supplied)

Procurement

Placebo (Ora-Sweet SF syrup) will be purchased and distributed in 16 oz. stock bottles by the Alliance Research Base Pharmacy. Participating institutions will order a starter supply of two bottles of placebo (Ora-Sweet SF syrup) from the Alliance Research Base Pharmacy. Fax or mail the Clinical Drug Order/Return Form request to the address listed in Section 10.1.

Each site is responsible to monitor their supplies and order additional bottles as required. One bottle of Ora-Sweet SF is considered to be a "bulk supply" and is to be reserved for the preparation of doses taken in the clinic. A site may order additional bottles of Ora-Sweet SF in advance of patient participation in the optional continuation phase. Each site will provide its own Sterile Water for Irrigation, Sterile Water for Injection, or distilled water, oral syringes and 4 oz. amber bottles.

At the end of the trial, any expired or remaining supplies should be destroyed according to institutional procedure.

Formulation

Ora-Sweet SF will be used as the base solution for preparing the placebo dose. Ora-Sweet SF is a flavored sugar-free syrup vehicle available in 473 mL (16 oz.) bottles. The product contains glycerin, sorbitol, sodium saccharin, xanthan bum, flavoring agent, and purified water. The solution is buffered with citric acid and sodium citrate and preserved with methylparaben, propylparaben, and potassium sorbate. No alcohol will be contained in the mixing solvents, which may cause stinging sensations.

Storage and Stability

Store at controlled room temperature (15º to 30º C, 59º to 86º F). A 473 mL (16 oz.) bottle is to be retained for the preparation of multiple doses. After the bottles have been opened for the first time, the site will assign an expiration date of one year, if this expiration date is shorter than the expiration date listed on the bottles.

Preparation

Cycle 1: The designated unblinded person at each institution will add 2.5 mL of Ora-Sweet SF oral solution to 2.5 mL of Sterile Water for Irrigation, Sterile Water for Injection, or distilled water just prior to administration. The total dose will be 5 mL.

Cycle 2/Continuation Phase: Sites will package Ora-Sweet SF 120 mL in a 4 oz. amber bottle. The prescription label will state "doxepin 10 mg/mL or placebo solution," with directions to dilute 2.5 mL with 2.5 mL of water. Assign an expiration date of one year, if this expiration date is shorter than the expiration date listed on the bottle. Patients continuing treatment at home during the continuation phase will be provided with a blinded bottle containing 120 mL of Ora-Sweet SF and should be instructed to use distilled water or tap water to dilute the Ora-Sweet SF solution.

Administration

Cycle 1: Patients will use the Ora-Sweet SF solution as an oral rinse for one minute, then will expectorate the rinse. Patients should not eat or drink anything for 15 minutes before and after taking the medication.

Cycle 2/Continuation Phase: Patients will measure 2.5 mL of Ora-Sweet SF solution and mix with 2.5 mL of distilled or tap water. Swish and gargle 5 mL oral rinse for one minute, then expectorate the rinse. Patients should not eat or drink anything for 15 minutes before and after taking the medication.

Drug Interactions

Not applicable.

Pharmacokinetics

Not applicable.

Adverse Events

Not applicable.

Nursing Guidelines

Because patients and staff administering doxepin and placebo will be blinded to the agent delivered, the nursing guidelines for doxepin (Section 10.1) should be followed for placebo.

11.0 MEASUREMENT OF EFFECT

At the time of enrollment, the toxicity grade of mucous membrane by the Acute Radiation Morbidity Scoring Criteria (http://www.rtog.org/researchassociates/adverseeventreporting/acuteradiationmorbidityscoringcriteria.aspx) will be recorded. For patient-reported outcomes, numerous OM severity assessment tools exist ranging in complexity from simple combined variable scoring scales to very detailed, objective mucositis rating scales.[2 4,14,41] The WHO OM scale is the most commonly reported and requires the least examiner experience; however, it has been criticized for combining symptoms, signs, and functional changes[14]. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 included separate subjective and objective scales for mucositis. However, in version 4.0, the objective scale based on clinical exam has been eliminated. The Oral Mucositis Assessment Scale is a psychometrically validated instrument for this patient population.[41] It is utilized to score nine anatomical sites of the oral mucosa with respect to ulceration/pseudomembrane formation and erythema.

Pain is the most important and bothersome subjective symptom of OM, and yet there are few validated assessment instruments measuring OM pain resulting from cancer therapy.[42] Two examples of validated tools are the Oral Mucositis Daily Questionnaire (OMDQ) and the Oral Mucositis Weekly Questionnaire-Head and Neck Cancer (OMWQ-HN).[43-45] A modified combination of both these instruments will be used to assess baseline OM symptoms. Questionnaires with eleven-point numerical analogue scales (0−10 scores) will be used to measure pain, unpleasant taste, stinging or burning, and drowsiness at defined intervals following doxepin or placebo rinse and in weekly follow-up if patients choose to continue using doxepin rinse. Numerical analog scales are validated measures of symptoms.[46-50] These are the same instruments utilized in the recently completed positive Alliance doxepin study. A standard conversion table for 24-hour morphine equivalence will also be used in the one-week continuation phase to convert different opioid regimens into comparable terms.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Treatment

During the 7-day continuation phase, the patient can opt out at any time when they believe that the treatment is no longer beneficial. Patients will then be treated per clinical practice recommendations off study.

12.2 Managing ineligible and canceled patients and major protocol violations

Baseline data must be submitted per Section 5.0 for patients deemed ineligible or canceled. See also the Forms Packet for full details of data submission requirements.

12.3 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Overview

This is a randomized, placebo-controlled, three-arm phase III trial to assess the efficacy of doxepin oral rinse or DLA versus placebo for the treatment of cancer therapy-related OM. Since each of the two treatment arms will be compared against placebo arm, the conservative Bonferroni approach (instead of Dunnett's multiple comparison procedure) will be used to adjust for multiplicity.

13.2 Sample Size, Accrual Time and Study Duration

13.2.1 Sample Size

In the recently completed phase III randomized, double-blind trial comparing doxepin to placebo for treatment of oral mucositis pain in patients undergoing high-dose, curative head and neck radiotherapy treatment,[39] we observed a pain AUC reduction of 9.1 (Standard deviation, SD = 7.9) with doxepin vs. 4.7 (SD = 6.1) in the placebo arm. This corresponded to a difference in pain AUC reduction 4.4, with a common estimate SD of 7.0. Considering a clinically meaningful difference in pain AUC reduction being 3.5 (i.e., half of the common SD = 7.0, according to Norman GR, [51] Sloan JA[52]), in a 2-arm study we would need a sample size of 156 patients (78 patients per arm) to have at least 80% power to detect such an effect size, using the two-sample *t*-test at the 2.5% significance level. As we have two treatment arms (doxepin or DLA versus placebo) in this 3-arm study design, doxepin, DLA or placebo, the sample size will be 234 patients in total (78 patients per arm). This sample size will be further inflated by 15% to 270 patients to account for patient ineligibility, cancellation, or major violations.

13.2.2 Accrual Rate and Accrual Duration

We anticipate accruing approximately 20 patients per month, based on our previous experience in clinical practice. This would mean completing the primary accrual within 14 months from study initiation and completing analysis within 18 months from study initiation.

13.2.3 Primary Endpoint Completion Date for ClinicalTrials.gov Reporting

For purpose of ClinicalTrial.gov reporting, the Primary Endpoint Completion Date (PECD) for this study is the time the last patient registered has been followed for at least one day.

13.3 Statistical Design and Analysis for the Primary Endpoint

13.3.1 Primary Endpoint

The primary endpoint of this study is the total pain reduction (mouth and throat) as measured by the numerical analogue scale of mouth pain in the questionnaires taken at baseline, and 5, 15, 30, 60, 120, 240 minutes after assigned treatment for doxepin or DLA vs. placebo. The total pain reduction will be calculated by the (average of mouth and throat) area under the curve (AUC) adjusting for baseline, with time scale replaced by a numerical scale of 1, 2, 3, 4, 5 and 6. The numerical scale will be used rather than the raw time scale in order to give proper weights to more immediate patient-reported mouth pain outcomes after treatment. The AUC will be prorated when there are terminal missing data. If the missing data are intermittent, simple imputation by trapezoidal rules will be applied to calculate the AUC. If a patient cancels, is missing baseline data, or only provides baseline data, he/she will be excluded from the statistical analysis.

13.3.2 Statistical Design

This is a three-arm parallel group design with neither cross-over nor interim analysis.

13.3.3 Study Operating Characteristics

Simulation studies of 10,000 clinical trials are conducted for the proposed parallel group design. The probabilities of rejecting null hypothesis for various effect sizes (in AUC reduction), i.e. global power are summarized for both Bonferroni and Dunnett's multiple comparison procedures in the following table. With a total sample size of 234 patients, the empirical global powers are approximately 90% at a family-wise 5% significance level. The Dunnett's single step procedure improves the power but only a small amount. The simulation for operating characteristics is conducted using EAST version 6.2.

Table 1. Power analysis for various effect sizes with a total sample size of 234 patients.

Scenario	Placebo	DLA	Doxepin	Multiple Comparison	Global Power (%)
1	4.4	6.15	7.9	Bonferroni	88.9
1	4.4	6.15	7.9	Dunnett's single step	89.3
2	4.4	4.5	7.9	Bonferroni	87.8
2	4.4	4.5	7.9	Dunnett's single step	88.1
3	4.4	7.8	7.9	Bonferroni	95.3
3	4.4	7.8	7.9	Dunnett's single step	95.6

13.3.4 Analysis Plan

A modified intent-to-treat principle will be applied for statistical analysis of efficacy in evaluable patients.[53] Evaluable patients are defined as all patients meeting the eligibility criteria who did not cancel prior to receiving treatment and had no major violations.

The primary analysis of the total pain reduction between arms will be conducted using the two-sample *t*-test or nonparametric Wilcoxon rank-sum testing. Transformation of AUC (such as log) may be taken if the empirical distribution of residuals is deemed far from anormal distribution. Supplementary analyses will be conducted to analyze these repeated measurements of mouth and throat pain in a longitudinal data model. Graphical procedures will include stream plots of individual patient mouth pain scales and plots of average values over time for each treatment arms.

13.4 Supplementary Analysis Plans

13.4.1 Secondary Endpoints

1) The total unpleasant taste of the oral rinse as measured by the numerical analogue scale of taste of the oral rinse in the questionnaires.
2) The total stinging or burning from the oral rinse as measured by the numerical analogue scale of stinging or burning from the oral rinse in the questionnaires.
3) The total drowsiness increase as measured by the numerical analogue scale of drowsiness questionnaires.
4) The incidence of using alternative analgesics between 1 and 4 hours after initial mouthwash.
5) Patient preference for continued therapy with oral rinse after initial test rinse phase, as measured by Item 9 in the patient-reported questionnaire after 4 hours.
6) The length of time, pain score, and alternative analgesics use in the Continuation Phase.

13.4.2 Secondary Analysis

Multiplicity will not be adjusted for secondary analyses, hence, statistically significant findings from secondary analyses are exploratory in nature and therefore shall be interpreted as such. Descriptive statistics and graphical approaches will form the basis for most secondary analyses.

1) Similar analysis as primary endpoint will be conducted for total unpleasant taste.
2) Similar analysis as primary endpoint will be conducted for total stinging or burning.
3) Similar analysis as primary endpoint will be conducted for total drowsiness increase.
4) The incidence of utilizing additional analgesics between 1-4 hours after initial mouthwash will be compared between the arms by the Chi-square test or Fisher's exact test.
5) Frequency will be used to summarize patient preference for continued therapy and Chi-square test may be applied, if appropriate.
6) Descriptive statistics and graphical procedures will be used to summarize the length of time, pain score, and alternative analgesics use in the Continuation Phase.

13.5 Study Monitoring

13.5.1 Adverse Event Stopping Rule

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below. Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as possible, probable, or definite) that satisfy the following criteria:

1) If 5 or more of the first 20 treated patients (or 25% of all patients after 20 patients have been accrued) experience a grade 3 or higher non-hematologic adverse event and the adverse event rate is higher in either active treatment arm.

2) If 3 or more of the first 20 treated patients (or 15% of all patients after 20 patients have been accrued) experience a grade 4 or higher non-hematologic adverse event and the adverse event rate is higher in either active treatment arm.

13.5.2 Accrual Monitoring Stopping Rule

Slow Accrual: Patient accrual will be closely monitored by the investigators and secondary statistician on a monthly basis. If the accrual rate falls below 50% of expected accrual rate, investigators will carefully review feedback from sites and consider taking measures to encourage patient enrollment.

13.6 Study Reporting

13.6.1 This study will be monitored by the Alliance Data Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every month as per NCI guidelines.

13.6.2 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrials.gov" web site. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov.

13.7 Descriptive Factors

None

13.8 Inclusion of Women and Minorities

All studies must address the issue of inclusion of women and minorities in clinical research and whether gender or race/ethnicity differences in the intervention effect are to be expected. The statisticians will provide statistical analysis of past Alliance phase III studies as well as how the review of the literature will be reflected in the statistical section. The minority/gender table from the PSW should be included here.

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	3	2	5
Not Hispanic or Latino	159	106	265
Ethnic Category: Total of all subjects	162	108	270
Racial Category			
American Indian or Alaskan Native	1	1	2
Asian	3	2	5
Black or African American	14	11	25
Native Hawaiian or other Pacific Islander	1	1	2
White	143	93	236
Racial Category: Total of all subjects	162	108	270

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15.0 MODEL CONSENT FORM

Study Title for Study Participants:

Testing doxepin and "magic mouthwash" as oral rinses for mucositis pain for patients receiving radiation therapy

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

Alliance A221304: A phase III placebo-controlled, randomized three-arm study of doxepin and a topical rinse in the treatment of acute oral mucositis pain in patients receiving radiotherapy with or without chemotherapy

What is the usual approach to my painful mouth sores?

You are being asked to take part in this research study because you have been diagnosed with cancer and will be receiving radiation therapy to your head and neck. It is known that this type of radiation therapy can cause painful mouth sores, which can interfere with activities of daily living, including eating and drinking. Patients who are not in this study are usually treated for these sores with rinses (or mouthwashes) containing different drugs such as diphenhydramine (e.g., Benadryl), lidocaine, and antacids. The combination of these drugs, which will be used for this study, is also known as "DLA."

Why is this study being done?

The purpose of this study is to test whether a mouthwash made with a drug called doxepin can reduce the pain caused by mouth sores resulting from radiation therapy. The effects of doxepin will be compared to DLA and placebo. A placebo is a liquid that tastes and looks like the study drug but contains no medication. There will be about 270 people taking part in this study.

Doxepin is approved by the Food and Drug Administration (FDA) for the treatment of depression, anxiety, long term pain management, and a cream for the management of rash. The doxepin used in this study is considered investigational, which means it has not been approved by the FDA for the use described in this study.

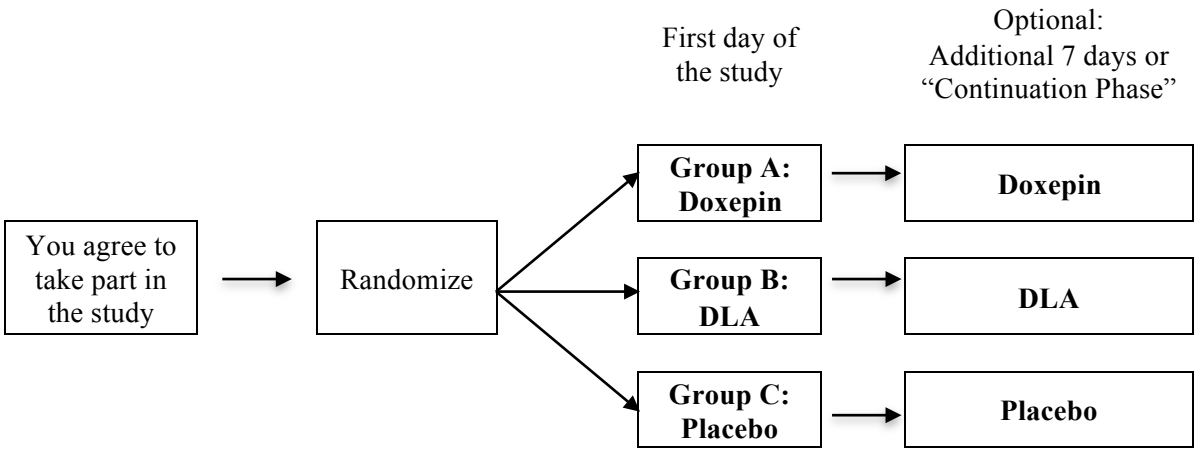
What are the study groups?

This study has three study groups.

- Group 1 will get doxepin mouthwash.
- Group 2 will get the DLA mouthwash often used for painful mouth sores.
- Group 3 will get a placebo mouthwash.

A computer will by chance assign you to treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the others.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



Day one of the study: On the first day of the study, you will receive a one-time single dose of the rinse to swish, gargle and spit. You will not know which of the three rinses you will receive. You will swish and gargle about 1 teaspoon of the rinse in your mouth for 1 minute and then spit it out.

Also on the first day, you will be asked to fill out seven questionnaires about your feelings of well-being and about your mouth pain. You will fill out the questionnaires in your study doctor's office before using the medication and then again at 5, 15, 30 and 60 minutes after you use the study rinse. You will then be able to leave the study doctor's office. You will be given directions for completing the questionnaires at 2 and 4 hours after you used the rinse. You may receive a phone call reminder to fill out the questionnaire at 2 and 4 hours. At each of these time points, it should take 5 minutes or less to complete the questionnaires.

You should not take viscous lidocaine, 'magic mouthwash', benzocaine, diphenhydramine or other medicated oral rinse on the first day of treatment (except saline or baking soda rinse). If possible, no pain medication or crushed ice should be used for one hour prior to and after the Day 1 rinse. Also, you should not eat or drink anything for 15 minutes before and after taking the study rinse.

Continuation Phase: For up to seven days after the first time you took the rinse, you may choose to start a daily regimen of using the rinse at home as needed for up to 1 week. This is called the "Continuation Phase" of the study. If you decide to participate in this one-week continuation phase, you will be given study rinse that you can take home with instructions on how to properly mix the rinse for use at home. You can use the study rinse as often as every 4 hours, if needed. If you feel that the rinse is not working, you may stop using it at any time.

You will also be asked to complete a questionnaire each day of that week. We ask that you complete the questionnaire at the same time each day, preferably in the evening, and return it to the study staff when it is completed. It should take five minutes or less each day to complete the questionnaire.

If possible, during the continuation phase you should avoid taking any medication for mouth pain for 60 minutes before and after the study medication. You may take oral pain medication 60 minutes after you receive the study medication if you feel the need for additional pain relief. You will be asked to record these medications in the questionnaire. You should also avoid eating for 15 minutes before and after using the study rinse.

How long will I be in this study?

You will be in the study for at least one day. If you choose to participate in the Continuation Phase, you will be in the study for up to an additional 7 days after you start the Continuation phase.

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

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

- You may lose time at work or home and spend more time than usual in the hospital or doctor's office
- You may be asked sensitive or private questions which you normally do not discuss

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.

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

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

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Study Group 1 - Possible side effects of doxepin

COMMON, SOME MAY BE SERIOUS In 100 people receiving doxepin as given in this study, more than 20 and up to 100 may have:
• Mild burning in your mouth • Stinging discomfort in your mouth • Mild taste change • Drowsiness

RARE, SOME MAY BE SERIOUS In 100 people receiving doxepin as given in this study, 3 or fewer may have:
• Constipation • Mouth dryness due to lack of saliva • Dizziness or lightheadedness • Sleepiness • Difficulty urinating • Lung infection • Weight gain • Nausea • Blurred vision • Decreased production of blood cells • Low blood pressure • Suicidal thoughts

Study Group 2 - Possible side effects of diphenhydramine, lidocaine, and antacid (DLA)

COMMON, SOME MAY BE SERIOUS In 100 people receiving DLA as given in this study, more than 20 and up to 100 may have:
• Mild burning in your mouth • Stinging discomfort in your mouth • Mild taste change

RARE, SOME MAY BE SERIOUS In 100 people receiving DLA as given in this study, 3 or fewer may have:
• Constipation or diarrhea • Mouth dryness due to lack of saliva • Dizziness or lightheadedness • Sleepiness • Difficulty urinating • Lung infection • Shortness of breath • Nausea • Blurred vision • Allergic reaction • Itching or mild skin reaction such as hives • Excessive sweating • Rash or flushing of the skin • Mild confusion or disorientation • Decreased production of blood cells • Low blood pressure • Life-threatening, irregular heartbeat • Kidney stones

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. While it is not expected that the amount of study rinse that will be absorbed in your bloodstream will be high, an accidental overdose of the study rinse may be damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

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

It is not possible to know at this time if the doxepin is better than the usual approach using mouth rinses with drugs intended to numb the pain, so this study may or may not help you. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

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

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

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, Institutional Review Board, or the FDA.

What are my rights in this study?

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

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

The doxepin, DLA and placebo will be supplied at no charge while you take part in this study. The cost of getting the rinses ready and giving it to you is not paid by the so you or your insurance company may have to pay for this.

You and/or your health plan/insurance company will need to pay for all of the other costs of care. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

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

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

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

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

- The Alliance for Clinical Trials in Oncology
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

Where can I get more information?

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

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

Who can answer my questions about this study?

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

My Signature Agreeing to Take Part in the Study

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

Participant's signature_____

Date of signature_____

APPENDIX I: ORAL PAIN ASSESSMENT

1. On a scale from 0 to 10, what number best describes your MOUTH PAIN due to your radiation treatment now? (circle one number)

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst pain imaginable or possible

Eligibility screening: When this question is asked for eligibility screening, an oral exam confirming the presence of mucositis should be performed by the enrolling clinician in addition to asking the patient this question.

Baseline/Day 1: This question is also to be asked on Day 1 prior to the first dose of study drug.

APPENDIX II: REGISTRATION FATIGUE/UNISCALE ASSESSMENT

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and recorded on the Registration Fatigue/Uniscale Assessment Form (see Forms Packet).

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

APPENDIX III: PATIENT COMPLETED ORAL SYMPTOMS BOOKLET (BASELINE TO 1 HOUR POST ADMINISTRATION)

PATIENT INFORMATION SHEET
Patient Completed Oral Symptoms Booklet
(Baseline to 60 minutes Post Administration)

You have been given booklets to complete for this study. The booklets contain questions about your oral symptoms as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You will be given two booklets on the first day you are on the study.

2. The first booklet will be filled out on the first day in the study doctor's office. Please fill out this first booklet at each of the following times:
    a. Baseline before oral rinse
    b. 5 minutes after oral rinse
    c. 15 minutes after oral rinse
    d. 30 minutes after oral rinse
    e. 60 minutes (1 hour) after oral rinse

3. Please return this booklet to your nurse or your physician before leaving the doctor's office. You will take the second booklet with you when you leave the doctor's office.

4. Directions on how to complete each set of questions are written on the top of each set.

5. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

Thank you for taking the time to help us.

Pre-treatment Questions

Before rinsing your mouth with the oral solution, please complete this page.

1. On a scale from 0 to 10, what number best describes your MOUTH PAIN due to your radiation treatment now? (circle one number)

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst pain imaginable or possible

2. On a scale from 0 to 10, what number best describes your THROAT PAIN (i.e., pain with swallowing) due to your radiation treatment now? (circle one number)

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst pain imaginable or possible

3. On a scale from 0 to 10, what number best describes your DROWSINESS now? (circle one number)

0	1	2	3	4	5	6	7	8	9	10
No drowsiness										Extreme drowsiness, leading to sleep

4. Did you use any medications for PAIN in the past 24 HOURS? (circle 'Yes' or 'No')

   Yes No

   If yes, Please list the medications you took for PAIN in the past 24 HOURS:

Name	Strength	Route	Frequency
For example *Oxycodone*	*5 mg*	*By mouth*	*Every 4 hours*

5. Do you currently smoke cigarettes? (circle 'Yes' or 'No')

   Yes No

6. Do you currently drink alcohol? (circle 'Yes' or 'No')

   Yes No

Treatment Information

Please now rinse your mouth with the oral rinsing medication. DO NOT SWALLOW the rinse. SWISH and GARGLE it around all portions of your mouth for a total of ONE MINUTE then SPIT IT OUT and record the current date and time:

Today's date: __ __ / __ __ / __ __ __ __ (MM/DD/YYYY)

Current time
(Enter time in the boxes and circle AM or PM.) For example [10] : [30] (AM) / PM

[ ] : [ ] AM / PM

You can keep track of the times to complete the questionnaires by using this table. Enter the current time onto the first row of the table and the schedule for completing the other time points today can be filled out.

Time point	**EXAMPLE**	**ACTUAL TIME**
Current time (just after you finished the rinse)	10:30 (AM) / PM	__ __ : __ __ AM / PM
		PLANNED TIMES
5 minutes	10:35 (AM) / PM	__ __ : __ __ AM / PM
15 minutes	10:45 (AM) / PM	__ __ : __ __ AM / PM
30 minutes	11:00 (AM) / PM	__ __ : __ __ AM / PM
60 minutes (1 hour)	11:30 (AM) / PM	__ __ : __ __ AM / PM
120 minutes (2 hours)	12:30 AM / (PM)	__ __ : __ __ AM / PM
240 minutes (4 hours)	2:30 AM / (PM)	__ __ : __ __ AM / PM

We hope you will feel better soon. Five minutes after the time you rinsed your mouth, please complete the next questionnaire page.

Questionnaire after 5 minutes

This page is to be completed 5 MINUTES after you rinsed with the oral solution for one minute and spit it out.

Current time
(Enter time in the boxes and circle AM or PM.) For example [10] : [30] (AM) / PM

[ ] : [ ] AM / PM

1. On a scale from 0 to 10, what number best describes your MOUTH PAIN due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

2. On a scale from 0 to 10, what number best describes your THROAT PAIN (i.e., pain with swallowing) due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

3. On a scale from 0 to 10, what number best describes any STINGING OR BURNING FROM THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No stinging or burning — Worst stinging or burning possible

4. On a scale from 0 to 10, what number best describes the TASTE OF THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Acceptable — Terrible

5. On a scale from 0 to 10, what number best describes your DROWSINESS now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No drowsiness — Extreme drowsiness, leading to sleep

6. Have you noticed any other side effects from the oral rinse? (circle 'Yes' or 'No')

   Yes No

   If yes, please explain

   _____

   _____

   _____

After 15 minutes from the time you rinsed your mouth (10 minutes from now), please complete the next questionnaire page.

Questionnaire after 15 minutes

This page is to be completed 15 MINUTES after you rinsed with the oral solution for one minute and spit it out.

Current time
(Enter time in the boxes and circle AM or PM.) For example [10] : [30] (AM) / PM

[ ] : [ ] AM / PM

1. On a scale from 0 to 10, what number best describes your MOUTH PAIN due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

2. On a scale from 0 to 10, what number best describes your THROAT PAIN (i.e., pain with swallowing) due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

3. On a scale from 0 to 10, what number best describes any STINGING OR BURNING FROM THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No stinging or burning — Worst stinging or burning possible

4. On a scale from 0 to 10, what number best describes the TASTE OF THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Acceptable — Terrible

5. On a scale from 0 to 10, what number best describes your DROWSINESS now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No drowsiness — Extreme drowsiness, leading to sleep

6. Have you noticed any other side effects from the oral rinse? (circle 'Yes' or 'No')

   Yes No

   If yes, please explain

   _____

   _____

   _____

After 30 minutes from the time you rinsed your mouth (about 15 minutes from now), please complete the next questionnaire page.

Questionnaire after 30 minutes

This page is to be completed 30 MINUTES after you rinsed with the oral solution for one minute and spit it out.

Current time
(Enter time in the boxes and circle AM or PM.) For example [10] : [30] (AM) / PM

[ ] : [ ] AM / PM

1. On a scale from 0 to 10, what number best describes your MOUTH PAIN due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

2. On a scale from 0 to 10, what number best describes your THROAT PAIN (i.e., pain with swallowing) due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

3. On a scale from 0 to 10, what number best describes any STINGING OR BURNING FROM THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No stinging or burning — Worst stinging or burning possible

4. On a scale from 0 to 10, what number best describes the TASTE OF THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Acceptable — Terrible

5. On a scale from 0 to 10, what number best describes your DROWSINESS now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No drowsiness — Extreme drowsiness, leading to sleep

6. Have you noticed any other side effects from the oral rinse? (circle 'Yes' or 'No')

   Yes No

   If yes, please explain

   _____

   _____

   _____

After 60 minutes (1 hour) from the time you rinsed your mouth (about 30 minutes from now), please complete the next questionnaire page.

Questionnaire after 60 minutes

This page is to be completed 60 MINUTES (1 HOUR) after you rinsed with the oral solution for one minute and spit it out.

Current time
(Enter time in the boxes and circle AM or PM.) For example [10] : [30] (AM) / PM

[ ] : [ ] AM / PM

1. On a scale from 0 to 10, what number best describes your MOUTH PAIN due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

2. On a scale from 0 to 10, what number best describes your THROAT PAIN (i.e., pain with swallowing) due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

3. On a scale from 0 to 10, what number best describes any STINGING OR BURNING FROM THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No stinging or burning — Worst stinging or burning possible

4. On a scale from 0 to 10, what number best describes the TASTE OF THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Acceptable — Terrible

5. On a scale from 0 to 10, what number best describes your DROWSINESS now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No drowsiness — Extreme drowsiness, leading to sleep

6. Have you noticed any other side effects from the oral rinse? (circle 'Yes' or 'No')

   Yes No

   If yes, please explain

   _____

   _____

   _____

Once you have completed this booklet, please give the booklet to your nurse or care provider.

After 120 minutes (2 hours) from the time you rinsed your mouth (about an hour from now), please complete the next questionnaire booklet.

You may complete the next booklet from home, if you prefer. You may receive a telephone reminder from the study staff about completing the next booklet.

APPENDIX IV: PATIENT COMPLETED ORAL SYMPTOMS BOOKLET (2 TO 4 HOURS POST ADMINISTRATION)

PATIENT INFORMATION SHEET
Patient Completed Oral Symptoms Booklet
(Two to Four Hours Post Administration)

You have been given booklets to complete for this study. The booklets contain questions about your oral symptoms as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You will be given two booklets on the first day you are on the study. You should have given the first booklet to the nurse or doctor before leaving the doctor's office.

2. This second booklet will be taken with you when you leave the doctor's office. Please fill this second booklet out at these time points:
    a. 120 minutes (2 hours) after oral rinse
    b. 240 minutes (4 hours) after oral rinse

3. After completing this booklet, please return it to your nurse or physician at your next visit or mail it back in the provided envelope.

4. It is very important that you return the booklets to us, whether you finish the study or not.

5. Directions on how to complete each set of questions are written at the beginning of each set.

6. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

Thank you for taking the time to help us.

Questionnaire after 120 minutes

This page is to be completed 120 MINUTES (2 HOURS) after you rinsed with the oral solution for one minute and spit it out.

Current time
(Enter time in the boxes and circle AM or PM.) For example [10] : [30] (AM) / PM

[ ] : [ ] AM / PM

1. On a scale from 0 to 10, what number best describes your MOUTH PAIN due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

2. On a scale from 0 to 10, what number best describes your THROAT PAIN (i.e., pain with swallowing) due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

3. On a scale from 0 to 10, what number best describes any STINGING OR BURNING FROM THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No stinging or burning — Worst stinging or burning possible

4. On a scale from 0 to 10, what number best describes the TASTE OF THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Acceptable — Terrible

5. On a scale from 0 to 10, what number best describes your DROWSINESS now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No drowsiness — Extreme drowsiness, leading to sleep

6. Have you noticed any other side effects from the oral rinse? (circle 'Yes' or 'No')

   Yes No

   If yes, please explain

   _____

   _____

   _____

7. Did you take any other pain medications over the last hour? (circle 'Yes' or 'No')

   Yes No

   If yes, please list the medications that you took:

Name	Strength	When
For example *Oxycodone*	*5 mg*	*one hour ago or within the last 60 minutes*

After 240 minutes (4 hours) from the time you rinsed your mouth (about 2 hours from now), please complete the next questionnaire page.

Questionnaire after 240 minutes

This page is to be completed 240 MINUTES (4 HOURS) after you rinsed with the oral solution for one minute and spit it out.

Current time
(Enter time in the boxes and circle AM or PM.) For example [10] : [30] (AM) / PM

[ ] : [ ] AM / PM

1. On a scale from 0 to 10, what number best describes your MOUTH PAIN due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

2. On a scale from 0 to 10, what number best describes your THROAT PAIN (i.e., pain with swallowing) due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

3. On a scale from 0 to 10, what number best describes any STINGING OR BURNING FROM THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No stinging or burning — Worst stinging or burning possible

4. On a scale from 0 to 10, what number best describes the TASTE OF THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Acceptable — Terrible

5. On a scale from 0 to 10, what number best describes your DROWSINESS now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No drowsiness — Extreme drowsiness, leading to sleep

6. Have you noticed any other side effects from the oral rinse? (circle 'Yes' or 'No')

   Yes No

   If yes, please explain

   _____

   _____

7. Did you take any other pain medications over the last two hours? (circle 'Yes' or 'No')

   Yes No

   If yes, please list the medications that you took

Name	Strength	When
For example *Oxycodone*	*5 mg*	*one hour ago or within the last 60 minutes*

   _____

   _____

   _____

   _____

8. Was the study medication rinse helpful in alleviating your mouth/throat pain at any time over the last 4 hours? (circle 'Yes' or 'No')

   Yes No

   Other comments

   _____

   _____

9. Based on your experience with this current oral rinsing medication, would you want to take another dose now if it were available? (circle 'Yes' or 'No')

   Yes No

   If yes, we encourage you to consider continuing with the study rinse for up to one week in the continuation phase of the study. Contact the study staff about how to do this when you return to the clinic.

   If no, please explain

   _____

   _____

This completes the questionnaires for today. Thank you very much for your participation in this study.

APPENDIX V: DAILY QUESTIONNAIRE FOR PATIENTS WHO CONTINUE WITH STUDY RINSES

PATIENT INFORMATION SHEET
Patient Completed Oral Symptoms Booklet
(Daily during Continuation Phase)

You have been given booklets to complete for this study. The booklets contain questions about your oral symptoms as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You will be given one booklet to take home with you while you are on the continuation phase of the study.

2. This booklet will be taken with you when you leave the doctor's office. Please fill this booklet out every day for 7 days unless you stop taking the oral rinse early. We ask that you complete each daily questionnaire at the same time each day, preferably in the evening.

3. After completing this booklet, please return it to your nurse or physician at your next visit or mail it back in the provided envelope.

4. It is very important that you return the booklets to us, whether you finish the study or not.

5. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

Thank you for taking the time to help us.

Today's date: __ __ / __ __ / __ __ __ __ (MM/DD/YYYY)

Current time
(Enter time in the boxes and circle AM or PM.) For example [10] : [30] AM / (PM)

[ ] : [ ] AM / PM

1. On a scale from 0 to 10, what number best describes your MOUTH PAIN due to your radiation treatment now? (circle one number)

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst pain imaginable or possible

2. Did you use any medications for PAIN over the past 24 HOURS? (circle 'Yes' or 'No')

   Yes No

   If yes, please list all of the pain medications (other than the study medication) and dosages that you used today:

Name	Strength	When
For example *Oxycodone*	*5 mg*	*9:00 AM*

3. Did you use the study rinse today? (circle 'Yes' or 'No')

   Yes **(If yes, answer questions 4 through 7, and skip question 8)**

   No **(If no, skip to question 8)**

4. Is the study medication rinse helpful in alleviating your mouth/throat pain? (circle 'Yes' or 'No')

   Yes No

5. On a scale from 0 to 10, what number best describes any STINGING OR BURNING FROM THE ORAL RINSE this day? (circle one number)

0	1	2	3	4	5	6	7	8	9	10
No stinging or burning										Worst stinging or burning possible

6. On a scale from 0 to 10, what number best describes the TASTE OF THE ORAL RINSE this day? (circle one number)

0	1	2	3	4	5	6	7	8	9	10
Acceptable										Terrible

7. Have you noticed any other side effects from the oral rinse this day? (circle 'Yes' or 'No')

   Yes No

   If yes, please explain

   _____

   _____

   _____

   Other comments:

   _____

   _____

8. If you did not use the study rinse this day, please state why you did not use the study rinse by checking one or more of the following:

   ___ Pain got better

   ___ Study rinse did not work

   ___ Didn't like side effects

   Which ones? _____

   ___ Other

   Please explain _____

This completes this day's questionnaire. Thank you for your continued participation in this study.

APPENDIX VI: RTOG ACUTE RADIATION MORBIDITY SCORING CRITERIA: MUCOUS MEMBRANE

Grade	0	1	2	3	4
Mucous Membrane	No change over baseline	Injection/ may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinitis discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis

Update #01
08/01/2015

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPADTE TO ALLIANCE A221304

A PHASE III PLACEBO-CONTROLLED, RANDOMIZED THREE-ARM STUDY OF DOXEPIN AND A TOPICAL RINSE IN THE TREATMENT OF ACUTE ORAL MUCOSITIS PAIN IN PATIENTS RECEIVING RADIOTHERAPY WITH OR WITHOUT CHEMOTHERAPY

Doxepin solution, placebo solution, and DLA (diphenhydramine, lidocaine, antacid) provided and distributed by Alliance Research Base Pharmacy

[X]	**Update:**	[ ]	**Status Change:**
[X]	Eligibility changes	[ ]	Pre-Activation
[ ]	Therapy / Dose Modifications / Study Calendar changes	[ ]	Activation
[X]	Informed Consent changes	[ ]	Closure
[ ]	Scientific / Statistical Considerations changes	[ ]	Suspension / temporary closure
[ ]	Data Submission / Forms changes	[ ]	Reactivation
[X]	Editorial / Administrative changes		
[ ]	Other:		

IRB approval (or disapproval) is required within 90 days. Full board review is recommended. Please follow your local IRB guidelines.

Cover Page
- "(IND Exempt)" has been added following "Doxepin solution" beneath the study title.
- The ClinicaTrials.gov Identifier has been added beneath the drug information.
- The contact information for Dr. Miller has been updated.
- The participating NCTN group, the Alliance, has been added to the bottom of this page.

Study Resources Page (p. 2)
Carrie O'Neill has replaced Breanna Weisbrod as the one of the nursing contacts for this study.

CTSU Address and contact information page (p. 3)
Because this study is open only to Alliance members, the third and fifth rows of the table are not applicable, and they have been removed.

Schema (p. 4)
The designations of Arms A, B, and C have been removed from the schema.

Table of Contents (pp. 5, 6)
The table of contents has been updated.

Section 3.1 On-study guidelines (p. 14)
A note about the previous use of other mouthwashes and doxepin has been added to the end of this section.

Section 3.2.6 Eligibility criteria (p. 14)
This criterion has been revised as follows, "No use of any anti-arrhythmic medication (except for beta-blockers and calcium channel blockers) including intravenous lidocaine, linezolid, ipratropium, or medications with ~~strong~~ high anti-cholinergic ~~properties~~ potency (including neostigmine, a tricyclic antidepressant or a monoamine oxidase inhibitor) within 2 weeks prior to registration."

Section 4.0 Patient registration (pp. 15-17)
This section has been rewritten to comply with the new NCI/CTSU template. In addition, the previous Section 4.2 is now Section 4.4. Finally, in the paragraph found in the second bullet of Section 4.4, the booklet ordering information has been corrected. Patient-completed booklets are to be ordered from the Statistics and Data Center and the order form can be found at the Alliance Website.

Section 5.0 Study Calendar (p. 18)
In the "Pre-study testing intervals" section, "pregnancy test" has been removed from the tests to be done within 7 days prior to registration, and moved to a new bullet stating that the test is to be done within 28 days before registration.

Section 6.0 (p. 19)
This section has been rewritten to comply with the new NCI/CTSU template.

Section 7.0 Treatment plan/intervention (p. 20)
- Two new paragraphs describing the washout requirements for this study have been added following the first two paragraphs of this section.
- The designations of Arms A, B, and C have been removed from the table.

Section 7.2 Optional continuation phase (p. 21)
- The following sentences have been added to the first paragraph of this section: "It is expected that patients will continue RT during the 7 days of the continuation phase. Chemotherapy is allowed during the continuation phase."
- In the first sentence of the second paragraph, "Arms A or C" has been replaced with "doxepin/placebo." In addition, the end of this sentence has been revised to read, ". . . will be provided with ~~one~~ 120 mL in a 4 ounce amber bottle of blinded study agent and a syringe for measurement."
- In the first sentence of the third paragraph, "Arm B" has been replaced with "DLA." In addition, the end of this sentence has been revised to read, ". . . will be provided with ~~one~~ 240 mL in an 8 ounce amber bottle of blinded study agent and a syringe for measurement."
- The following new paragraph has been inserted following the third paragraph of this section:

  "It is understood that for patients receiving DLA during the continuation phase of the study, they and/or caregivers may be aware that they are receiving DLA. It is expected however, that for patients randomized to receive doxepin or placebo, they and their caregivers will continue to be blinded to the treatment."

Section 8.1.3 Ancillary therapy (p. 21)
This section has been removed, as this information can now be found in the "Washout" paragraphs in Section 7.0.

Section 8.2 Unblinding procedures (p. 22)
- In the first sentence of the "Procedures for unblinding upon patient choice" paragraph, the phrase "during the Continuation Phase" has been moved to follow the word, "unblinded." This sentence now comprises the first paragraph of this section.
- A new paragraph has been inserted following this paragraph stating that patients may also be unblinded following completion of all protocol treatment.
- The previous last sentence of this section, describing procedures for unblinding in these cases, now comprises its own paragraph.

Section 10.1 Doxepin (pp. 26, 27)
- The reference to the CTSU Web site has been removed from the third paragraph of this section.
- A new "Drug Accountability" paragraph has been inserted following the "Procurement" section.
- A new "IND Status" paragraph, describing the IND exempt status of doxepin for this study, has been inserted following the "Drug Accountability" section.
- The following sentence has been added to the Cycle 1 paragraph under "Preparation:" "The syringe label will state 'Doxepin 25 mg/DLA/Placebo 5 mL'."

Section 10.2 DLA (p. 28)
- In the second sentence of the first paragraph under "Procurement," the starter supply of antacid has been changed from two bottles to one bottle.
- After the first sentence of the second paragraph of this section, two new sentences have been inserted to provide more information on the starter supplies of DLA. The previous second sentence of this paragraph has been removed, and the previous third and fourth sentences now comprise a new third paragraph of this section and have been revised as follows, "A site may order additional bottles of diphenhydramine hydrochloride, lidocaine hydrochloride, and antacid ~~in advance of patient participation in the optional continuation phase~~ as needed to maintain an adequate supply for in-clinic and at-home administration cycles. Each site will provide its own syringes and 8 oz. amber bottles."
- A new "Drug Accountability" paragraph has been inserted following the "Procurement" section.
- In the first sentence of the Cycle 1 paragraph under "Preparation," ". . . a total dose of 5.0 mL" has been corrected to read, " . . . a total volume 5.1 mL." The following sentence has been added to this section, "Cycle 1 for the DLA is blinded, therefore 5 mL of the resulting mixture should be drawn up (please note approval to round dose from 5.1 mL) and the syringe label will read, 'Doxepin 25 mg/DLA/Placebo 5 mL.'"
- The parenthetical statement noting approval to round the dose from 5.1 mL has been removed from both of the following Cycle 2 paragraphs, as this approval is now noted in the preceding paragraph.

Section 10.3 Placebo (pp. 29, 30)
- In the second sentence of the first paragraph under "Procurement," the starter supply has been changed from two bottles to one bottle.
- The second and third sentences of the second paragraph of this section have been replaced with three new sentences providing updated information on the starter supplies of placebo.
- A new "Drug Accountability" paragraph has been inserted following the "Procurement" section.
- The following sentence has been added to the Cycle 1 paragraph under "Preparation:" "The syringe label will state 'Doxepin 25 mg/DLA/Placebo 5 mL'."

Section 13.8 Inclusion of Women and Minorities (p. 35)
The accrual table has been updated to match the new NCI-required format.

Section 15.0 Model consent: What is the usual approach to my painful mouth sores? (p. 40)
The first sentence of this section has been clarified to read, "You are being asked to take part in this research study because you have been diagnosed with cancer and are (or will be) receiving radiation therapy to your head and neck."

Section 15.0 Model consent: What are my other choices if I do not take part in this study? (p. 40)
This section, which was inadvertently omitted from the model consent form, has been added following the "What is the usual approach to my painful mouth sores?" section.

Section 15.0 Model consent: What are the study groups? (pp. 41, 42)
- The designations of Groups A, B, and C have been removed from the diagram.
- At the end of the third to last paragraph of this section, a sentence has been added indicating that patients should return any unused portion of study rinse after the continuation phase.

Section 15.0 Model consent: What possible risks can I expect from taking part in this study? (p. 42)
The third bullet in the paragraph about making side effects less of a problem has been removed, as there are no dose modifications for this study.

Section 15.0 Model consent: What are the costs of taking part in this study? (p. 45)
In the second sentence of this section, the word, "study," has been inserted following the words, "is not paid by the. . ."

Section 15.0 Model consent: Who will see my medical information? (p. 45)
The second-to-last sentence of this paragraph has been clarified to read, "Some of your health information~~, and/or information about your specimen~~, from this study will be kept in ~~a~~ the Alliance central database for research."

A replacement protocol has been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A221304

A PHASE III PLACEBO-CONTROLLED, RANDOMIZED THREE-ARM STUDY OF DOXEPIN AND A TOPICAL RINSE IN THE TREATMENT OF ACUTE ORAL MUCOSITIS PAIN IN PATIENTS RECEIVING RADIOTHERAPY WITH OR WITHOUT CHEMOTHERAPY

Doxepin solution (IND Exempt), placebo solution, and DLA (diphenhydramine, lidocaine, antacid) provided and distributed by Alliance Research Base Pharmacy

ClinicaTrials.gov Identifier: NCT02229539

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Study Resources

Expedited Adverse Event Reporting
https://eapps-ctep.nci.nih.gov/ctepaers/

Medidata Rave® iMedidata portal
https://login.imedidata.com

OPEN (Oncology Patient Enrollment Network)
https://open.ctsu.org

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Protocol-related questions may be directed as follows:

Questions	Contact (via email)
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document:	Protocol Coordinator
Questions related to IRB issues and model consent revisions:	Regulatory Affairs Manager: *regulatory@alliancenctn.org*
Questions regarding CTEP AERS reporting:	*regulatory@alliancenctn.org*

Document History	**Effective Date:**
Pre-Activation	08/15/2014
Activation	11/01/2014
Update 01	08/01/2015

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead National Clinical Trial Network (NCTN) Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206	Please refer to the patient enrollment section for instructions on using the OPEN system.	All participating sites will submit study data via Medidata Rave System. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
For patient eligibility or treatment-related questions see the Protocol Contacts, Page 2.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org.		
The CTSU Web site is located at https://www.ctsu.org.		

A PHASE III PLACEBO-CONTROLLED, RANDOMIZED THREE-ARM STUDY OF DOXEPIN AND A TOPICAL RINSE IN THE TREATMENT OF ACUTE ORAL MUCOSITIS PAIN IN PATIENTS RECEIVING RADIOTHERAPY WITH OR WITHOUT CHEMOTHERAPY

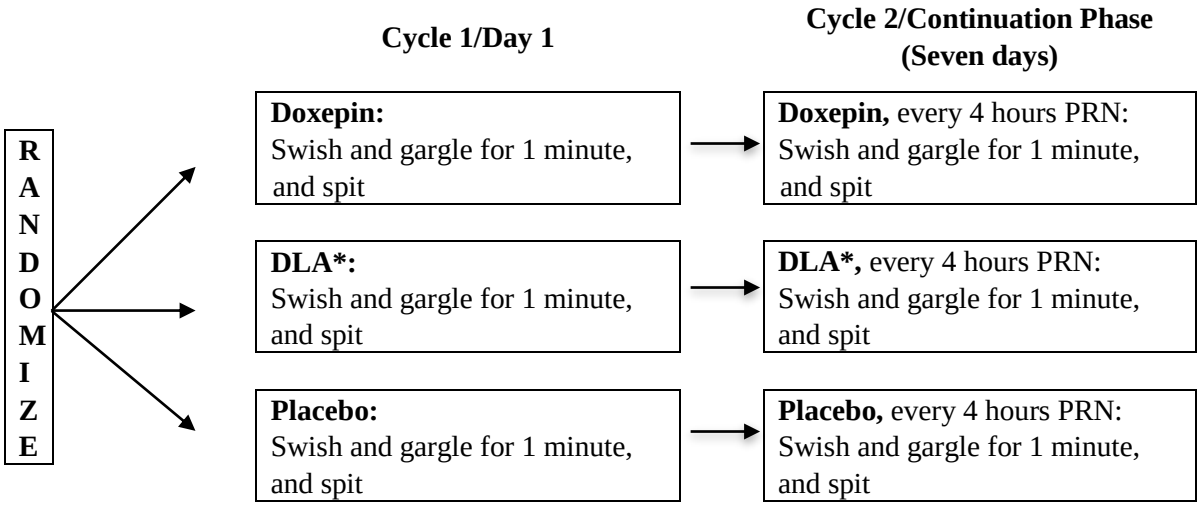
Eligibility Criteria

Histologic documentation of malignancy currently undergoing a course of RT including the oral cavity and/or oropharyngeal area to a dose of at least 4500 cGy using more than 5 fractions (See § 3.2.1)
Physical exam demonstrating evidence of radiotherapy-related mucositis in the visible oral cavity and/or oropharynx consistent with mucous membrane toxicity greater than 0 using the Acute Radiation Morbidity Scoring Criteria (See § 3.2.2)
At least 4 (out of 10) patient-reported oral pain related to oral mucositis secondary to RT for which the patient seeks relief (See § 3.2.3)
Ability to complete questionnaire(s) by themselves or with assistance.
No known allergy to diphenhydramine, lidocaine, antacid, doxepin, tricyclic antidepressants (See § 3.2.5)
No use of any anti-arrhythmic medication (See § 3.2.6)
No current diagnosed untreated or unresolved oral candidiasis or oral HSV infection.
No history of untreated narrow angle glaucoma within 6 weeks prior to registration.
No untreated urinary retention within 6 weeks prior to registration.
No current use of glutamine or sucralfate powders at the time of registration.
No cryotherapy for prophylactic mucosal protection within 6 weeks prior to registration.
Not pregnant (see § 3.2.12)
Age ≥ 18 years
ECOG Performance Status 0, 1, or 2.

Required Initial Lab Values

None

Schema



* Diphenhydramine HCl, Lidocaine HCl, and Antacid Suspension

Continuation Phase: Following Day 1, patients may begin the 7-day continuation phase and take doxepin/DLA/placebo up to every 4 hours as needed for pain. If desired, initiation of the Cycle 2/Continuation Phase may be delayed for up to one week after Cycle1/Day 1.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Table Of Contents

1.0 BACKGROUND

1.1 Definition and epidemiology of oral mucositis

Oral mucositis (OM) related pain is a significant problem in patients undergoing head and neck radiation therapy with or without chemotherapy. Acute OM refers to an inflammatory process of the mucosa of the oral cavity and oropharynx manifested as painful, erythematous, ulcerative lesions. These lesions typically develop within 7−14 days of the initiation of cytotoxic chemotherapy or radiotherapy (RT)[1-3]. The pain and associated dysgeusia caused by OM frequently require treatment with systemic analgesics. They also decrease patients' oral intake and nutrition leading to dehydration, weight loss, and declining performance status that may require intravenous fluid hydration, feeding tube placement, and hospitalization[4]. When severe, OM increases the risk of infection and may compromise clinical outcomes by necessitating treatment breaks, dosage reductions, and reduced compliance with therapy[2,5,6].

A majority of patients with head and neck cancer (HNC) treated with RT with or without chemotherapy experience painful OM. Standard fractionated head and neck RT can cause OM in doses as low as 10 Gy, but most patients experience ulcerative OM by the end of the third week of RT, after receiving 30 Gy[7-9]. In a systematic review of 33 studies reporting OM in 6181 such patients, Trotti and colleagues found that the mean overall incidence of OM was 80%[4]. Elting et al. reported that OM occurred in 91% of 204 consecutive patients with HNC treated with RT with or without chemotherapy at M.D. Anderson Cancer in 2002. OM was severe (grade 3−4) in 66%[7]. OM was more common among patients who received concomitant chemotherapy (98%), who had oral cavity or oropharyngeal primaries, or who were treated with altered RT fractionation schemes. OM typically developed after the second week of RT and persisted for an average of 5 weeks. Patients who developed OM were significantly more likely to have severe pain (54% vs. 6%; $p < 0.001$) and incurred incremental costs of $1700−$6000 depending on OM severity. Vera-Llonch et al. conducted a nationwide survey of 154 medical and radiation oncologists collecting OM data on 450 patients with HNC treated with RT with or without chemotherapy. They found that 83% of patients developed OM and in 29% it was severe[10]. Similarly, OM was more common when patients received concurrent chemotherapy or when they had nasopharyngeal or oropharyngeal primaries. In a series of in-depth interviews with 33 patients who had undergone RT with or without chemotherapy, painful OM was the single most debilitating reported side effect[11].

1.2 Pathophysiology, Prevention, and Treatment of OM

Historically, OM has been viewed as the consequence of cytotoxic therapy (either chemical or radiation) in which rapidly dividing cells are preferentially killed—be they cancer or normal mucosal epithelium[12]. When the mucosa is damaged, the epithelial cells are not replenished, resulting in ulcer formation that persists until treatment is stopped or reduced. Sonis has proposed a 5-phase model for the pathophysiology of OM that modifies this traditional linear view[8,13,14]. In this model, initiation (phase I) of OM occurs immediately following chemotherapy or RT which directly damage mucosal DNA, generate reactive oxygen species, damage lipids and connective tissue, and initiate apoptosis by stimulating sphingomyelinase and ceramide synthase pathways. All of this leads to upregulation and messenger generation (phase II) in which the cells' normal molecular damage response pathways are turned on, creating a positive feedback loop. This upregulation of transcription factors (most notably nuclear factor-κB) triggers release of pro-inflammatory cytokines (tissue necrosis factor [TNF]-α, interleukin [IL]-I, IL-2, and IL-6), that result in further signaling and amplification (phase III) of tissue injury. This leads to clinically and symptomatically significant ulceration (phase IV) in which the extracellular membrane swells weakening attachments between the submucosa and epithelium creating deep, broad-based, erosions. This exposes free nerve endings causing pain[15]. Finally,

healing (phase V) occurs as a pseudomembrane of fibrin and dead cells forms over the ulcer, COX-2 likely stimulates new angiogenesis, epithelial cells from the periphery migrate and multiply to close the wound, and submucosal cells regenerate usually over a 2−3 week period.

1.3 Prevention and Treatment of OM

Numerous prophylactic agents and interventions have been investigated but relatively few have demonstrated benefit in decreasing the incidence or severity of cancer therapy-related OM[16]. The authors of the current National Comprehensive Cancer Network guidelines for OM note that the only effective preventive strategies are oral cryotherapy used in conjunction with bolus 5-FU, melphalan, or edatrexate and palifermin used to prevent HSCT-related OM[17]. Palifermin (Kepivance®, recombinant human keratinocyte growth factor) is the only FDA-approved preventive therapy for OM. This approval was based largely on a phase III trial in 212 patients undergoing conditioning with high-dose chemotherapy and TBI followed by autologous HSCT for hematologic malignancies[18]. Compared to placebo, palifermin decreased both the incidence of World Health Organization (WHO) grade 3−4 OM (63% vs. 98%, $p < 0.001$) and median duration of grade 3−4 OM (3 days vs. 9 days, $p < 0.001$). A report of a phase III trial involving 188 patients with locally advanced HNC treated with chemoradiotherapy demonstrated that palifermin again reduced both the incidence of WHO grade 3−4 OM (54% vs. 69%, $p = 0.041$) and median duration of grade 3−4 OM (5 days vs. 26 days, p = NS)[19].

Many cancer patients experience significant therapy-related OM pain. Management strategies include bland rinses (e.g., 0.9% normal saline or a solution with a ½ teaspoon baking soda in 1 cup warm water), topical anesthetics/analgesics, mucosal coating agents (e.g., benzydamine) and systemic analgesics[2,17,20]. Consistent with the WHO pain management ladder, most patients require opioid analgesia as OM severity increases. Topical anesthetics/analgesics can be used for mild to moderate OM pain and as adjuncts for more severe pain. Commonly utilized agents include lidocaine, benzocaine, dyclonine, and diphenhydramine[2,17,20]. There are several concerns with the use of topical anesthetics[21-23]. The duration of pain relief is typically less than 90 minutes. They can cause burning or stinging pain on first contact with damaged mucosa and then temporarily diminish or abolish taste and the gag reflex. Finally, there is the possibility of increased systemic absorption through a breached mucosal barrier. The latter concern was addressed in a small prospective study comparing plasma lidocaine levels after an oral rinse with 5 mL of 2% lidocaine solution for 1 minute in 5 patients with severe OM related to HSCT and five healthy control subjects[21]. Plasma lidocaine levels, while lower than the therapeutic range (0.2 μg/mL vs. 1.5−5.5 μg/mL), were measurable in the cancer patients; whereas, in the controls lidocaine was undetectable, indicative of minor systemic absorption resulting from lack of mucosal integrity.

1.4 Doxepin as an Analgesic Agent for OM-related Pain

Clinical pharmacology of doxepin: Doxepin is a dibenzoxepin tricyclic compound ($C_{19}H_{21}NO$•HCl or N,N-dimethyldibenz(b,e)oxepin-propylamine hydrochloride) with a molecular weight of 316 belonging to the tricyclic antidepressant (TCA) class of medications[23]. TCAs have been used since the early 1960s to treat patients with major depression[24]. Doxepin is FDA-approved in the United States for treatment of depression and anxiety with or without associated alcoholism or psychoneurosis and topically for short-term management of moderate pruritus. It is recommended for off-label prevention of migraine headaches and as an adjunctive therapy in chronic pain syndromes[25-28].

Mechanism of Action: Doxepin has effects on both the central and peripheral nervous system. With respect to topical OM pain relief, the main mechanism of action is peripheral. Though the exact mechanism of doxepin's efficacy in neuropathic pain is not entirely clear, doxepin's anesthetic and analgesic effects may be due to the fact that it is a potent Na^+ channel blocker

thereby limiting conduction of noxious stimuli in cutaneous nociceptors[24]. Doxepin also has potent peripheral H_1 and H_2 receptor blocker activity making it an effective topical anti-pruritic agent[23,25]. Also, doxepin likely has a synergistic effect with endogenous and exogenous opioids. Systemic administration resulted in a significant increase in plasma enkephalin-like activity compared to placebo, in patients with chronic cervical or low back pain[27]. Rat models have demonstrated that doxepin potentiates opioid analgesia and is a strong local anesthetic when administered via sciatic nerve injection, intraperitoneally, intrathecally, or topically[24,26,28,29]. In the CNS, doxepin increases synaptic concentration of serotonin (5HT) and norepinephrine (NE) by inhibiting receptor reuptake at the presynaptic neuronal membrane, the therapeutic site of its antidepressive action[23,24,30]. 5HT and NE re-uptake inhibition is also believed to activate the descending anti-nociceptive system[23,29]. Doxepin may also act as a modulator of N-methyl-D-aspartate (NMDA) receptors, involved in spinal nociception, decreasing afferent input through the spinothalamic tract[23,30,31]. A few TCAs, including doxepin and amitriptyline, are tertiary amines making them more lipophilic than other antidepressants and therefore better able to penetrate nerve fibers[24].

Epstein and colleagues conducted two non-randomized, open-label, prospective trials of an oral doxepin rinse that reported a significant short duration of anesthesia followed by more extended analgesia for patients with OM[22,23,32,33]. In the first trial, 41 patients with OM pain (37 from cancer therapy and 4 from other causes) were given a single dose of 5 mL of a doxepin (5 mg/mL) suspension containing 0.1% alcohol and sorbitol[23]. Baseline assessment of OM included evaluation of 9 oral sites for erythema and ulceration using the Oral Mucositis Assessment Scale (OMAS) and the patients rated their oral pain at rest and with most recent food intake. Patients swished for 1 minute and then spit out the rinse. At 5, 15, 30 minutes, 1 hour and then at 30 minute increments through 4 hours, patients utilized a Visual Analogue Scale (VAS) to grade their pain (0 = none, 10 = severe), stinging or burning (0 = none, 10 = severe), taste (0 = terrible, 5 = acceptable, 10 = excellent), and drowsiness (0 = none, 10 = severe, leading to sleep). Pain was again assessed 24 hours after the single dose of doxepin rinse. 34 patients had oral ulcerations and erythema was seen in 38. Maximum pain reduction was seen at 15 minutes with a mean decrease of 2.79 units (1.89 vs. 4.68 at baseline). Significant pain relief persisted for 3 hours, with a mean reduction of 1.21 units (3.50 vs. 4.68). Only one patient (2%) found the taste unacceptable, and only four patients (9%) reported stinging or burning discomfort. Drowsiness attributable to doxepin rinse was unable to be adequately evaluated due to lack of baseline assessment.

Epstein and his co-investigators enrolled 14 more patients with painful OM from cancer therapy (excluding the four non-cancer therapy related patients) for a total of 51 patients treated in the same manner with a single dose doxepin rinse[32]. In the subsequent report of this more homogenous cohort, they found a 56% maximum pain reduction from baseline that occurred 15 minutes after rinsing (mean decrease = 3.0 units, range 2.0−5.0). The median duration of pain reduction lasted 145 minutes (range 25−235). Pain recurrence was slow, with 19 patients (37%) continuing to report pain reduction at 4 hours when the study ended. Mild burning or stinging discomfort from the rinse was reported by 16 patients (31%) with a median score of 2 out of 10.

In a second separate study, Epstein et al. treated nine patients with OM due to cancer therapy with the same doxepin rinse, used three to six times daily, for one week[22,33]. Patients were evaluated in a similar manner to the previous study with baseline OMAS and VAS assessments. Oral pain following doxepin rinse was assessed with a VAS at the first visit and again one week later at the same time intervals as in the previous study. Patients kept diaries of systemic analgesic and doxepin rinse usage during the week between visits. After the first doxepin dose, pain decreased significantly from a median baseline score of 5, to 3 units at 5 minutes after rinsing, down to a median score of 1 unit at 15 minutes, and persisted for a median of 2 hours. Patients reported similar reductions in pain scores at 5 and 15 minutes after doxepin rinse in

their inter-visit diaries. They also reported decreased pain with eating and at rest. At the 1-week follow-up visit, median baseline pain scores had decreased from 5 to 3 units, and patients reported continued immediate and durable reduction of pain scores. Side effects of bad taste, burning or stinging discomfort, and drowsiness did not change over the one-week trial period.

1.5 Emerging Data Supporting the Clinical Efficacy of Doxepin in the Alliance

Recently, Miller and colleagues[34,38] reported the final results of N09C6, a phase III randomized, double-blind trial comparing doxepin to placebo for treatment of oral mucositis pain in patients undergoing high-dose, curative head and neck radiotherapy treatment. One hundred and fifty-five (155) patients were randomized to receive either a single dose of doxepin or placebo on Day 1, and then cross over to receive the other agent on a subsequent day. A pain questionnaire was administered at baseline and 6 scheduled time points after drug administration. The primary endpoint was met, showing a significant reduction in mouth and throat pain by doxepin (AUC, -9.1) compared to a placebo (AUC, -4.7, p=0.0003, Figure 1). Crossover analysis also confirmed the superiority of the doxepin arm compared to placebo (p<0.001). Doxepin was well tolerated, but did have more stinging/burning sensation, unpleasant taste, and greater drowsiness, compared to placebo. A majority of patients expressed a desire to continue doxepin treatment after initial testing of doses.

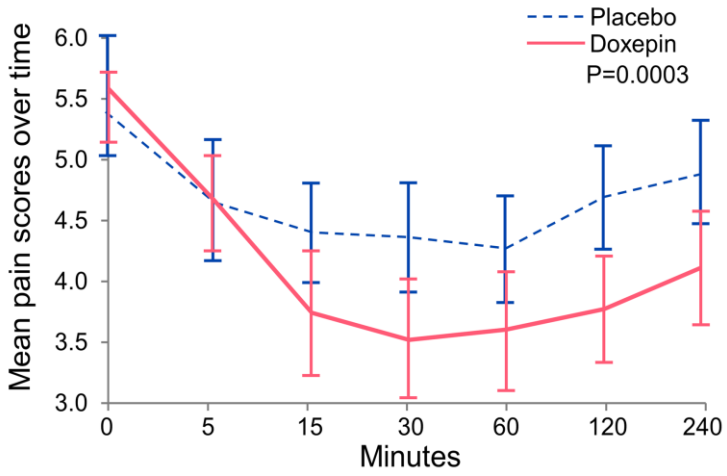


Figure 1. Mean pain scores of mouth and throat vs. time (N=140). The clinical effect of doxepin is shown in this graph. The blue dashed line shows a good example of the placebo effect, with a mean reduction in pain score of 1.0. The dark red line shows an average reduction in mean pain score of approximately 2.0 (on a scale of 0 to 10), following doxepin administration. This represented the primary end point of the doxepin study, which was met statistically ($AUC_{Doxepin}$=-9.1, $AUC_{Placebo}$=-4.7, P=0.0003, Miller *et al.*, ASTRO 2012, plenary session).

1.6 Diphenhydramine, Lidocaine, and Antacid (DLA) rinse

A number of "Magic" mouth rinse preparations exist for patients with treatment-related oral mucositis pain. They all require prescription from a medical practitioner. A common preparation contains 3 active ingredients including diphenhydramine hydrochloride, lidocaine hydrochloride, and antacid (such as Maalox®) for oral care. Diphenhydramine (2-(diphenylmethoxy)-N,N-dimethylethanamine) is an over-the-counter medication, which belongs to the first-generation antihistamine family. It has a number of pharmacologic properties

including anticholinergic, antitussive, sedative, and most commonly, anti-allergic. It is used for a variety of common medical conditions such as seasonal allegories, cold, insomnia, pruritus, and Parkinsonian's extrapyramidal symptoms. Lidocaine (2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide) is commonly used as a local anesthetic, which is also well known for its antiarrhythmic properties when consumed systemically. When applied topically, lidocaine can relieve itching, pain and burning symptoms caused by local irritation or inflammation, making it a popular choice for dentistry and general surgery. The onset of its pharmacological action is immediate. For the antacid component (trade name: Maalox®) of a topical rinse mouthwash, it usually contains a number of components including aluminum hydroxide ($Al(OH)_3$), magnesium hydroxide ($Mg(OH)_2$), and a small amount of simethicone ($(C_2H_6OSi)_n•(SiO_2)_m$). Aluminum hydroxide is a common antacid itself: it works as a base by interacting with excess acid in the stomach, therefore, neutralizing the acidity in the physiologic environment and provide symptoms relief. By itself, magnesium hydroxide is also known as Milk of Magnesia® due to its milk-like appearance; it is an aqueous, mildly alkaline solution, which has the dual action of being an antacid for neutralizing stomach acid and also as a laxative. Simethicone is anti-foaming, which acts as a stabilizer and helps reduce bloating and discomfort in the abdomen. When the three compounds (diphendydramine, lidocaine, and antacid) are mixed with other solvent components, a homogeneous suspension is produced ready for clinical use (suitable for rinse, spit or swallow).

Mechanism of Action: DLA mouthwash, or other similar preparations, is commonly prescribed for radiation- or chemotherapy-induced oral mucositis. Its mechanism of action, due to its various components, is multi-faceted. Depending on formulation, it has the pharmacologic properties of an antihistaminic for local anesthesia (diphenhydramine), analgesic/pain relieving (lidocaine), and anti-acidic (aluminum/magnesium hydroxide, Maalox). Other components may include nystatin, sucralfate, tetracycline and erythromycin. The most popular components of anti-mucositic mouthwash, however, are diphenhydramine, lidocaine and antacid (DLA).

The commonly prescribed mouthwash preparations can be used every four to six hours, as needed for pain. Patients are generally instructed to hold the mixture in the mouth for 1 to 2 minutes, then either split it out or slowly swallow. It is also recommended not to drink or eat 15 minutes after mouthwash use, so the medication can have a chance to work.

1.7 Limited Evidence for the DLA Mouthwash Being Analgesic for OM

Even though many preparations for DLA or "Magic" mouthwash rinsing are used clinically[35], a paucity of controlled data exist regarding this topic. Large-scale, randomized studies with positive results are lacking. In the largest published randomized clinical trial, Dodd et al.,[36] tested the effectiveness of three commonly used mouthwashes ("magic" mouthwash with lidocaine, diphenhydramine and Maalox®; chlorhexidine; and salt with soda) in 200 patients undergoing chemotherapy and experiencing mucositis. There were no significant differences among the three arms. Over 70% of the patients stopped having mucositis symptoms in less than 12 days, although it is not clear if this would have been any different from a placebo arm. No placebo-controlled trials are published.

Currently, due to the lack of high-quality evidence regarding the use of "magic mouthwash" preparations, multiple clinical practice guidelines[37-39] agree that this area represents a gap in our knowledge about whether these mouthwash preparations are truly useful (although very commonly used by many oncologists). Correspondingly, the Cochrane review[37] found inconclusive evidence regarding whether these "magic mouthwashes" truly decrease the severity and/or duration of oral mucositis pain.

1.8 Significance of the Positive Randomized, Placebo-controlled Doxepin Data

Do the above-described pilot data and the results of the recently completed randomized, double blinded, cross-over clinical trial, establish that doxepin should be preferentially used for patients with radiation therapy-induced oral mucosal pain? The positive nature of these data supports that doxepin is a reasonable treatment to utilize in this situation. ASTRO chose the abstract for a plenary session, something that they only do for abstracts that they believe are practice-changing. The manuscript from this abstract has been accepted for publication by a prominent clinical oncology journal, also supporting that the results are quite intriguing.

Further research is indicated at this time. Dr. Robert Dworkin, a noted expert with regard to pain studies, was a discussant for an abstract presentation regarding the completed Alliance doxepin trial at a recent Symptom Management and Health-related Quality of Life Steering Committee meeting. He felt that further research was indicated to further delineate the efficacy of doxepin in patients with oral mucosal pain related to radiation therapy. He noted that in pain research, experts believe that a positive study should be replicated before general acceptance into clinical practice. In addition, he raised the question as to whether doxepin was better than any other standard therapy (such as the number of "magic mouthwashes" that are commonly used for this condition). He recommended that a follow-up clinical trial be conducted to compare doxepin to another common clinically used mouthwash. Pending the results of such a trial, the question of whether doxepin added anything to the use of a "magic mouthwash" remained open. Pursuant to this, the current proposal has been developed.

1.9 Study design

This 3-arm study is designed to evaluate the effect of doxepin rinse or DLA versus a placebo on OM-induced pain in patients with head and neck cancer undergoing RT to the oral cavity.

This trial will utilize the same dose of 25 mg doxepin rinse used in the phase I-II trials by Epstein et al. [22,23,32,33] and the phase III trial by Miller et al.[34] This dose was reported to be effective and resulted in minimal side effects, and was well tolerated in the phase III study[34]. The doxepin oral concentrate is available in a 10 mg/mL formulation (desired test dose is 25 mg in 5 mL). It is expected that minimal systemic absorption of doxepin will occur despite compromise of the mucosal barrier by mucositis because patients will swish the oral cavity for one minute, then expectorate the solution. Should complete transmucosal absorption occur, this oral rinse dose would be less than the usual starting oral daily dose of 75−150 mg prescribed for depression or anxiety[23,24,27]. During radiation therapy treatments, the patient will be invited to participate in the study when s/he develops at least 4 (out of 10) oral pain thought to be related to oral mucositis secondary to radiation treatment, for which the patient would like to seek relief. After consent, the patient will then be registered/randomized to this study.

In addition to the initial dose evaluation (for the primary endpoint), a one-week continuation phase will be allowed in the current study. Within one week after the first dose of their study drug, patients will be allowed to initiate a 1-week continuation phase, where patients may repeat dosing every 4 hours PRN (as needed for pain). On each treatment day of the continuation phase, a patient-reported outcome (PRO) measure will be completed. The patient will be allowed to continue the study drug for up to one week for relief of OM-related pain. During the planned continuation phase, patients may opt out if/when they believe that the treatment is no longer beneficial. Should that be the case, the patient's treatment will be unblinded and s/he will be treated per clinical practice recommendations off study.

1.10 Registration fatigue/uniscale assessment

QOL measurements of fatigue and overall perception of QOL are routinely included in Alliance studies and will be assessed upon registration in this study. Evidence has arisen indicating that

baseline single-item assessments of fatigue and overall QOL are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses recently presented at ASCO, the first involving 23 NCCTG and Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates.[40]

2.0 OBJECTIVES

2.1 Primary objective

Determine whether the doxepin rinse or DLA rinse is more effective than placebo in reducing OM-related pain in patients undergoing RT to the oral cavity, as measured by a patient-reported questionnaire at baseline, 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours.

2.2 Secondary objectives

2.2.1 Assess the adverse event profile of the doxepin rinse, the DLA rinse agent, and the placebo using a patient-reported questionnaire at 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours for domains of unpleasant taste, burning or stinging discomfort, and drowsiness.

2.2.2 Compare the incidence of using additional analgesics between 1 and 4 hours after the initial mouthwash, between the doxepin oral rinse, the DLA rinse agent, and the placebo arms.

2.2.3 Compare the length of time that each study product is used by patients in the one-week continuation phase.

2.2.4 Compare the daily pain scores in the one-week continuation phase for the three study arms.

2.2.5 Compare the 24-hour morphine equivalent dose used in the continuation phase for the three study arms.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Contact Information page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness, which would prevent the patient from giving informed consent.

In addition:

- Women and men of reproductive potential must agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of radiation therapy and potential side effects of study rinses. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

NOTE: Patients may have used either other mouthwashes for mucositis or doxepin (tablet or rinse) previous to enrolling on this study. Use of these agents must be discontinued at midnight 2 nights (i.e., approximately 32 to 40 hours) prior to the time that study drug is administered.

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

___ **3.2.1 Documentation of Disease:**

Histologic documentation of malignancy currently undergoing a course of RT (with or without chemotherapy) including the oral cavity and/or oropharyngeal area to a dose of at least 4500 cGy using more than 5 fractions (i.e., stereotactic body radiation therapy [SBRT] is not allowed).

___ **3.2.2 Physical exam demonstrating evidence of radiotherapy-related mucositis** in the visible oral cavity and/or oropharynx consistent with mucous membrane toxicity greater than 0 using the Acute Radiation Morbidity Scoring Criteria (see Appendix VI or www.rtog.org/researchassociates/adverseeventreporting/acuteradiationmorbidityscoringcriteria.aspx).

___ **3.2.3 At least 4 (out of 10) patient-reported oral pain** related to oral mucositis secondary to RT for which the patient seeks relief, as measured on the Oral Pain Assessment (see Appendix I). Note: The pain score must be at least 4 at the time that the patient starts the first dose of study medication. The patient may be enrolled to the study if s/he, at times, has a pain score of at least 4, so long as initiation of study treatment begins when the pain score is at least 4.

___ **3.2.4 Ability to complete questionnaire(s) by themselves or with assistance.**

___ **3.2.5 No known allergy** to diphenhydramine, lidocaine, antacid (aluminum hydroxide, magnesium hydroxide, and simethicone), doxepin, tricyclic antidepressants, or any known component of the drug formulation in the testing arms.

___ **3.2.6 No use of any anti-arrhythmic medication** (except for beta-blockers and calcium channel blockers) including intravenous lidocaine, linezolid, ipratropium, or medications with high anti-cholinergic potency (including neostigmine, a tricyclic antidepressant or a monoamine oxidase inhibitor) within 2 weeks prior to registration.

___ **3.2.7 No current diagnosed untreated or unresolved oral candidiasis or oral HSV infection.**

___ **3.2.8 No history of untreated narrow angle glaucoma** within 6 weeks prior to registration.

___ **3.2.9 No untreated urinary retention** within 6 weeks prior to registration.

___ **3.2.10 No current use of glutamine or sucralfate powders** at the time of registration (no washout required).

___ **3.2.11 No cryotherapy for prophylactic mucosal protection** within 6 weeks prior to registration.

___ **3.2.12 Not pregnant,** because patients eligible for this study will be receiving radiotherapy, which has known genotoxic, mutagenic and teratogenic effects.

Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 28 days prior to registration is required.

___ **3.2.13 Age ≥ 18 years**

___ **3.2.14 ECOG Performance Status 0, 1, or 2.**

4.0 PATIENT REGISTRATION

4.1 CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed Statement of Investigator Form (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed Supplemental Investigator Data Form (IDF)
- a completed Financial Disclosure Form (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the CTEP Investigator Registration Help Desk by email at <pmbregpend@ctep.nci.nih.gov>.

4.2 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

4.3 CTSU Site Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

4.3.1 Submitting Regulatory Requirements

Submit completed forms along with a copy of your IRB Approval, and Model Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

4.3.2 Checking Your Site's Registration Status

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

4.4 Patient registration requirements

- **Informed consent:** The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.
- **Patient completed booklets:** Patient questionnaire booklets are to be ordered prior to the registration of any patients. Patient completed booklets can be ordered by downloading and completing the booklet order form (located under the supplemental documents section of the A221304 website) and faxing the form to Attn: Operational Support Clerk at 507-284-1902. Samples of the booklets are found in Appendices III-V, which are to be used for reference and IRB submission only. They are not to be used for patient completion.

4.5 Patient Registration/Randomization Procedures

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. A user manual is available for OPEN users on the CTSU site.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.

All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.6 Stratification Factors

4.6.1 Patient Sex: Male vs. Female

4.6.2 Concurrent use of chemotherapy: No vs. Yes

4.6.3 Patient age at registration: < 60 years old vs. ≥ 60 years old

4.6.4 RTOG Acute Radiation Morbidity Criteria: 1 vs. 2 vs. 3 or more

4.7 Treatment assignments and blinding

4.7.1 The factors defined in Section 4.3 will be used as stratification factors.

4.7.2 After the patient has been registered to the study, the values of the stratification factors will be recorded and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure, which balances the marginal distributions of the stratification factors between the treatment groups.[38]

- Doxepin
- Diphenhydramine HCl, Lidocaine HCl, and Antacid Suspension
- Placebo

4.7.3 Procedures for blinding the treatment assignment: At the time that the site has registered/randomized the patient in OPEN and received an Alliance patient ID number, the Alliance Registration Office will also be notified. The Registration Office will contact the designated site contact person with the assigned treatment, "Doxepin, DLA, or Placebo." The name of this person and his/her contact information will be entered in OPEN on the Enrollment Form. This contact person may not be involved in assessing adverse events or any other outcome measure. The institutional pharmacist or designated contact person will maintain records that identify the patient and his/her corresponding treatment assignment.

5.0 STUDY CALENDAR

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Pre-Study Testing Intervals

- To be completed within 7 DAYS before registration: History and physical and oral pain assessment.
- To be completed within 28 DAYS before registration: Pregnancy test

	Prior to Registration	**Day 1 Baseline** before oral rinse	**Day 1** In clinic*	**Day 1** At home**	**Continuation Phase*** **
Tests & Observations					
History and physical, PS	X				
Oral Pain Assessment	X(1)	X(1)			
Adverse Event Assessment (for CTCAE)			X		A
Oral Symptoms Booklet		X (2)	X (2)	X (3)	
Daily Questionnaire					X (4)
Fatigue/Uniscale Assessment	B				
Laboratory Studies Serum or urine HCG	C				

* To be completed by the patient in clinic at 5, 15, 30, and 60 minutes after oral rinse

** To be completed by the patient at 2 and 4 hours after oral rinse (may be completed at home). It is recommended that site staff give the patient a reminder by telephone at two and four hours post-administration to complete the questionnaires.

*** Daily for up to 7 days, beginning within 1 week of Day 1.

A As clinically indicated during Continuation Phase RT assessment(s).

B Within 21 days prior to registration (see Appendix II).

C For women of childbearing potential. Must be done within 28 days prior to registration.

1 See Appendix I

2 See Appendix III

3 See Appendix IV

4 See Appendix V. Also, note that patients should be instructed to complete the daily questionnaire at the time every day, preferably in the evening.

6.0 DATA SUBMISSION

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

A Schedule of Forms is available on the Alliance study webpage, within the Case Report Forms section.

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients (see Section 4.4). Samples of questionnaire booklets are available in Appendices III-V for reference and IRB submission only. They are not to be used for patient completion. Booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff either in person or by mail and site staff will enter patient and caregiver responses into the Rave database.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin within 14 days of registration. For questions regarding treatment, please see the Study Resources page.

Protocol therapy will consist of 2 cycles. Cycle One will consist of one day. Cycle Two will consist of an optional continuation phase lasting up to 7 days. Initiation of the Cycle 2/Continuation Phase may be delayed up to one week after Cycle 1/Day1.

Washout: No washout period is required for patches or extended duration pain medications. If the patient experiences oral pain of 4 or greater while on these medications, s/he may participate in the study and continue the extended duration pain medication (patch may remain).

Patients may have used either other mouthwashes (e.g., viscous lidocaine, 'magic mouthwash', benzocaine, diphenhydramine) for mucositis or doxepin (tablet or rinse) before participation on this study. With the exception of 0.9 normal saline or baking soda rinse, use of these agents must be discontinued at midnight 2 nights prior to the day study drug is administered (i.e., approximately 32 to 40 hours before treatment).

Agent	Dose	Route	Cycle 1	Cycle 2: Optional Continuation Phase
			1 Day	7 Days
Doxepin rinse	2.5 mL (25 mg) doxepin and 2.5 mL water**	Oral swish and gargle for 1 minute then spit	Taken in clinic	Taken at home every 4 hours, PRN, for OM pain
DLA*	5.0 mL DLA	Oral swish and gargle for 1 minute then spit	Taken in clinic	Taken at home every 4 hours, PRN, for OM pain
Placebo rinse	2.5 mL placebo and 2.5 mL water**	Oral swish and gargle for 1 minute then spit	Taken in clinic	Taken at home every 4 hours, PRN, for OM pain

* Diphenhydramine HCl, Lidocaine HCl, and Antacid Suspension (see Section 10.2)

** For Cycle 1, study agent will be diluted with sterile water for irrigation, sterile water for injection, and/or distilled water by site staff. For Cycle 2, the patient will use distilled water or tap water to dilute the oral rinse at home.

7.1 Day 1 of study intervention

Prior to the first dose of doxepin/DLA/placebo, the care provider or nurse will confirm that oral pain is at least 4 out of 10 severity level at the time of the rinse on the first day of the study (Appendix I). Patients will then be asked to complete the baseline evaluation in the Oral Symptoms booklet (Appendix III). If the pain score is less than 4 prior to administration of doxepin/placebo, administration should be delayed until pain is at least 4.

Doxepin/DLA/placebo 5 mL (doxepin/placebo) or 5.1 mL (DLA) will be given to patients to swish and gargle and then expectorate. The study dose should be prepared in the clinic just prior to administration.

Oral symptoms booklet: The patient will remain at the treating location for the first hour and complete the questionnaires in the Oral Symptoms booklet (Appendix III) at time zero (prior to the oral swish, gargle and spit), and at 5, 15, 30 and 60 minutes post-administration.

After completing the booklet at 60 minutes, patients may then leave the clinic and complete the 2- and 4-hour assessments at home (Appendix IV). The patient will be instructed on timing of questionnaire completion at two and four hours post-administration. It is recommended that site staff give the patient a reminder by telephone at two and four hours post-administration to complete the questionnaires.

7.2 Optional continuation phase

Within 7 days following Day 1 (ideally, on the first clinic day following Day 1), patients will be encouraged to continue treatment with the study agent for an additional week. It is expected that patients will continue RT during the 7 days of the continuation phase. Chemotherapy is allowed during the continuation phase.

Patients randomized to doxepin/placebo who elect to continue with study treatment during the Continuation Phase (Cycle 2), will be provided with 120 mL in a 4 ounce amber bottle of blinded study agent and a syringe for measurement. This should supply at least 42 doses after dilution. Patients will be instructed on preparation of the appropriate dose by dilution of the agent.

Patients randomized to DLA who elect to continue with study treatment during the Continuation Phase (Cycle 2), will be provided with one 240 mL in an 8 ounce amber bottle containing 80 mL each of diphenhydramine HCl, lidocaine HCl, and antacid suspension and a syringe for measurement. This should supply at least 42 doses. Patients will be instructed to measure 5 mL of DLA.

It is understood that for patients receiving DLA during the continuation phase of the study, they and/or caregivers may be aware that they are receiving DLA. It is expected however, that for patients randomized to receive doxepin or placebo, they and their caregivers will continue to be blinded to the treatment.

All patients may repeat dosing every 4 hours PRN (as needed for pain) during the seven days of Cycle 2. On each day of that week at approximately the same time each day, preferably in the evening, a patient-reported outcome (PRO) measure will be completed (Appendix V). The patient will be asked by study staff on radiation treatment days in clinic if they feel that they are receiving enough benefit from the therapy to continue using it. If so, they will be allowed to continue for up to a week. Adverse event evaluations (for CTCAE events) should be done as clinically indicated during weekly RT assessments.

During the Continuation Phase, the patient can opt out at any time if/when they believe that the treatment is no longer beneficial. If the patient does not feel that they are receiving benefit from the therapy, s/he may be unblinded and the patient can be treated for OM at the treating physician's discretion.

8.0 ANCILLARY THERAPY, UNBLINDING

8.1 Ancillary therapy, concomitant medications, and supportive care

8.1.1 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions.

8.1.2 No analgesics or crushed ice should be given for mucositis pain for 60 minutes prior to and after the Day 1 dose. .Patients will be allowed to take analgesics after 60 minutes if they feel the need for pain relief. They will be asked to record such usage on the timed questionnaires. If they utilize any other agents, aside from the test rinse, their data will be censored at the time of such use.

8.2 Unblinding Procedures

Emergency unblinding will be available 24 hours a day, every day, according to the criteria below.

Unblinding can be done in the event of an emergency or when the patient feels s/he is no longer receiving benefit from the study agent during the Continuation Phase. Please note that, if treatment is unblinded due to an emergency, the patient must permanently discontinue all protocol therapy.

Emergency Unblinding Procedures:

Examples of emergencies include 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose. Expected adverse events are listed in the "Toxicities" section below.

Contact the Alliance Executive Officer on call by calling 773-702-6800, pressing 1 to speak with an operator, and then asking for pager ID 8625 to return the call.

The institution must provide the following information to the Alliance Executive Officer:

- Alliance study ID (i.e., "A221304")
- Alliance patient ID number (e.g., "999999")
- Patient initials (e.g., "L, FM")
- Institution name
- Name and telephone number of treating physician
- Name and contact information of person requesting the unblinding procedure
- Name and contact information of person to inform of treatment assignment
- Reason for emergency unblinding

Please remember that an emergency unblinding request may be authorized only by an Alliance Executive Officer, and emergency unblinding applies only if unblinding would influence management of the medical situation.

After the Executive Officer deems unblinding is warranted, the treatment assignment will be provided to the contact person at the treating site.

Procedures for unblinding upon patient choice

Study participants can be unblinded during the continuation phase when the patient feels s/he is no longer receiving benefit from the study agent and all appropriate study forms have been completed.

In addition, if patients find they are receiving benefit from the study agent, they may also be unblinded after all protocol treatment and all study forms have been completed. Please be aware that doxepin therapy for mucositis is not FDA-approved.

To receive patient treatment assignment in either of these cases, contact the Alliance Registration Office at 507-284-4130 during regular business hours.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. The CTCAE is available at http://ctep.cancer.gov/ reporting/ctc.html. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

9.1 Routine adverse event reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, the Adverse Events form is used for routine AE reporting in Rave.

9.2 Expedited adverse event reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined below. Alliance investigators are required to notify the Alliance Central Protocol Operations Program Office, the Study Chair, and their Institutional Review Board if a patient has an adverse event requiring expedited reporting. All such events must be reported in an expedited manner using the CTEP Adverse Event Reporting System (CTEP-AERS). In the rare occurrence when internet connectivity is lost, a 24-hour notification is to be made to the Alliance Central Protocol Operations Office. Once internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

The Alliance requires investigators to route all expedited adverse event reports through the Alliance Central Protocol Operations Program Office for Alliance coordinated studies.

Be sure to read this entire protocol section, as requirements are described in both the table and bullet points following the table. Note that the additional instructions or exclusions are protocol specific, and in the case of a conflict, the additional instructions or exclusions supersede the table.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.2.1 Alliance A221304 reporting requirements

Expedited reporting requirements for adverse events that occur within 30 Days of the last dose of treatment [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour;
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

NOTE: Deaths clearly due to progressive disease should NOT be reported via CTEP-AERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exclusions:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- Treatment expected adverse events include those listed in Section 10.0 and in the package insert.
- All new malignancies must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e., solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), and in situ tumors. In CTCAE version 4.0, the new malignancies (both second and secondary) may be reported as one of the following: (1) Leukemia secondary to oncology chemotherapy, (2) Myelodysplastic syndrome, (3) Treatment-related secondary malignancy, or (4) Neoplasms benign, malignant and unspecified—other. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how it was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.
- All pregnancies and suspected pregnancies occurring in female patients or in the partner of a male patient during therapy or within 28 days after completion of treatment on A221304 must be reporting via CTEP-AERS. In CTCAE version 4.0, use the event term, *"pregnancy, puerperium, and perinatal condition-other, fetal exposure (grade 4)".*
  - CTEP-AERS reports should be amended upon completion of the pregnancy to report pregnancy outcome (e.g. normal, spontaneous abortion, therapeutic abortion, fetal death, congenital abnormalities).
  - The CTEP-AERS report should be amended for any neonatal deaths or complications occurring within 28 days of birth independent of attribution. Infant deaths occurring after 28 days considered to be related to in utero exposure to the agents used in this trial should be reported via CTEP-AERS.
- The reporting of adverse events described above is in addition to, and does not supplant, the reporting of adverse events as part of the reporting of the results of the clinical trial, e.g. routine reporting.

10.0 DRUG INFORMATION

10.1 **Doxepin (Supplied)** IND Exempt

Procurement

Doxepin hydrochloride oral solution will be purchased and distributed in 4 oz. (120 mL) stock bottles by the Alliance Research Base Pharmacy. Participating institutions will order a starter supply of two bottles of doxepin HCl solution from the Alliance Research Base Pharmacy. Complete the Clinical Drug Order/Return Form, which is available on the A221304 page of the Alliance (www.allianceforclinicaltrialsinononcology.org) web site. Fax or mail the completed form to:

Medical Oncology Pharmacist
Mayo Clinic
Gonda 10-178
Rochester, MN 55905
Fax (507) 284-3464

Each site is responsible to monitor their supplies and order additional bottles as required. One bottle of doxepin HCl solution is considered to be a "bulk supply" and is to be reserved for the preparation of doses taken in the clinic. A site may order additional bottles of doxepin HCl solution in advance of patient participation in the optional continuation phase. Each site will provide their own Sterile Water for Irrigation, Sterile Water for Injection, or distilled water, oral syringes, and 4 oz. amber bottles.

At the end of the trial, any expired or remaining supplies should be destroyed according to institutional procedure.

Drug accountability

Agent disposition (receipt, dispensing, transfer, return or authorized local destruction of un-dispensed agent) shall be documented on the NCI Investigational Agent (Drug) Accountability Record (DARF) or the NCI Investigational Agent Accountability Record for Oral Agents (Oral DARF) as appropriate. Electronic accountability systems may be used. Paper printouts of electronic DARFs must be identical to the NCI DARF.

IND Status

Doxepin is IND exempt as used in this trial. This exemption has been determined by attestation that neither the investigator nor sponsor intends to seek a new indication for use or to support any other significant change in the labeling or product advertising for doxepin. This investigation will use an approved route of administration and dosage of doxepin and has no factors that increase the risk of the product. This investigation will be in compliance with 21CFR parts 56, 50, and 312.7 and neither the investigator nor sponsor will promote or represent that doxepin is safe or effective for the context that is under investigation in this study. This investigation will not commercially distribute or test market the study agent, and will not unnecessarily prolong an investigation.

Formulation

Each mL of solution contains doxepin hydrochloride equivalent to 10 mg doxepin. Inactive ingredients are glycerin, methlyparaben, propylparaben, flavoring agent and purified water.

Storage and Stability

Store at 20º to 25º C (68º to 77º F). A 4 oz. (120 mL) bottle is to be retained for the preparation of multiple doses. After the bottle has been opened for the first time, the site will assign an

expiration date of one year, if this expiration date is shorter than the expiration date listed on the bottle.

Preparation

Cycle 1: The designated unblinded person at each institution will add 2.5 mL of doxepin HCl oral solution to 2.5 mL of Sterile Water for Irrigation, Sterile Water for Injection, or distilled water just prior to administration. This yields a dose of 25 mg doxepin in 5 mL. The syringe label will state "Doxepin 25 mg/DLA/Placebo 5 mL"

Cycle 2/Continuation Phase: Sites will package doxepin 120 mL in a 4 oz. amber bottle. The prescription label will state "doxepin 10 mg/mL or placebo solution," with directions to dilute 2.5 mL with 2.5 mL of water. Assign an expiration date of one year, if this expiration date is shorter than the expiration date listed on the bottle. Patients continuing treatment at home during the continuation phase will be provided with a blinded bottle containing 120 mL of doxepin and should be instructed to use distilled water or tap water to dilute the doxepin solution.

Administration

Cycle 1: Patients will use the doxepin HCl solution as an oral rinse for one minute, then will expectorate the rinse. Patients should not eat or drink anything for 15 minutes before and after taking the medication.

Cycle 2/Continuation Phase: Patients will measure 2.5 mL of doxepin HCl 10 mg/mL solution and mix with 2.5 mL of distilled or tap water. Swish and gargle 25 mg/5 mL oral rinse for one minute, then expectorate the rinse. Patients should not eat or drink anything for 15 minutes before and after taking the medication.

Drug Interactions

Doxepin solution is not physically compatible with a number of carbonated beverages.

Pharmacokinetics

Doxepin is being used as an oral rinse for this study and no pharmacokinetics are available for this route of administration.

Adverse Events

Side effects are expected to be minimal. Based on experience in previous clinical trials, mild burning or stinging discomfort, unpleasant taste, and fatigue have been reported when the solution was used as an oral rinse.

At least minimal absorption through the oral mucosa is expected. Side effects reported when therapeutic oral doses are administered include weight gain, constipation, nausea, xerostomia, dizziness, somnolence, blurred vision, urinary retention, upper respiratory infection, low blood pressure, decreased production of blood cells, and suicidal thoughts.

Nursing Guidelines

- If solution needs to be diluted, use only water. Doxepin is not compatible with numerous carbonated beverages.
- Patients may experience a mild burning or stinging sensation after use.
- Patients may experience taste alterations.
- Because this agent is being used as an oral rinse, the normal systemic side effects of this agent are not expected. However a minimal amount of absorption through the oral mucosa is expected. Normal side effects when Doxepin is administered at full oral doses are: weight gain, constipation, nausea, xerostomia, dizziness, somnolence, blurred vision, urinary retention, and upper respiratory infection. Patients should be instructed to report any of these side effects to the study team.

10.2 DLA (diphenhydramine hydrochloride, lidocaine hydrochloride, and antacid) (Supplied)

Procurement

DLA will be provided by the Alliance Research Base Pharmacy in separate stock bottles of diphenhydramine hydrochloride, lidocaine hydrochloride, and antacid. Participating institutions will order a starter supply of two bottles of diphenhydramine hydrochloride, two bottles of viscous lidocaine hydrochloride, and one bottle of antacid from the Alliance Research Base Pharmacy. Fax or mail the Clinical Drug Order/Return Form request to the address listed in Section 10.1.

Each site is responsible to monitor their supplies and order additional bottles as required. The starter supply can be used to prepare doses at the clinic or for at home administration during the continuation phase. However, after the bottle has been opened for the first time, the site will assign an expiration date of one year, if this expiration date is sooner than the expiration date listed on the bottle.

A site may order additional bottles of diphenhydramine hydrochloride, lidocaine hydrochloride, and antacid as needed to maintain an adequate supply for in-clinic and at-home administration cycles. Each site will provide its own syringes and 8 oz. amber bottles.

At the end of the trial, any expired or remaining supplies should be destroyed according to institutional procedure.

Drug accountability

Agent disposition (receipt, dispensing, transfer, return or authorized local destruction of un-dispensed agent) shall be documented on the NCI Investigational Agent (Drug) Accountability Record (DARF) or the NCI Investigational Agent Accountability Record for Oral Agents (Oral DARF) as appropriate. Electronic accountability systems may be used. Paper printouts of electronic DARFs must be identical to the NCI DARF.

Formulation

Diphenhydramine hydrochloride 12.5 mg/5 mL alcohol free liquid is available in 120 mL bottles. Inactive ingredients are anhydrous citric acid, flavor, purified water, sodium benzoate, sodium chloride, sodium citrate, and sorbitol solution.

Lidocaine 2% viscous solution is available in 100 mL bottles. Inactive ingredients are flavoring, methylparaben, propylparaben, sodium carboxymethylcellulose, and sodium saccharin.

Antacid suspension (aluminum hydroxide 200 mg/magnesium hydroxide 200 mg/simethicone 20 mg) is available as 355 mL bottles. Inactive ingredients are butylparaben, carboxymethylcellulose sodium, flavor, hypromellose, microcrystalline cellulose, propylparaben, purified water, saccharin sodium, simethicone emulsion, and sorbitol.

Storage and Stability

Store at controlled room temperature (20° to 25° C, 68° to 77° F). Each bottle of diphenhydramine, lidocaine, and antacid will be used for the preparation of multiple doses. After the bottles have been opened for the first time, the site will assign an expiration date of one year, if this expiration date is shorter than the expiration date listed on the bottles.

Preparation

Cycle 1: The designated person at each institution will mix 1.7 mL of each of diphenhydramine hydrochloride, lidocaine hydrochloride, and antacid from each of the bulk bottles for a total volume of 5.1 mL. Cycle 1 for the DLA is blinded, therefore 5 mL of the resulting mixture should be drawn up (please note approval to round dose from 5.1 mL) and the syringe label will read, “Doxepin 25 mg/DLA/Placebo 5 mL.”

Cycle 2/Continuation Phase: Sites will package 240 mL of DLA by mixing 80 mL each of diphenhydramine hydrochloride, lidocaine hydrochloride, and antacid in an 8 oz. Amber bottle immediately prior to dispensing to the patient. No tap or distilled water for dilution will be required. The prescription label will state DLA (diphenhydramine hydrochloride, lidocaine hydrochloride, antacid 1:1:1) with directions to take 5 mL. Assign an expiration date of 14 days under refrigeration.

Administration

Cycle 1: Patients will use the DLA solution as an oral rinse for one minute, then will expectorate the rinse. Patients should not eat or drink anything for 15 minutes before and after taking the medication.

Cycle 2/Continuation Phase: Patients will shake the suspension well, then measure 5 mL of DLA solution. Swish and gargle 5 mL oral rinse for one minute, then expectorate the rinse. Patients should not eat or drink anything for 15 minutes before and after taking the medication

Drug Interactions: Not applicable.

Pharmacokinetics: Not applicable.

Adverse Events

As an oral rinse the patient may experience taste disturbances and burning/tingling in the oral cavity. Minimal systemic absorption through the oral mucosa is expected. Side effects with therapeutic oral doses are drowsiness or any CNS adverse effects, constipation, diarrhea, nausea and dry mouth.

Nursing Guidelines

- Patients should be instructed to rinse with the DLA solution for 1 minute and then expectorate the rinse. Patients should avoid food or drink for 15 minutes before and after administration.
- Warn patients of the possibility of loss of sensation to the mouth and tongue and to use caution when eating.
- As the rinse is not swallowed expected systemic side effects from the ingredients would not be expected. Instruct patient to report any unexpected side effects to the study team.

10.3 Placebo (Supplied)

Procurement

Placebo (Ora-Sweet SF syrup) will be purchased and distributed in 16 oz. stock bottles by the Alliance Research Base Pharmacy. Participating institutions will order a starter supply of one bottle of placebo (Ora-Sweet SF syrup) from the Alliance Research Base Pharmacy. Fax or mail the Clinical Drug Order/Return Form request to the address listed in Section 10.1.

Each site is responsible to monitor their supplies and order additional bottles as required. The starter supply can be used to prepare doses at the clinic or for at-home administration during the continuation phase. However, after the bottle has been opened for the first time, the site will assign an expiration date of one year, if this expiration date is sooner than the expiration date listed on the bottle. A site may order additional bottles of Ora-Sweet SF as needed to maintain an adequate supply for in-clinic and at-home administration cycles. Each site will provide its own Sterile Water for Irrigation, Sterile Water for Injection, or distilled water, oral syringes and 4 oz. amber bottles.

At the end of the trial, any expired or remaining supplies should be destroyed according to institutional procedure.

Drug accountability

Agent disposition (receipt, dispensing, transfer, return or authorized local destruction of un-dispensed agent) shall be documented on the NCI Investigational Agent (Drug) Accountability Record (DARF) or the NCI Investigational Agent Accountability Record for Oral Agents (Oral DARF) as appropriate. Electronic accountability systems may be used. Paper printouts of electronic DARFs must be identical to the NCI DARF.

Formulation

Ora-Sweet SF will be used as the base solution for preparing the placebo dose. Ora-Sweet SF is a flavored sugar-free syrup vehicle available in 473 mL (16 oz.) bottles. The product contains glycerin, sorbitol, sodium saccharin, xanthan bum, flavoring agent, and purified water. The solution is buffered with citric acid and sodium citrate and preserved with methylparaben, propylparaben, and potassium sorbate. No alcohol will be contained in the mixing solvents, which may cause stinging sensations.

Storage and Stability

Store at controlled room temperature (15º to 30º C, 59º to 86º F). A 473 mL (16 oz.) bottle is to be retained for the preparation of multiple doses. After the bottles have been opened for the first time, the site will assign an expiration date of one year, if this expiration date is shorter than the expiration date listed on the bottles.

Preparation

Cycle 1: The designated unblinded person at each institution will add 2.5 mL of Ora-Sweet SF oral solution to 2.5 mL of Sterile Water for Irrigation, Sterile Water for Injection, or distilled water just prior to administration. The total dose will be 5 mL. The syringe label will read Doxepin 25 mg/DLA/Placebo 5 mL.

Cycle 2/Continuation Phase: Sites will package Ora-Sweet SF 120 mL in a 4 oz. amber bottle. The prescription label will state "doxepin 10 mg/mL or placebo solution," with directions to dilute 2.5 mL with 2.5 mL of water. Assign an expiration date of one year, if this expiration date is shorter than the expiration date listed on the bottle. Patients continuing treatment at home during the continuation phase will be provided with a blinded bottle containing 120 mL of Ora-Sweet SF and should be instructed to use distilled water or tap water to dilute the Ora-Sweet SF solution.

Administration

Cycle 1: Patients will use the Ora-Sweet SF solution as an oral rinse for one minute, then will expectorate the rinse. Patients should not eat or drink anything for 15 minutes before and after taking the medication.

Cycle 2/Continuation Phase: Patients will measure 2.5 mL of Ora-Sweet SF solution and mix with 2.5 mL of distilled or tap water. Swish and gargle 5 mL oral rinse for one minute, then expectorate the rinse. Patients should not eat or drink anything for 15 minutes before and after taking the medication.

Drug Interactions: Not applicable.

Pharmacokinetics: Not applicable.

Adverse Events: Not applicable.

Nursing Guidelines

Because patients and staff administering doxepin and placebo will be blinded to the agent delivered, the nursing guidelines for doxepin (Section 10.1) should be followed for placebo.

11.0 MEASUREMENT OF EFFECT

At the time of enrollment, the toxicity grade of mucous membrane by the Acute Radiation Morbidity Scoring Criteria (http://www.rtog.org/researchassociates/adverseeventreporting/acuteradiationmorbidityscoringcriteria.aspx) will be recorded. For patient-reported outcomes, numerous OM severity assessment tools exist ranging in complexity from simple combined variable scoring scales to very detailed, objective mucositis rating scales.[2 4,14,41] The WHO OM scale is the most commonly reported and requires the least examiner experience; however, it has been criticized for combining symptoms, signs, and functional changes[14]. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 included separate subjective and objective scales for mucositis. However, in version 4.0, the objective scale based on clinical exam has been eliminated. The Oral Mucositis Assessment Scale is a psychometrically validated instrument for this patient population.[41] It is utilized to score nine anatomical sites of the oral mucosa with respect to ulceration/pseudomembrane formation and erythema.

Pain is the most important and bothersome subjective symptom of OM, and yet there are few validated assessment instruments measuring OM pain resulting from cancer therapy.[42] Two examples of validated tools are the Oral Mucositis Daily Questionnaire (OMDQ) and the Oral Mucositis Weekly Questionnaire-Head and Neck Cancer (OMWQ-HN).[43-45] A modified combination of both these instruments will be used to assess baseline OM symptoms. Questionnaires with eleven-point numerical analogue scales (0−10 scores) will be used to measure pain, unpleasant taste, stinging or burning, and drowsiness at defined intervals following doxepin or placebo rinse and in weekly follow-up if patients choose to continue using doxepin rinse. Numerical analog scales are validated measures of symptoms.[46-50] These are the same instruments utilized in the recently completed positive Alliance doxepin study. A standard conversion table for 24-hour morphine equivalence will also be used in the one-week continuation phase to convert different opioid regimens into comparable terms.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Treatment

During the 7-day continuation phase, the patient can opt out at any time when they believe that the treatment is no longer beneficial. Patients will then be treated per clinical practice recommendations off study.

12.2 Managing ineligible and canceled patients and major protocol violations

Baseline data must be submitted per Section 5.0 for patients deemed ineligible or canceled. See also the Forms Packet for full details of data submission requirements.

12.3 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Overview

This is a randomized, placebo-controlled, three-arm phase III trial to assess the efficacy of doxepin oral rinse or DLA versus placebo for the treatment of cancer therapy-related OM. Since each of the two treatment arms will be compared against placebo arm, the conservative Bonferroni approach (instead of Dunnett's multiple comparison procedure) will be used to adjust for multiplicity.

13.2 Sample Size, Accrual Time and Study Duration

13.2.1 Sample Size

In the recently completed phase III randomized, double-blind trial comparing doxepin to placebo for treatment of oral mucositis pain in patients undergoing high-dose, curative head and neck radiotherapy treatment,[39] we observed a pain AUC reduction of 9.1 (Standard deviation, SD = 7.9) with doxepin vs. 4.7 (SD = 6.1) in the placebo arm. This corresponded to a difference in pain AUC reduction 4.4, with a common estimate SD of 7.0. Considering a clinically meaningful difference in pain AUC reduction being 3.5 (i.e., half of the common SD = 7.0, according to Norman GR, [51] Sloan JA[52]), in a 2-arm study we would need a sample size of 156 patients (78 patients per arm) to have at least 80% power to detect such an effect size, using the two-sample *t*-test at the 2.5% significance level. As we have two treatment arms (doxepin or DLA versus placebo) in this 3-arm study design, doxepin, DLA or placebo, the sample size will be 234 patients in total (78 patients per arm). This sample size will be further inflated by 15% to 270 patients to account for patient ineligibility, cancellation, or major violations.

13.2.2 Accrual Rate and Accrual Duration

We anticipate accruing approximately 20 patients per month, based on our previous experience in clinical practice. This would mean completing the primary accrual within 14 months from study initiation and completing analysis within 18 months from study initiation.

13.2.3 Primary Endpoint Completion Date for ClinicalTrials.gov Reporting

For purpose of ClinicalTrial.gov reporting, the Primary Endpoint Completion Date (PECD) for this study is the time the last patient registered has been followed for at least one day.

13.3 Statistical Design and Analysis for the Primary Endpoint

13.3.1 Primary Endpoint

The primary endpoint of this study is the total pain reduction (mouth and throat) as measured by the numerical analogue scale of mouth pain in the questionnaires taken at baseline, and 5, 15, 30, 60, 120, 240 minutes after assigned treatment for doxepin or DLA vs. placebo. The total pain reduction will be calculated by the (average of mouth and throat) area under the curve (AUC) adjusting for baseline, with time scale replaced by a numerical scale of 1, 2, 3, 4, 5 and 6. The numerical scale will be used rather than the raw time scale in order to give proper weights to more immediate patient-reported mouth pain outcomes after treatment. The AUC will be prorated when there are terminal missing data. If the missing data are intermittent, simple imputation by trapezoidal rules will be applied to calculate the AUC. If a patient cancels, is missing baseline data, or only provides baseline data, he/she will be excluded from the statistical analysis.

13.3.2 Statistical Design

This is a three-arm parallel group design with neither cross-over nor interim analysis.

13.3.3 Study Operating Characteristics

Simulation studies of 10,000 clinical trials are conducted for the proposed parallel group design. The probabilities of rejecting null hypothesis for various effect sizes (in AUC reduction), i.e. global power are summarized for both Bonferroni and Dunnett's multiple comparison procedures in the following table. With a total sample size of 234 patients, the empirical global powers are approximately 90% at a family-wise 5% significance level. The Dunnett's single step procedure improves the power but only a small amount. The simulation for operating characteristics is conducted using EAST version 6.2.

Table 1. Power analysis for various effect sizes with a total sample size of 234 patients.

Scenario	Placebo	DLA	Doxepin	Multiple Comparison	Global Power (%)
1	4.4	6.15	7.9	Bonferroni	88.9
1	4.4	6.15	7.9	Dunnett's single step	89.3
2	4.4	4.5	7.9	Bonferroni	87.8
2	4.4	4.5	7.9	Dunnett's single step	88.1
3	4.4	7.8	7.9	Bonferroni	95.3
3	4.4	7.8	7.9	Dunnett's single step	95.6

13.3.4 Analysis Plan

A modified intent-to-treat principle will be applied for statistical analysis of efficacy in evaluable patients.[53] Evaluable patients are defined as all patients meeting the eligibility criteria who did not cancel prior to receiving treatment and had no major violations.

The primary analysis of the total pain reduction between arms will be conducted using the two-sample *t*-test or nonparametric Wilcoxon rank-sum testing. Transformation of AUC (such as log) may be taken if the empirical distribution of residuals is deemed far from anormal distribution. Supplementary analyses will be conducted to analyze these repeated measurements of mouth and throat pain in a longitudinal data model. Graphical procedures will include stream plots of individual patient mouth pain scales and plots of average values over time for each treatment arms.

13.4 Supplementary Analysis Plans

13.4.1 Secondary Endpoints

1) The total unpleasant taste of the oral rinse as measured by the numerical analogue scale of taste of the oral rinse in the questionnaires.
2) The total stinging or burning from the oral rinse as measured by the numerical analogue scale of stinging or burning from the oral rinse in the questionnaires.
3) The total drowsiness increase as measured by the numerical analogue scale of drowsiness questionnaires.
4) The incidence of using alternative analgesics between 1 and 4 hours after initial mouthwash.
5) Patient preference for continued therapy with oral rinse after initial test rinse phase, as measured by Item 9 in the patient-reported questionnaire after 4 hours.
6) The length of time, pain score, and alternative analgesics use in the Continuation Phase.

13.4.2 Secondary Analysis

Multiplicity will not be adjusted for secondary analyses, hence, statistically significant findings from secondary analyses are exploratory in nature and therefore shall be interpreted as such. Descriptive statistics and graphical approaches will form the basis for most secondary analyses.

1) Similar analysis as primary endpoint will be conducted for total unpleasant taste.
2) Similar analysis as primary endpoint will be conducted for total stinging or burning.
3) Similar analysis as primary endpoint will be conducted for total drowsiness increase.
4) The incidence of utilizing additional analgesics between 1-4 hours after initial mouthwash will be compared between the arms by the Chi-square test or Fisher's exact test.
5) Frequency will be used to summarize patient preference for continued therapy and Chi-square test may be applied, if appropriate.
6) Descriptive statistics and graphical procedures will be used to summarize the length of time, pain score, and alternative analgesics use in the Continuation Phase.

13.5 Study Monitoring

13.5.1 Adverse Event Stopping Rule

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below. Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as possible, probable, or definite) that satisfy the following criteria:

1) If 5 or more of the first 20 treated patients (or 25% of all patients after 20 patients have been accrued) experience a grade 3 or higher non-hematologic adverse event and the adverse event rate is higher in either active treatment arm.

2) If 3 or more of the first 20 treated patients (or 15% of all patients after 20 patients have been accrued) experience a grade 4 or higher non-hematologic adverse event and the adverse event rate is higher in either active treatment arm.

13.5.2 Accrual Monitoring Stopping Rule

Slow Accrual: Patient accrual will be closely monitored by the investigators and secondary statistician on a monthly basis. If the accrual rate falls below 50% of expected accrual rate, investigators will carefully review feedback from sites and consider taking measures to encourage patient enrollment.

13.6 Study Reporting

13.6.1 This study will be monitored by the Alliance Data Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every month as per NCI guidelines.

13.6.2 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrials.gov" web site. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov.

13.7 Descriptive Factors

None

13.8 Inclusion of Women and Minorities

All studies must address the issue of inclusion of women and minorities in clinical research and whether gender or race/ethnicity differences in the intervention effect are to be expected. The statisticians will provide statistical analysis of past Alliance phase III studies as well as how the review of the literature will be reflected in the statistical section. The minority/gender table from the PSW should be included here.

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	1	1	0	0	2
Asian	3	2	0	0	5
Native Hawaiian or Other Pacific Islander	1	1	0	0	2
Black or African American	13	10	1	1	25
White	141	92	2	1	236
More Than One Race	0	0	0	00	0
Total	159	106	3	2	270

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15.0 MODEL CONSENT FORM

Study Title for Study Participants:

Testing doxepin and "magic mouthwash" as oral rinses for mucositis pain for patients receiving radiation therapy

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

Alliance A221304: A phase III placebo-controlled, randomized three-arm study of doxepin and a topical rinse in the treatment of acute oral mucositis pain in patients receiving radiotherapy with or without chemotherapy

What is the usual approach to my painful mouth sores?

You are being asked to take part in this research study because you have been diagnosed with cancer and are (or will be) receiving radiation therapy to your head and neck. It is known that this type of radiation therapy can cause painful mouth sores, which can interfere with activities of daily living, including eating and drinking. Patients who are not in this study are usually treated for these sores with rinses (or mouthwashes) containing different drugs such as diphenhydramine (e.g., Benadryl), lidocaine, and antacids. The combination of these drugs, which will be used for this study, is also known as "DLA."

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

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

- You may choose to have the usual approach described above,
- you may choose to take part in another study, if one is available,
- or you may choose not to be treated for painful mouth sores.

Why is this study being done?

The purpose of this study is to test whether a mouthwash made with a drug called doxepin can reduce the pain caused by mouth sores resulting from radiation therapy. The effects of doxepin will be compared to DLA and placebo. A placebo is a liquid that tastes and looks like the study drug but contains no medication. There will be about 270 people taking part in this study.

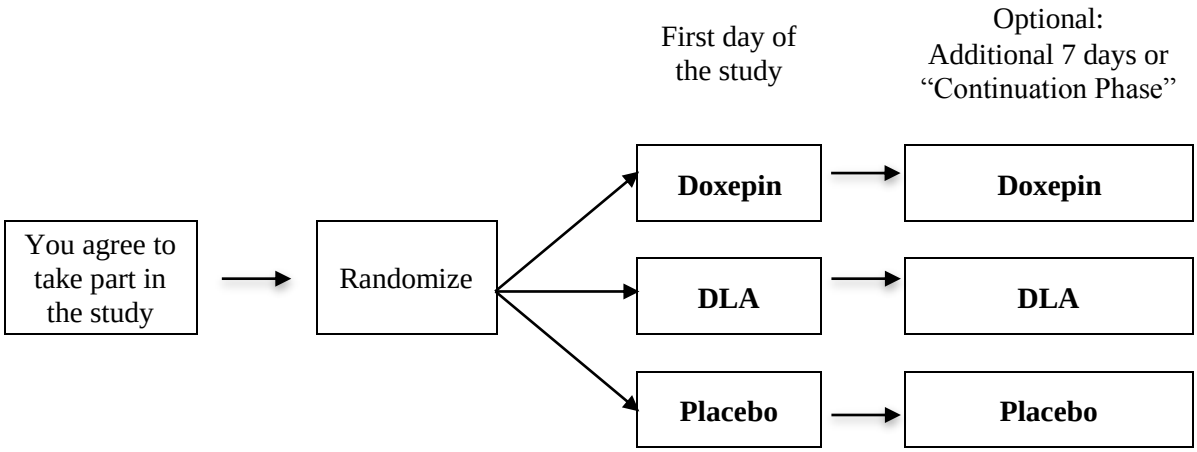
Doxepin is approved by the Food and Drug Administration (FDA) for the treatment of depression, anxiety, long term pain management, and a cream for the management of rash. The doxepin used in this study is considered investigational, which means it has not been approved by the FDA for the use described in this study.

What are the study groups?

This study has three study groups.

- Group 1 will get doxepin mouthwash.
- Group 2 will get the DLA mouthwash often used for painful mouth sores.
- Group 3 will get a placebo mouthwash.

A computer will by chance assign you to treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the others.
Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



Day one of the study: On the first day of the study, you will receive a one-time single dose of the rinse to swish, gargle and spit. You will not know which of the three rinses you will receive. You will swish and gargle about 1 teaspoon of the rinse in your mouth for 1 minute and then spit it out.

Also on the first day, you will be asked to fill out seven questionnaires about your feelings of well-being and about your mouth pain. You will fill out the questionnaires in your study doctor's office before using the medication and then again at 5, 15, 30 and 60 minutes after you use the study rinse. You will then be able to leave the study doctor's office. You will be given directions for completing the questionnaires at 2 and 4 hours after you used the rinse. You may receive a phone call reminder to fill out the questionnaire at 2 and 4 hours. At each of these time points, it should take 5 minutes or less to complete the questionnaires.

You should not take viscous lidocaine, 'magic mouthwash', benzocaine, diphenhydramine or other medicated oral rinse on the first day of treatment (except saline or baking soda rinse). If possible, no pain medication or crushed ice should be used for one hour prior to and after the Day 1 rinse. Also, you should not eat or drink anything for 15 minutes before and after taking the study rinse.

Continuation Phase: For up to seven days after the first time you took the rinse, you may choose to start a daily regimen of using the rinse at home as needed for up to 1 week. This is called the "Continuation Phase" of the study. If you decide to participate in this one-week continuation phase, you will be given study rinse that you can take home with instructions on how to properly mix the rinse for use at home. You can use the study rinse as often as every 4 hours, if needed. If you feel that the rinse is not working, you may stop using it at any time. After you have stopped using the rinse during the continuation phase, you should return any unused portion to the study staff at your next clinic visit.

You will also be asked to complete a questionnaire each day of that week. We ask that you complete the questionnaire at the same time each day, preferably in the evening, and return it to the study staff when it is completed. It should take five minutes or less each day to complete the questionnaire.

If possible, during the continuation phase you should avoid taking any medication for mouth pain for 60 minutes before and after the study medication. You may take oral pain medication 60 minutes after you receive the study medication if you feel the need for additional pain relief. You will be asked to record these medications in the questionnaire. You should also avoid eating for 15 minutes before and after using the study rinse.

How long will I be in this study?

You will be in the study for at least one day. If you choose to participate in the Continuation Phase, you will be in the study for up to an additional 7 days after you start the Continuation phase.

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

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

- You may lose time at work or home and spend more time than usual in the hospital or doctor's office
- You may be asked sensitive or private questions which you normally do not discuss

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.

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

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

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Study Group 1 - Possible side effects of doxepin

COMMON, SOME MAY BE SERIOUS In 100 people receiving doxepin as given in this study, more than 20 and up to 100 may have:
• Mild burning in your mouth • Stinging discomfort in your mouth • Mild taste change • Drowsiness

RARE, SOME MAY BE SERIOUS In 100 people receiving doxepin as given in this study, 3 or fewer may have:
• Constipation • Mouth dryness due to lack of saliva • Dizziness or lightheadedness • Sleepiness • Difficulty urinating • Lung infection • Weight gain • Nausea • Blurred vision • Decreased production of blood cells • Low blood pressure • Suicidal thoughts

Study Group 2 - Possible side effects of diphenhydramine, lidocaine, and antacid (DLA)

COMMON, SOME MAY BE SERIOUS In 100 people receiving DLA as given in this study, more than 20 and up to 100 may have:
• Mild burning in your mouth • Stinging discomfort in your mouth • Mild taste change

RARE, SOME MAY BE SERIOUS In 100 people receiving DLA as given in this study, 3 or fewer may have:
• Constipation or diarrhea • Mouth dryness due to lack of saliva • Dizziness or lightheadedness • Sleepiness • Difficulty urinating • Lung infection • Shortness of breath • Nausea • Blurred vision • Allergic reaction • Itching or mild skin reaction such as hives • Excessive sweating • Rash or flushing of the skin • Mild confusion or disorientation • Decreased production of blood cells • Low blood pressure • Life-threatening, irregular heartbeat • Kidney stones

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. While it is not expected that the amount of study rinse that will be absorbed in your bloodstream will be high, an accidental overdose of the study rinse may be damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

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

It is not possible to know at this time if the doxepin is better than the usual approach using mouth rinses with drugs intended to numb the pain, so this study may or may not help you. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

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

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

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, Institutional Review Board, or the FDA.

What are my rights in this study?

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

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

The doxepin, DLA and placebo will be supplied at no charge while you take part in this study. The cost of getting the rinses ready and giving it to you is not paid by the study so you or your insurance company may have to pay for this.

You and/or your health plan/insurance company will need to pay for all of the other costs of care. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

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

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

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

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

- The Alliance for Clinical Trials in Oncology
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

Where can I get more information?

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

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

Who can answer my questions about this study?

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

My Signature Agreeing to Take Part in the Study

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

Participant's signature_____

Date of signature_____

APPENDIX I: ORAL PAIN ASSESSMENT

1. On a scale from 0 to 10, what number best describes your MOUTH PAIN due to your radiation treatment now? (circle one number)

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst pain imaginable or possible

Eligibility screening: When this question is asked for eligibility screening, an oral exam confirming the presence of mucositis should be performed by the enrolling clinician in addition to asking the patient this question.

Baseline/Day 1: This question is also to be asked on Day 1 prior to the first dose of study drug.

APPENDIX II: REGISTRATION FATIGUE/UNISCALE ASSESSMENT

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and recorded on the Registration Fatigue/Uniscale Assessment Form (see Forms Packet).

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

APPENDIX III: PATIENT COMPLETED ORAL SYMPTOMS BOOKLET (BASELINE TO 1 HOUR POST ADMINISTRATION)

PATIENT INFORMATION SHEET
Patient Completed Oral Symptoms Booklet
(Baseline to 60 minutes Post Administration)

You have been given booklets to complete for this study. The booklets contain questions about your oral symptoms as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You will be given two booklets on the first day you are on the study.

2. The first booklet will be filled out on the first day in the study doctor's office. Please fill out this first booklet at each of the following times:
    a. Baseline before oral rinse
    b. 5 minutes after oral rinse
    c. 15 minutes after oral rinse
    d. 30 minutes after oral rinse
    e. 60 minutes (1 hour) after oral rinse

3. Please return this booklet to your nurse or your physician before leaving the doctor's office. You will take the second booklet with you when you leave the doctor's office.

4. Directions on how to complete each set of questions are written on the top of each set.

5. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

Thank you for taking the time to help us.

Pre-treatment Questions

Before rinsing your mouth with the oral solution, please complete this page.

1. On a scale from 0 to 10, what number best describes your MOUTH PAIN due to your radiation treatment now? (circle one number)

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst pain imaginable or possible

2. On a scale from 0 to 10, what number best describes your THROAT PAIN (i.e., pain with swallowing) due to your radiation treatment now? (circle one number)

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst pain imaginable or possible

3. On a scale from 0 to 10, what number best describes your DROWSINESS now? (circle one number)

0	1	2	3	4	5	6	7	8	9	10
No drowsiness										Extreme drowsiness, leading to sleep

4. Did you use any medications for PAIN in the past 24 HOURS? (circle 'Yes' or 'No')

   Yes No

   If yes, Please list the medications you took for PAIN in the past 24 HOURS:

Name	Strength	Route	Frequency
For example *Oxycodone*	*5 mg*	*By mouth*	*Every 4 hours*

5. Do you currently smoke cigarettes? (circle 'Yes' or 'No')

   Yes No

6. Do you currently drink alcohol? (circle 'Yes' or 'No')

   Yes No

Treatment Information

Please now rinse your mouth with the oral rinsing medication. DO NOT SWALLOW the rinse. SWISH and GARGLE it around all portions of your mouth for a total of ONE MINUTE then SPIT IT OUT and record the current date and time:

Today's date: __ __ / __ __ / __ __ __ __ (MM/DD/YYYY)

Current time
(Enter time in the boxes and circle AM or PM.) For example [10] : [30] (AM) / PM

[ ] : [ ] AM / PM

You can keep track of the times to complete the questionnaires by using this table. Enter the current time onto the first row of the table and the schedule for completing the other time points today can be filled out.

Time point	**EXAMPLE**	**ACTUAL TIME**
Current time (just after you finished the rinse)	10:30 (AM) / PM	__ __ : __ __ AM / PM
		PLANNED TIMES
5 minutes	10:35 (AM) / PM	__ __ : __ __ AM / PM
15 minutes	10:45 (AM) / PM	__ __ : __ __ AM / PM
30 minutes	11:00 (AM) / PM	__ __ : __ __ AM / PM
60 minutes (1 hour)	11:30 (AM) / PM	__ __ : __ __ AM / PM
120 minutes (2 hours)	12:30 AM / (PM)	__ __ : __ __ AM / PM
240 minutes (4 hours)	2:30 AM / (PM)	__ __ : __ __ AM / PM

We hope you will feel better soon. Five minutes after the time you rinsed your mouth, please complete the next questionnaire page.

Questionnaire after 5 minutes

This page is to be completed 5 MINUTES after you rinsed with the oral solution for one minute and spit it out.

Current time
(Enter time in the boxes and circle AM or PM.) For example [10] : [30] (AM) / PM

[ ] : [ ] AM / PM

1. On a scale from 0 to 10, what number best describes your MOUTH PAIN due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

2. On a scale from 0 to 10, what number best describes your THROAT PAIN (i.e., pain with swallowing) due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

3. On a scale from 0 to 10, what number best describes any STINGING OR BURNING FROM THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No stinging or burning — Worst stinging or burning possible

4. On a scale from 0 to 10, what number best describes the TASTE OF THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Acceptable — Terrible

5. On a scale from 0 to 10, what number best describes your DROWSINESS now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No drowsiness — Extreme drowsiness, leading to sleep

6. Have you noticed any other side effects from the oral rinse? (circle 'Yes' or 'No')

   Yes No

   If yes, please explain

   _____

   _____

   _____

After 15 minutes from the time you rinsed your mouth (10 minutes from now), please complete the next questionnaire page.

Questionnaire after 15 minutes

This page is to be completed 15 MINUTES after you rinsed with the oral solution for one minute and spit it out.

Current time
(Enter time in the boxes and circle AM or PM.) For example 10 : 30 (AM) / PM

[ ] : [ ] AM / PM

1. On a scale from 0 to 10, what number best describes your MOUTH PAIN due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

2. On a scale from 0 to 10, what number best describes your THROAT PAIN (i.e., pain with swallowing) due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

3. On a scale from 0 to 10, what number best describes any STINGING OR BURNING FROM THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No stinging or burning — Worst stinging or burning possible

4. On a scale from 0 to 10, what number best describes the TASTE OF THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Acceptable — Terrible

5. On a scale from 0 to 10, what number best describes your DROWSINESS now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No drowsiness — Extreme drowsiness, leading to sleep

6. Have you noticed any other side effects from the oral rinse? (circle 'Yes' or 'No')

   Yes No

   If yes, please explain

   _____

   _____

   _____

After 30 minutes from the time you rinsed your mouth (about 15 minutes from now), please complete the next questionnaire page.

Questionnaire after 30 minutes

This page is to be completed 30 MINUTES after you rinsed with the oral solution for one minute and spit it out.

Current time
(Enter time in the boxes and circle AM or PM.) For example 10 : 30 (AM) / PM

[ ] : [ ] AM / PM

1. On a scale from 0 to 10, what number best describes your MOUTH PAIN due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

2. On a scale from 0 to 10, what number best describes your THROAT PAIN (i.e., pain with swallowing) due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

3. On a scale from 0 to 10, what number best describes any STINGING OR BURNING FROM THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No stinging or burning — Worst stinging or burning possible

4. On a scale from 0 to 10, what number best describes the TASTE OF THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Acceptable — Terrible

5. On a scale from 0 to 10, what number best describes your DROWSINESS now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No drowsiness — Extreme drowsiness, leading to sleep

6. Have you noticed any other side effects from the oral rinse? (circle 'Yes' or 'No')

   Yes No

   If yes, please explain

   _____

   _____

   _____

After 60 minutes (1 hour) from the time you rinsed your mouth (about 30 minutes from now), please complete the next questionnaire page.

Questionnaire after 60 minutes

This page is to be completed 60 MINUTES (1 HOUR) after you rinsed with the oral solution for one minute and spit it out.

Current time
(Enter time in the boxes and circle AM or PM.) For example 10 : 30 (AM) / PM

[ ] : [ ] AM / PM

1. On a scale from 0 to 10, what number best describes your MOUTH PAIN due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

2. On a scale from 0 to 10, what number best describes your THROAT PAIN (i.e., pain with swallowing) due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

3. On a scale from 0 to 10, what number best describes any STINGING OR BURNING FROM THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No stinging or burning — Worst stinging or burning possible

4. On a scale from 0 to 10, what number best describes the TASTE OF THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Acceptable — Terrible

5. On a scale from 0 to 10, what number best describes your DROWSINESS now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No drowsiness — Extreme drowsiness, leading to sleep

6. Have you noticed any other side effects from the oral rinse? (circle 'Yes' or 'No')

   Yes No

   If yes, please explain

   _____

   _____

   _____

Once you have completed this booklet, please give the booklet to your nurse or care provider.

After 120 minutes (2 hours) from the time you rinsed your mouth (about an hour from now), please complete the next questionnaire booklet.

You may complete the next booklet from home, if you prefer. You may receive a telephone reminder from the study staff about completing the next booklet.

APPENDIX IV: PATIENT COMPLETED ORAL SYMPTOMS BOOKLET (2 TO 4 HOURS POST ADMINISTRATION)

PATIENT INFORMATION SHEET
Patient Completed Oral Symptoms Booklet
(Two to Four Hours Post Administration)

You have been given booklets to complete for this study. The booklets contain questions about your oral symptoms as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You will be given two booklets on the first day you are on the study. You should have given the first booklet to the nurse or doctor before leaving the doctor's office.

2. This second booklet will be taken with you when you leave the doctor's office. Please fill this second booklet out at these time points:
    a. 120 minutes (2 hours) after oral rinse
    b. 240 minutes (4 hours) after oral rinse

3. After completing this booklet, please return it to your nurse or physician at your next visit or mail it back in the provided envelope.

4. It is very important that you return the booklets to us, whether you finish the study or not.

5. Directions on how to complete each set of questions are written at the beginning of each set.

6. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

Thank you for taking the time to help us.

Questionnaire after 120 minutes

This page is to be completed 120 MINUTES (2 HOURS) after you rinsed with the oral solution for one minute and spit it out.

Current time
(Enter time in the boxes and circle AM or PM.) For example 10 : 30 (AM) / PM

[ ] : [ ] AM / PM

1. On a scale from 0 to 10, what number best describes your MOUTH PAIN due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

2. On a scale from 0 to 10, what number best describes your THROAT PAIN (i.e., pain with swallowing) due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

3. On a scale from 0 to 10, what number best describes any STINGING OR BURNING FROM THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No stinging or burning — Worst stinging or burning possible

4. On a scale from 0 to 10, what number best describes the TASTE OF THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Acceptable — Terrible

5. On a scale from 0 to 10, what number best describes your DROWSINESS now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No drowsiness — Extreme drowsiness, leading to sleep

6. Have you noticed any other side effects from the oral rinse? (circle 'Yes' or 'No')

   Yes No

   If yes, please explain

   _____

   _____

   _____

7. Did you take any other pain medications over the last hour? (circle 'Yes' or 'No')

   Yes No

   If yes, please list the medications that you took:

Name	Strength	When
For example *Oxycodone*	*5 mg*	*one hour ago or within the last 60 minutes*

After 240 minutes (4 hours) from the time you rinsed your mouth (about 2 hours from now), please complete the next questionnaire page.

Questionnaire after 240 minutes

This page is to be completed 240 MINUTES (4 HOURS) after you rinsed with the oral solution for one minute and spit it out.

Current time
(Enter time in the boxes and circle AM or PM.) For example 10 : 30 (AM) / PM

[ ] : [ ] AM / PM

1. On a scale from 0 to 10, what number best describes your MOUTH PAIN due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

2. On a scale from 0 to 10, what number best describes your THROAT PAIN (i.e., pain with swallowing) due to your radiation treatment now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No pain — Worst pain imaginable or possible

3. On a scale from 0 to 10, what number best describes any STINGING OR BURNING FROM THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No stinging or burning — Worst stinging or burning possible

4. On a scale from 0 to 10, what number best describes the TASTE OF THE ORAL RINSE now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Acceptable — Terrible

5. On a scale from 0 to 10, what number best describes your DROWSINESS now? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
No drowsiness — Extreme drowsiness, leading to sleep

6. Have you noticed any other side effects from the oral rinse? (circle 'Yes' or 'No')

   Yes No

   If yes, please explain

   _____

   _____

7. Did you take any other pain medications over the last two hours? (circle 'Yes' or 'No')

   Yes No

   If yes, please list the medications that you took

Name	Strength	When
For example *Oxycodone*	*5 mg*	*one hour ago or within the last 60 minutes*

   _____

   _____

   _____

   _____

8. Was the study medication rinse helpful in alleviating your mouth/throat pain at any time over the last 4 hours? (circle 'Yes' or 'No')

   Yes No

   Other comments

   _____

   _____

9. Based on your experience with this current oral rinsing medication, would you want to take another dose now if it were available? (circle 'Yes' or 'No')

   Yes No

   If yes, we encourage you to consider continuing with the study rinse for up to one week in the continuation phase of the study. Contact the study staff about how to do this when you return to the clinic.

   If no, please explain

   _____

   _____

This completes the questionnaires for today. Thank you very much for your participation in this study.

APPENDIX V: DAILY QUESTIONNAIRE FOR PATIENTS WHO CONTINUE WITH STUDY RINSES

PATIENT INFORMATION SHEET
Patient Completed Oral Symptoms Booklet
(Daily during Continuation Phase)

You have been given booklets to complete for this study. The booklets contain questions about your oral symptoms as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You will be given one booklet to take home with you while you are on the continuation phase of the study.

2. This booklet will be taken with you when you leave the doctor's office. Please fill this booklet out every day for 7 days unless you stop taking the oral rinse early. We ask that you complete each daily questionnaire at the same time each day, preferably in the evening.

3. After completing this booklet, please return it to your nurse or physician at your next visit or mail it back in the provided envelope.

4. It is very important that you return the booklets to us, whether you finish the study or not.

5. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

Thank you for taking the time to help us.

Today's date: __ __ / __ __ / __ __ __ __ (MM/DD/YYYY)

Current time
(Enter time in the boxes and circle AM or PM.) For example [10] : [30] AM / (PM)

[ ] : [ ] AM / PM

1. On a scale from 0 to 10, what number best describes your MOUTH PAIN due to your radiation treatment now? (circle one number)

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst pain imaginable or possible

2. Did you use any medications for PAIN over the past 24 HOURS? (circle 'Yes' or 'No')

   Yes No

   If yes, please list all of the pain medications (other than the study medication) and dosages that you used today:

Name	Strength	When
For example *Oxycodone*	*5 mg*	*9:00 AM*

3. Did you use the study rinse today? (circle 'Yes' or 'No')

   Yes **(If yes, answer questions 4 through 7, and skip question 8)**

   No **(If no, skip to question 8)**

4. Is the study medication rinse helpful in alleviating your mouth/throat pain? (circle 'Yes' or 'No')

   Yes No

5. On a scale from 0 to 10, what number best describes any STINGING OR BURNING FROM THE ORAL RINSE this day? (circle one number)

0	1	2	3	4	5	6	7	8	9	10
No stinging or burning										Worst stinging or burning possible

6. On a scale from 0 to 10, what number best describes the TASTE OF THE ORAL RINSE this day? (circle one number)

0	1	2	3	4	5	6	7	8	9	10
Acceptable										Terrible

7. Have you noticed any other side effects from the oral rinse this day? (circle 'Yes' or 'No')

   Yes No

   If yes, please explain

   _____

   _____

   _____

   Other comments:

   _____

   _____

8. If you did not use the study rinse this day, please state why you did not use the study rinse by checking one or more of the following:

   ___ Pain got better
   ___ Study rinse did not work
   ___ Didn't like side effects
   Which ones? _____
   ___ Other
   Please explain _____

This completes this day's questionnaire. Thank you for your continued participation in this study.

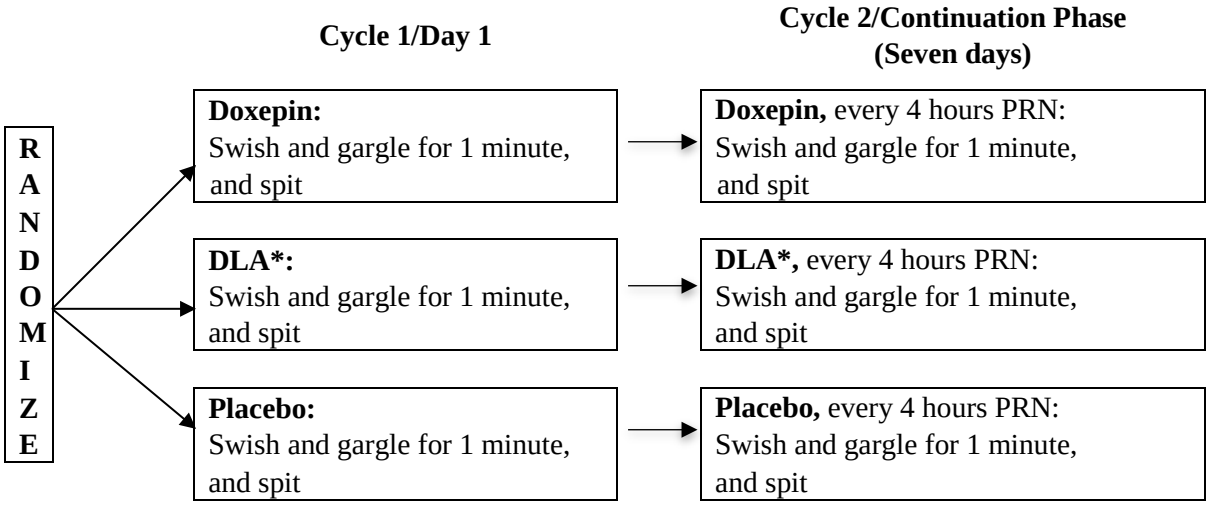
APPENDIX VI: RTOG ACUTE RADIATION MORBIDITY SCORING CRITERIA: MUCOUS MEMBRANE

Grade	0	1	2	3	4
Mucous Membrane	No change over baseline	Injection/ may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinitis discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis

A221304: A Phase III Placebo-Controlled, Randomized Three-Arm Study of Doxepin and a Topical Rinse in the Treatment of Acute Oral Mucositis Pain in Patients Receiving Radiotherapy With or Without Chemotherapy

Statistical Analysis Plan

Schema



* Diphenhydramine HCl, Lidocaine HCl, and Antacid Suspension

Continuation Phase: Within one week of Day 1, patients may begin the 7-day continuation phase and take doxepin/DLA/placebo up to every 4 hours as needed.

OBJECTIVES

Primary objectives

Determine whether the doxepin rinse is more effective than placebo in reducing OM-related pain in patients undergoing RT to the oral cavity, as measured by a patient-reported questionnaire at baseline, 5 minutes, 15 minutes, 30 minutes, 1 hour and then at 2 and 4 hours.

Secondary objective(s)

1 Determine whether the oral DLA rinse is more effective than placebo in reducing OM-related pain in patients undergoing RT to the oral cavity, as measured by a patient-reported questionnaire at 5 minutes, 15 minutes, 30 minutes, 1 hour and then at 2 and 4 hours.

2 Assess the adverse event profile of doxepin rinse, DLA rinse agent, and the placebo using a patient-reported questionnaire at 5 minutes, 15 minutes, 30 minutes, 1 hour and then at 2 and 4 hours for domains of unpleasant taste, burning or stinging discomfort, and drowsiness.

3 Compare the incidence of using alternative analgesics before 4 hours, between the doxepin oral rinse, the DLA rinse agent, and the placebo arms.

4 Compare the length of time that each study product is used by patients in the one-week continuation phase.

5 Compare the daily pain scores in the one-week continuation phase for the three study arms.

6 Compare the morphine equivalent units used in the continuation week for the three study arms.

Stratification Factors

1 **Patient Sex:** Male vs. Female

2 **Concurrent use of chemotherapy:** No vs. Yes

3 **Patient age at registration:** Less than 60 years old vs. 60 or more years old

Treatment assignments and blinding

1 The factors defined in the previous section will be used as stratification factors.

2 After the patient has been registered to the study, the values of the stratification factors will be recorded and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure, which balances the marginal distributions of the stratification factors between the treatment groups.

- Doxepin
- Diphenhydramine HCl, Lidocaine HCl, and Antacid Suspension
- Placebo

3 To ensure both the patient and the medical professionals who care for the patient are blinded to the identity of the treatment assignment, the Registration Specialist will follow double-blinding procedures.

4 **Procedures for blinding the treatment assignment:** After the treatment assignment as been ascertained in the OPEN application, the patient's study medication code number will be displayed on the confirmation of registration screen. The institutional pharmacist or designated contact person will maintain records that identify the patient and their corresponding study medication code number.

MEASUREMENT OF EFFECT

The Oral Mucositis Assessment Scale is a psychometrically validated instrument for this patient population. It is utilized to score nine anatomical sites of the oral mucosa with respect to ulceration/pseudomembrane formation and erythema. The OMAS will be utilized to assess the severity of OM prior to the first study dose.

Pain is the most important and bothersome subjective symptom of OM, and yet there are few validated assessment instruments measuring OM pain resulting from cancer therapy. Two examples

of validated tools are the Oral Mucositis Daily Questionnaire (OMDQ) and the Oral Mucositis Weekly Questionnaire-Head and Neck Cancer (OMWQ-HN). A modified combination of both these instruments will be used to assess baseline OM symptoms. Questionnaires with eleven-point numerical analogue scales (0−10 scores) will be used to measure pain, unpleasant taste, stinging or burning, and drowsiness at defined intervals following doxepin or placebo rinse and in weekly follow-up if patients choose to continue using doxepin rinse. Numerical analog scales are validated measures of symptoms.

STATISTICAL CONSIDERATIONS

Study Overview

This is a randomized, double-blind, placebo-controlled, three-arm phase III trial to assess the efficacy of doxepin oral rinse or DLA versus placebo for the treatment of cancer therapy-related OM. Since each of the two treatment arms will be compared against placebo arm, the conservative Bonferroni approach (instead of Dunnett's multiple comparion procedure) will be used to adjust for multiplicity.

Sample Size, Accrual Time and Study Duration

Sample Size

In the recently completed phase III randomized, double-blind trial comparing doxepin to placebo for treatment of oral mucositis pain in patients undergoing high-dose, curative head and neck radiotherapy treatment,[39] we observed a pain AUC reduction of 9.1 (Standard deviation, SD = 7.9) with doxepin vs. 4.7 (SD = 6.1) in the placebo arm. This corresponded to a difference in pain AUC reduction 4.4, with a common estimate SD of 7.0. Considering a clinically meaningful difference in pain AUC reduction being 3.5 (i.e., half of the common SD = 7.0, according to Norman GR, [40] Sloan JA[41]), in a 2-arm study we would need a sample size of 156 patients (78 patients per arm) to have at least 80% power to detect such an effect size, using the two-sample *t*-test at the 2.5% significance level. As we have two treatment arms (Doxepin or DLA versus placebo) in this 3-arm study design, Doxepin or DLA, the sample size will be 234 patients in total (78 patients per arm). This sample size will be further inflated by 15% to 270 patients to account for patient ineligibility, cancellation, or major violations.

Accrual Rate and Accrual Duration

We anticipate accruing approximately 20 patients per month, based on our previous experience in clinical practice. This would mean completing the primary accrual within 14 months from study initiation and completing analysis within 15 months from study initiation.

Primary Endpoint Completion Date for ClinicalTrials.gov Reporting

For purpose of ClinicalTrial.gov reporting, the Primary Endpoint Completion Date (PECD) for this study is the time the last patient registered has been followed for at least one day.

Statistical Design and Analysis for the Primary Endpoint

Primary Endpoint

The primary endpoint of this study is the total pain reduction (mouth and throat) as measured by the numerical analogue scale of mouth pain in the questionnaires taken at

baseline, and 5, 15, 30, 60, 120, 240 minutes after assigned treatment for doxepin or DLA vs. placebo. The total pain reduction will be calculated by the (average of mouth and throat) area under the curve (AUC) adjusting for baseline, with time scale replaced by a numerical scale of 1, 2, 3, 4, 5 and 6. The numerical scale will be used rather than the raw time scale in order to give proper weights to more immediate patient-reported mouth pain outcomes after treatment. The AUC will be prorated when there are terminal missing data. If the missing data are intermittent, simple imputation by trapezoidal rules will be applied to calculate the AUC. If a patient cancels, is missing baseline data, or only provides baseline data, he/she will be excluded from the statistical analysis.

Statistical Design

This is a three-arm parallel group design with neither cross-over nor interim analysis.

Study Operating Characteristics

Simulation studies of 10,000 clinical trials are conducted for the proposed parallel group design. The probabilities of rejecting null hypothesis for various effect sizes (in AUC reduction), i.e. global power are summarized for both Bonferroni and Dunnett's multiple comparison procedures in the following table. With a total sample size of 234 patients, the empirical global powers are approximately 90% at a family-wise 5% significance level. The Dunnett's single step procedure improves the power but only a small amount. The simulation for operating characteristics are conducted using EAST version 6.2.

Scenario	Placebo	DLA	Doxepin	Multiple Comparison	Global Power (%)
1	4.4	6.15	7.9	Bonferroni	88.9
1	4.4	6.15	7.9	Dunnett's single step	89.3
2	4.4	4.5	7.9	Bonferroni	87.8
2	4.4	4.5	7.9	Dunnett's single step	88.1
3	4.4	7.8	7.9	Bonferroni	95.3
3	4.4	7.8	7.9	Dunnett's single step	95.6

Power analysis for various effect sizes with a total sample size of 234 patients.

Analysis Plan

A modified intent-to-treat principle will be applied for statistical analysis of efficacy in evaluable patients. Evaluable patients are defined as all patients meeting the eligibility criteria who did not cancel prior to receiving treatment and had no major violations.

The primary analysis of the total pain reduction between arms will be conducted using the two-sample *t*-test or nonparametric Wilcoxon rank-sum testing. Transformation of AUC (such as log) may be taken if the empirical distribution of residuals is deemed far from normal distribution. Supplementary analyses will be conducted to analyze these repeated measurements of mouth and throat pain in longitudinal data model. Graphical procedures will include stream plots of individual patient mouth pain scales and plots of average values over time for each treatment arms.

Supplementary Analysis Plans

Secondary Endpoints

1) The total unpleasant taste of the oral rinse as measured by the numerical analogue scale of taste of the oral rinse in the questionnaires.
2) The total stinging or burning from the oral rinse as measured by the numerical analogue scale of stinging or burning from the oral rinse in the questionnaires.
3) The total drowsiness increase as measured by the numerical analogue scale of drowsiness questionnaires.
4) The incidence of using alternative analgesics before 4 hours.
5) Patient preference for continued therapy with oral rinse after initial test rinse phase, as measured by item 8 in the patient-reported questionnaire.

Secondary Analysis

Multiplicity will not be adjusted for secondary analyses, hence, statistically significant findings from secondary analyses are exploratory in nature and therefore shall be interpreted as such. Descriptive statistics and graphical approaches will form the basis for most secondary analyses.

1) Similar analysis as primary endpoint will be conducted for total unpleasant taste.
2) Similar analysis as primary endpoint will be conducted for total stinging or burning.
3) Similar analysis as primary endpoint will be conducted for total drowsiness increase.
4) The incidence of utilizing additional analgesics between 1-4 hours after initial mouthwash will be compared between the arms by the Chi-square test or Fisher's exact test.
5) Descriptive statistics and graphical procedures will be used to summarize patient preference for continued therapy.

Study Monitoring

Adverse Event Stopping Rule

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below. Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as possible, probable, or definite) that satisfy the following criteria:

1) If 5 or more of the first 20 treated patients (or 25% of all patients after 20 patients have been accrued) experience a grade 3 or higher non-hematologic adverse event and the adverse event rate is higher in the active treatment arm.
2) If 3 or more of the first 20 treated patients (or 15% of all patients after 20 patients have been accrued) experience a grade 4 or higher non-hematologic adverse event and the adverse event rate is higher in the active treatment arm.

Accrual Monitoring Stopping Rule

Slow Accrual: Patient accrual will be closely monitored by the investigators and secondary statistician on a monthly basis. If the accrual rate falls below 50% of expected accrual rate, investigators will carefully review feedback from sites and consider taking measures to encourage patient enrollment.

Descriptive Factors: None

Required Analyses:

Demographics and Reason Off Study

Figure 1: Patient Consort Diagram (by arm)
Table 1: Patient Enrollment (for each study site by arm)
Table 2: Patient Characteristics (summaires of all baseline demographics and stratification factors by arm)
Conparisons between arms use Kruskal-Wallis tests for continuous variables and Fisher's Exact test for categorical variables
Table 3: End of Treatment Reason (by arm)
One table for cycle 1 (the end of the randomized study) and one table for cycle 2 (the continuation phase)
Comparison between arms use Fisher's exact tests.

Primary Analysis:
Table 4A1-2: Summary of Cycle 1Total Pain Calculated by AUC adjusting for baseline (one table comparing Doxepin vs. Placebo; one table for DLA vs. Placebo; comparisons between arms useWilcoxon Rank Sum Tests)
Table 4B1-3: Repeated Measures Analysis of Cycle 1 Average Pain (one model for Doxepin vs. Placebo; one model for DLA vs. Placebo; one model for DLA vs.Doxepin vs. Placebo)
Models are repeated measures mixed models using an unstructured covariance matrix. Models are adjusted for gender, age, concurrent use of chemotherapy, and mucous membrance scores. Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.
Table 4C1-2: Summary of Cycle 1 Average Pain Scores at each timepoints (one table for Doxepin vs. Placebo; one table for DLA vs. Placebo; comparisons at each time point usingWilcoxon Rank Sum Tests)

Figure 2A: Mean Plot of Cycle 1 Average Pain Scores over time (DLA vs. Doxepin vs. Placebo)
Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.
Figure 2B: Stream Plot of Cycle 1Average Pain Scores (DLA vs. Doxepin vs. Placebo)
Plots of pain scores for individual patients. Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.
Figure 2C1-2: Bug Plot of Change from Baseline Average Pain Scores at Cycle 1(one plot comparing Doxepin vs. Placebo; one plot comparing DLA vs. Placebo)
Plots of pain scores for individual patients. Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.

Table 5A1-2: Summary of Cycle 1 Mouth Pain Scores at each time points (one table for Doxepin vs. Placebo; one table for DLA vs. Placebo; comparisons between arms use Wilcoxon Rank Sum Tests)

Figure 3A: Mean Plot of Cycle 1 Mouth Pain Scores over time (DLA vs. Doxepin vs. Placebo)
Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.
Figure 3B: Stream Plot of Cycle 1 Mouth Pain Scores (DLA vs. Doxepin vs. Placebo)
Plots of pain scores for individual patients. Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.
Figure 3C1-2: Bug Plot of Cycle 1 Mouth Pain (one plot comparing Doxepin vs. Placebo; one plot comparing DLA vs. Placebo)
Plots of pain scores for individual patients. Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.

Table 6A1-2: Summary of Cycle 1 Throat Pain Scores at each timepoints (one table for Doxepin vs. Placebo; one table for DLA vs. Placebo; comparisons between arms using Wilcoxon Rank Sum Test)
Figure 4A: Mean Plot of Cycle 1 Throat Pain Scores over time (DLA vs. Doxepin vs. Placebo)
Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.
Figure 4B: Stream Plot of Cycle 1 Throat Pain Scores (DLA vs. Doxepin vs. Placebo)
Plots of pain scores for individual patients. Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.
Figure 4C1-2: Bug Plot of Cycle Throat Pain Scores (one plot comparing Doxepin vs. Placebo; one plot comparing DLA vs. Placebo)
Plots of pain scores for individual patients. Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.

<u>Secondary Analysis:</u>
Table 7A1-2: Summary of Cycle 1 Drowsiness Calculated by AUC adjusting for baseline (one table for Doxepin vs. Placebo; one table for DLA vs. Placebo; comparisons between groups using Wilcoxon Rank Sum Test)
Table 7B1-3: Repeated Measures Analysis of Cycle 1 Drowsiness Scores (one model for Doxepin vs. Placebo; one model for DLA vs. Placebo; one model for DLA vs.Doxepin vs. Placebo)
Models are repeated measures mixed models using an unstructured covariance matrix. Models are adjusted for gender, age, concurrent use of chemotherapy, and mucous membrance scores. Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.
Table 7C1-2: Summary of Cycle 1 Drowsiness Scores at each timepoints (one table for Doxepin vs. Placebo; one table for DLA vs. Placebo; comparisons between groups using Wilcoxon Rank Sum Tests)
Figure 5A: Mean Plot of Cycle 1 Drowsiness Scores over time (DLA vs. Doxepin vs. Placebo)
Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.
Figure 5B: Stream Plot of Cycle 1 Drowsiness Scores (DLA vs. Doxepin vs. Placebo)
Plots of pain scores for individual patients. Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.
Figure 5C1-2: Bug Plot of Cycle 1 Drowsiness Scores (one plot comparing Doxepin vs. Placebo; one plot comparing DLA vs. Placebo)
Plots of pain scores for individual patients. Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.

Table 8A1-2: Summary of Cycle 1 Unpleasant Taste Calculated by AUC starting at 5 minutes to 240 minutes (one table for Doxepin vs. Placebo; one table for DLA vs. Placebo; comparisons between groups using Wilcoxon Rank Sum Tests)

Table 8B1-3: Repeated Measures Analysis of Cycle 1 Unpleasant Taste Scores (one model for Doxepin vs. Placebo; one model for DLA vs. Placebo; one model for DLA vs.Doxepin vs. Placebo)

Models are repeated measures mixed models using an unstructured covariance matrix. Models are adjusted for gender, age, concurrent use of chemotherapy, and mucous membrance scores. Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.

Table 8C1-2: Summary of Cycle 1 Unpleasant Taste Scores at each timepoints (one table for Doxepin vs. Placebo; one table for DLA vs. Placebo; comparisons between groups using Wilcoxon Rank Sum Test)

Figure 6A: Mean Plot of Cycle 1 Unpleasant Taste Scores over time (DLA vs. Doxepin vs. Placebo)

Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.

Figure 6B: Stream Plot of Cycle 1 Unpleasant Taste Scores (DLA vs. Doxepin vs. Placebo)

Plots of pain scores for individual patients. Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.

Figure 6C1-2: Bug Plot of Cycle 1 Unpleasant Taste Scores (one plot comparing Doxepin vs. Placebo; one plot comparing DLA vs. Placebo)

Plots of pain scores for individual patients. Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.

Table 9A1-2: Summary of Cycle 1 Burning/Stinging Calculated by AUC starting at 5 minutes to 230 minutes (one table for Doxepin vs. Placebo; one table for DLA vs. Placebo; comparisons between groups using Wilcoxon Rank Sum Test)

Table 9B1-3: Repeated Measures Analysis of Cycle 1 Burning/Stinging Scores (one model for Doxepin vs. Placebo; one model for DLA vs. Placebo; one model for DLA vs.Doxepin vs. Placebo)

Models are repeated measures mixed models using an unstructured covariance matrix. Models are adjusted for gender, age, concurrent use of chemotherapy, and mucous membrance scores. Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.

Table 9C1-2: Summary of Cycle 1 Burning/Stinging Scores at each time points (one table for Doxepin vs. Placebo; one table for DLA vs. Placebo; comparisons between groups usingWilcoxon Rank Sum Test)

Figure 7A: Mean Plot of Cycle 1 Burning/Stinging Scores over time (DLA vs. Doxepin vs. Placebo)

Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.

Figure 7B: Stream Plot of Cycle 1 Burning/Stinging Scores (DLA vs. Doxepin vs. Placebo)

Plots of pain scores for individual patients. Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.

Figure 7C1-2: Bug Plot of Cycle 1 Burning/Stinging Scores (one plot comparing Doxepin vs. Placebo; one plot comparing DLA vs. Placebo)

Plots of pain scores for individual patients. Time points are integers from 0 to 6 with 0=baseline, 1=5 minute, 2=15 minutes, 3=30 minutes, 4=60 minutes, 5=120 minutes, and 6=240 minutes.

Table 10A-B: Incidence Use of Additional Analgesics at Pre-treatment/2/4 hours (comparisons at baseline, 120 minutes, and 240 minutes; one table for Doxepin vs. Placebo; one table for DLA vs. Placebo; comparisons between groups using chi-square tests)

Table 11A-B: Incidence of Side Effects from the Oral Rinse Over time (comparisons at each time point; one table for Doxepin vs Placebo; one table for DLA vs Placebo; comparisons between groups using chi-square tests)

Table 12A-B: Frequency of Pain Relief from Study Medication Rinse (comparisons at 240 minutes; one table for Doxepin vs Placebo, one table for DLA vs Placebo; comparisons between groups using chi-squarea tests)
Table 13A-B: Frequency of Patient Preference for Continued therapy with Oral Rinse (comparisons at 240 minutes; one table for Doxepin vs Placebo, one table for DLA vs Placebo; comparisons between groups using chi-squarea tests)

Table 14A-B: Adverse Events Summary at Cycle 1 (compare maximum reported grade for each AE; one table comparing Doxepin vs. Placebo; one table comparing DLA vs. Placebo; comparisons between groups using Wilcoxon Rank Sum Tests)

Cycle 2 Optional Continuation Phase Analysis:
Table 15A1-2: Summary of Cycle 2 Mouth Pain Scores at each day in cycle 2 (one table for Doxepin vs. Placebo; one table for DLA vs. Placebo; comparisons between groups using Wilcoxon Rank Sum Tests)
Figure 8A: Mean Plot of Cycle 2 Mouth Pain Scores over time (time points are days 1-7 in cycle 2; DLA vs. Doxepin vs. Placebo)
Figure 8B: Stream Plot of Cycle 2 Mouth Pain Scores at each day in cycle 2 (one plot for each arm: DLA vs. Doxepin vs. Placebo)
Figure 8C1-2: Bug Plot of Cycle 2 Mouth Pain Scores at each day in cycle 2 (one plot comparing Doxepin vs. Placebo; one plot comparing DLA vs. Placebo)

Table 16A1-2: Summary of Cycle 2 Unpleasant Taste Scores at each day in cycle 2 (one table for Doxepin vs. Placebo; one table for DLA vs. Placebo; comparisons between groups usingWilcoxon Rank Sum Test)
Figure 9A: Mean Plot of Cycle 2 Unpleasant Taste Scores at each day in cycle 2 (DLA vs. Doxepin vs. Placebo)
Figure 9B: Stream Plot of Cycle 2 Unpleasant Taste Scores (one plot for each arm: DLA vs. Doxepin vs. Placebo)
Figure 9C1-2: Bug Plot of Cycle 2 Unpleasant Taste Scores (one plot comparing Doxepin vs. Placebo; one plot comparing DLA vs. Placebo)

Table 17A1-2: Summary of Cycle 2 Burning/Stinging Scores at each day in cycle 2 (one table for Doxepin vs. Placebo; one table for DLA vs. Placebo; comparisons between groups using Wilcoxon Rank Sum Test)
Figure 10A: Mean Plot of Cycle 2 Burning/Stinging Scores over each day in cycle 2 (DLA vs. Doxepin vs. Placebo)
Figure 10B: Stream Plot of Cycle 2 Burning/Stinging Scores over each day in cycle 2 (one plot for each arm: DLA vs. Doxepin vs. Placebo)
Figure 10C1-2: Bug Plot of Cycle 2 Burning/Stinging Scores over each day in cycle 2 (one plot for Doxepin vs. Placebo; one plot for DLA vs. Placebo)

Table 18A-B: Incidence Use of Additional Analgesics at each day in Cycle 2 (one table comparing Doxepin vs Placebo; one table comparing DLA vs Placebo; comparisons between groups using chi-square tests)
Table 19A-B: Incidence of Side Effects from the Oral Rinse at each day in Cycle 2 (one table comparing Doxepin vs Placebo; one table comparing DLA vs Placebo; comparisons between groups using chi-square tests)
Table 20A-B: Frequency of Study Rinse Used at each day in Cycle 2 (one table comparing Doxepin vs Placebo; one table comparing DLA vs Placebo; comparisons between groups using Fisher's exact tests)

Table 21A-B: Frequency of Pain Relief from Study Medication Rinse at each day in Cycle 2 (one table for Doxepin vs Placebo; one table for DLA vs Placebo; comparisons between groups using chi-square tests)

Table 22A-B: Adverse Events Summary at Cycle 2 (maximum grade of each AE reported for a patient in cycle 2; one table for Doxepin vs. Placebo; one table for DLA vs. Placebo; comparisons between groups using Wilcoxon Rank Sum Tests)