The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Doxepin Rinse Versus Placebo in the Treatment of Acute Oral Mucositis Pain in Patients Receiving Head and Neck Radiotherapy With or Without Chemotherapy: A Phase III, Randomized Double-blind Trial (NCCTG N09C6 [Alliance])

Leenstra, et al.

DOI: 10.1200/JCO.2013. 53.2630

N09C6

North Central Cancer Treatment Group

Randomized Double-Blind Study of Doxepin Rinse versus Placebo in the Treatment of Acute Oral Mucositis Pain in Patients Receiving Radiotherapy with or without Chemotherapy

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Drug Availability

Supplied Commercial Agent: doxepin (IND Exempt)

***Investigator having NCI responsibility for this protocol**

√Study contributor(s) not responsible for patient care.

Document History	**(Effective Date)**
Activation	December 17, 2010
Addendum 1	February 11, 2011
Addendum 2	May 27, 2011
Update 1	May 27, 2011

Study Participants	**Date Activated**
Entire NCCTG	December 17, 2010

NCI Version Date: May 9, 2011

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- No waivers of eligibility per NCI

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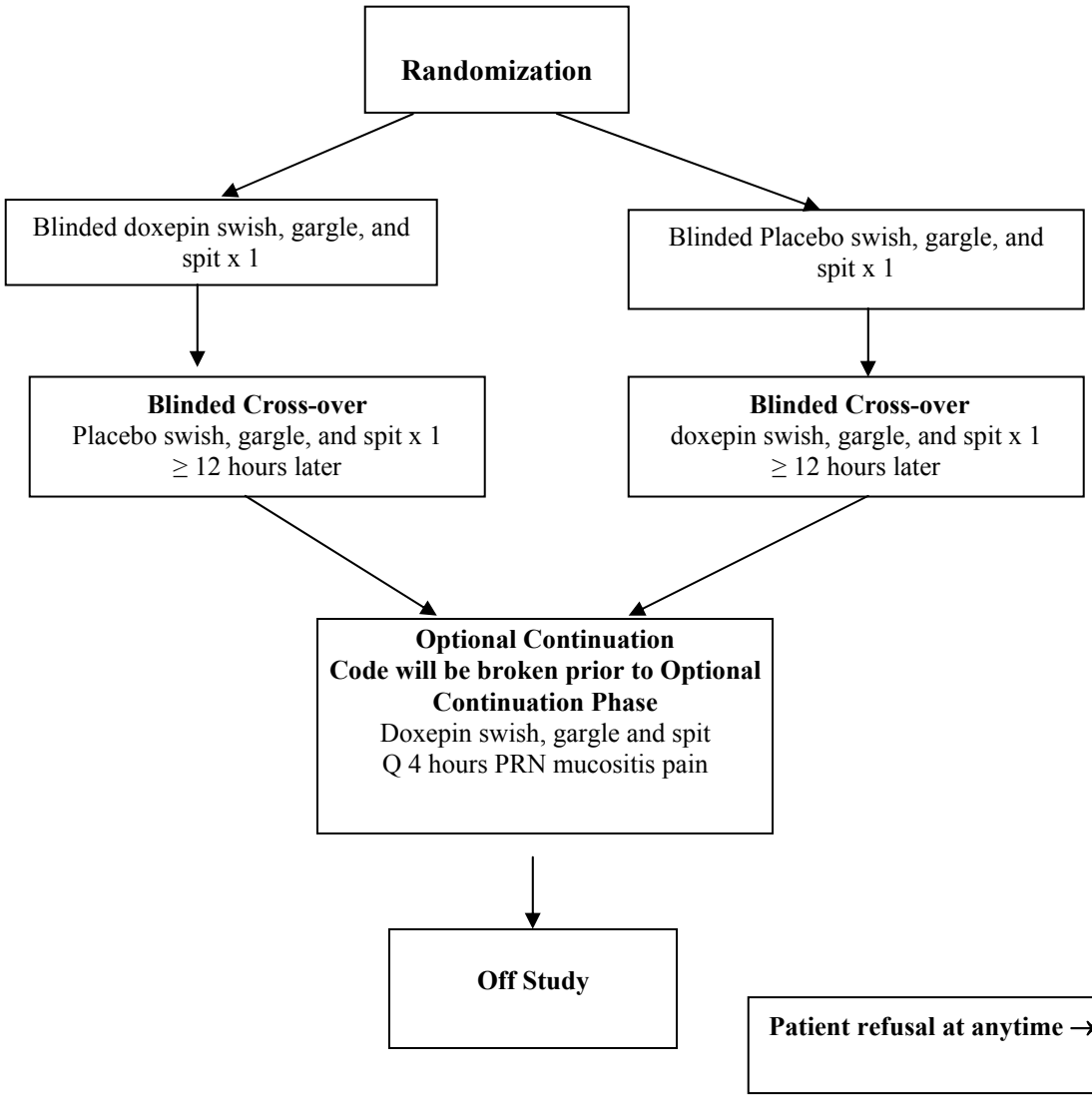
Schema



Add 2

Cycle 1 length = 1 day
Cycle 2 length = 1 day
Cycles 3-10 (Optional continuation) = weekly during radiation (7 days)

NOTE: Cycle is an NCCTG data management tool to facilitate consistent remote data entry.

Add 2

Generic name: Doxepin Brand name(s): Sinequan® NCCTG Abbreviation: Availability: NCCTG Research Base Pharmacy	Generic name: Placebo NCCTG Abbreviation: PLACEB Availability: NCCTG Research Base Pharmacy

1.0 Background

1.1 Oral mucositis (OM) related pain is a significant problem in patients undergoing head and neck radiation therapy with or without chemotherapy.

1.11 *Definition of OM:* 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].

1.12 *Epidemiology of OM:* The 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 if patients received concurrent chemotherapy or if 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

1.21 *Pathophysiology 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.

1.22 *Prevention 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 preliminary 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].

1.23 *Treatment of OM:* 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 tsp 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.

1.3 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, 24]. TCAs have been used since the early 1960s to treat patients with major depression [25]. 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 [24, 26-28]. It is recommended for off-label prevention of migraine headaches and as an adjunctive therapy in chronic pain syndromes [27].

1.31 *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 [25]. Doxepin also has potent peripheral H_1 and H_2 receptor blocker activity making it an effective topical anti-pruritic agent [23, 28]. 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 [29]. Rat models have demonstrated that doxepin potentiates opioid analgesia and is a strong local anesthetic when administered via sciatic nerve injection, interaperitoneally, intrathecally, or topically [25, 30-32]. 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, 25, 33]. 5HT and NE re-uptake inhibition is also believed to activate the descending anti-nociceptive system [23, 32]. 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, 33, 34]. 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 [25].

1.32 *Metabolism:* Doxepin has a half-life of 17 hours and is hepatically metabolized to desmethyldoxepin, an active metabolite with a half-life of 52 hours. It is renally excreted [24, 26, 35].

1.33 *Safety profile*: The most common side effect of oral doxepin is drowsiness which

tends to disappear as therapy is continued [27]. Other side effects include dizziness, xerostomia, blurred vision, bloating, weight gain, constipation, and urinary retention. Because of its anticholinergic activity, systemic doxepin is contraindicated in patients with untreated narrow angle glaucoma or urinary retention [26, 27]. Hypersensitivity reactions are rare but have been reported with both topical and oral formulations [28]. Serious interactions are possible when doxepin is administered concomitantly with monoamine oxidase inhibitors [24, 26, 27]. Doxepin is pregnancy class C [24, 26, 27].

1.34 *Formulation*: Doxepin HCl is available in the United States as a generic product or under the trade name Sinequan® or Adapin in tablet form (10−150 mg) and as an oral concentrate (10 mg/mL) [24, 26, 27]. A topical 5% cream is available under the trade name Zonalon® from Doak Dermatologics [26, 27, 35].

1.4 Evidence indicates that doxepin may be effective in providing analgesia for OM.

1.41 Epstein and colleagues have 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, 36, 37]. 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.

1.42 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 [36]. 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.

1.43 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, 37]. 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.

1.44 Radiation oncologists at Mayo have been extremely impressed with the claimed efficacy of doxepin for mucositis; on behalf of multiple patients with radiation-induced mucositis and corresponding pain relief from such. It has become a part of their standard practice.

1.5 Proposed study

1.51 To our knowledge, there has never been a randomized placebo-controlled trial confirming the efficacy of doxepin oral rinse as an analgesic in OM pain caused by cancer therapy. This protocol will evaluate the effect of doxepin oral rinse on OM pain in patients with cancer undergoing RT to the oral cavity. Secondary endpoints include measurement of adverse effects and patient preference for continuation of doxepin oral rinse.

1.511 Consideration has been given to comparison of doxepin to another active agent (e.g., viscous lidocaine) instead of an inert placebo. The placebo has been chosen for the reasons noted in section 1.2: Topical anesthetics/analgesics often cause initial burning or stinging pain to damaged mucosa and then temporarily diminish or abolish taste and the gag reflex.

1.512 Formulation of the doxepin and placebo oral rinses.

1.5121 This trial will utilize the same dose of 25 mg used in the phase I-II trials by Epstein et al. [22, 23, 36, 37]. This dose was found to be effective and to result in minimal side effects. Furthermore, if patients choose to continue with repeated doxepin rinses every 4 hours as needed after the initial test rinse(s), the maximum total daily dose of doxepin to which they would be exposed is 150 mg. It is expected that there will be minimal systemic absorption of doxepin despite compromise of the mucosal barrier by

mucositis because the patients will expectorate the solution. Even if there were complete transmucosal absorption, this dose is comparable to the usual starting daily dose of 75−150 mg utilized when doxepin is prescribed for depression or anxiety [24, 26, 27, 35].

1.5122 The use of 0.1% alcohol as a diluent by Epstein et al. will be omitted to avoid possible irritation and exacerbation of xerostomia caused by this agent.This omission will also allow for use of a truly inert placebo that does not include these agents; hence, avoiding potential harm to patients in the control arm of the trial. Because doxepin oral concentrate is available in a 10 mg/mL formulation, the test rinse will be created by mixing 2.5 mL of test solution (either placebo or active agent) with 2.5 mL of Sterile Water for Irrigation, USP; 2.5 mL Sterile Water for Injection, USP; or 2.5 mL of distilled water.

Add 2

1.5123 The placebo formulation will not exactly match the doxepin HCl solution in appearance or taste. A pharmacist, pharmacy technician, study nurse, or designated data manager at each site must be unblinded and must prepare the active or placebo dose. It will be important that the patient and medical professionals who care for the patient are blinded as to the identity of active or placebo solution.

1.52 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, 38]. 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 [39]. The Oral Mucositis Assessment Scale is a psychometrically validated instrument for this patient population [38]. It is utilized to score nine anatomical sites of the oral mucosa with respect to ulceration/ pseudomembrane formation and erythema (see Appendix III). The OMAS will be utilized to assess the severity of OM prior to 1st and 2nd rinses and at weekly radiotherapy management visits (if patients choose to continue to use the active agent).

1.53 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 [40]. Two examples of validated tools are the Oral Mucositis Daily Questionnaire (OMDQ) and the Oral Mucositis Weekly Questionnaire-Head and Neck Cancer (OMWQ-HN) [41-43]. A modified combination of both these instruments will be used to assess baseline OM symptoms (see Appendix III). 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 [44-48].

2.0 Goals

2.1 Primary goal

2.11 Determine whether doxepin oral rinse is effective 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 (see Appendix V and VI).

2.2 Secondary goals

2.21 Assess the adverse event profile of doxepin rinse using a patient-reported questionnaire at 5 minutes, 15 minutes, 30 minutes, 1 hour and then at 2 and 4 hours (see Appendix V and VI) for domains of unpleasant taste, burning or stinging discomfort, and drowsiness.

2.22 Compare the incidence of using alternative analgesics before 4 hours, between the doxepin oral rinse and placebo arms.

2.23 Assess patient preference for continued therapy with oral rinse after initial test rinse or after the cross-over phase, as measured by item 8 in the patient-reported questionnaire at 4 hours and the actual participation rate.

2.3 Tertiary goals (only applies to patients who have the blinded cross-over phase or the optional continuation of doxepin oral rinse after the first two phases).

2.31 Assess pain reduction and other adverse event profile in the blinded cross-over phase using the same patient-reported questionnaire for patients that agree to testing of a second rinse with the agent they did not receive at first testing (either doxepin or placebo) (see Appendix V and VI).

2.32 Assess pain reduction and other adverse event profile in the optional continuation phase of doxepin oral rinse therapy (see Appendix VII).

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 ≥ 18 years of age.

3.12 Histologic proof of malignancy currently undergoing a course RT (with or without chemotherapy) to a dose of ≥ 5000 cGy using 1.60 to 2.20 Gy per fraction.
Note: At least one third of the oral cavity mucosa must be included in the radiation therapy fields.

3.13 ≥ 4 oral pain felt to be related to mucositis for which the patient wants relief, as measured by asking the following question (appendix IV):

"On a scale of 0 to 10 (0 = no oral pain; 10 = worst oral pain), what number best describes your mouth or throat pain (right now) due to your radiation treatment?"

Note: An oral exam confirming the presence of mucositis should be performed by the enrolling clinician in addition to asking the patient this question.

3.14 Ability to complete questionnaire(s) by themselves or with assistance.

3.15 ECOG Performance Status (PS) 0, 1, or 2. This form is now on the NCCTG website https://ncctg.mayo.edu/ncctg/forms/NonProtocolSpecificForms.

3.16 Provide informed written consent.

3.17 Willingness to return to NCCTG enrolling institution for follow-up.

3.2 Exclusion Criteria

3.21 Known allergy to doxepin, tricyclic antidepressants, or any known component of the drug formulation.

3.22 Use of a tricyclic antidepressant or monoamine oxidase inhibitor within the 2 weeks prior to registration.

3.23 Current untreated or unresolved oral candidiasis or oral HSV infection.

3.24 Current untreated narrow angle glaucoma.

3.26 Current untreated urinary retention ≤ 6 weeks prior to registration.

3.27 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.28 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

4.0 **Test Schedule**

Tests and procedures	Active Monitoring Phase				
	≤ 7 days prior to registration	Dose 1 of study treatment	Dose 2 crossover[3]	Optional Continuation Phase (weekly during RT)	End of study
History and, PS	X				
Pregnancy test[4]	X				
Provider Assessment Form/Exam (OMAS Scale, App. III)	X				
Eligibility screening question: Numeric measure of oral pain (Appendix IV)	X	X	X		
Adverse event assessment		X	X	X	X
Patient Questionnaire[1], Daily (App V and VI)		X[2]	X[2]		
Patient Questionnaire[1], Weekly (App VII)				X	
Patient Phone Call[5]		X	X		

1. Patient Questionnaire booklets **must** be used; copies are not acceptable for this submission.
2. Patient Questionnaire booklets will be administered prior to doxepin/placebo rinse and then at the time points specified in section 7.0 after the rinse.
3. Dose 2 should be ≥12 hours after dose 1 treatment with rinse.
4. Women of child-bearing potential only at the discretion of the treating physician.
5. If possible, the patient will receive a phone call reminder from the care provider's assistant at two and four hours post-administration.

5.0 Stratification Factors

5.1 Gender: Female vs. Male.

5.2 Concurrent radiosensitizing chemotherapy: Yes vs. No.

5.3 Age: < 60 vs ≥ 60.

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

6.11 To register a patient, fax (507-284-0885) a completed eligibility checklist to the North Central Cancer Treatment Group (NCCTG) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.12 IRB approval(s) is required for each treating site. A signed Cancer Trials Support Unit (CTSU) IRB Certification Form is to be on file at the CTSU Regulatory Office (fax 215-569-0206). This form can be found at the following Web site: www.ctsu.org/rss2_page.asp. Guidelines can be found under Quick Fact Sheets.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the CTSU Regulatory Office (fax 215-569-0206). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the CTSU is no longer necessary.

6.13 At the time of registration, the registration application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information.

6.14 Treatment on this protocol must commence at the accruing membership under the supervision of an NCCTG member physician.

6.15 Treatment cannot begin prior to registration and must begin ≤ 14 days after registration.

6.16 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.17 Study drug is available on site.

6.18 Patient questionnaire booklet is available on site; copies are not acceptable for this submission.

6.2 Randomization Procedures

6.21 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.22 After the patient has been registered into 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[56].

- Doxepin-placebo
- Placebo-doxepin

6.23 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 the double-blinding procedures outlined in section 6.3.

6.3 Procedures for Double-Blinding the Treatment Assignment

6.31 After the treatment assignment has been ascertained by randomization, the registration specialist will notify the designated data manager/nurse/pharmacist at the patient's institution. The name of this contact person is to be indicated on the eligibility checklist at the time of registration. This contact person may not be involved in assessing adverse events or any other outcome measure and should not be the same person listed on page one of the Eligibility Checklist Form as the person completing the form. Page three of the Eligibility Checklist Form should provide the source of communication, either fax or e-mail, and the appropriate contact information. The registration specialist will then communicate the treatment assignment "active or placebo" to designated contact at the patient's institution.

Add 2

6.32 The treatment assignment will be either doxepin-placebo or placebo-doxepin. The dose will be prepared and labeled as "doxepin HCl OR placebo, 25 mg/5 mL" so that the contents are not discernible to the person administering the treatment.

6.33 The pharmacist or designated contact person will maintain records that indicate the identity of the patient and their corresponding treatment assignment.

6.4 Optional Continuation Phase

6.41 The double-blind cross-over phase of the study must be completed prior to the treatment code being broken; that is, after the treating site has received the completed patient questionnaire booklet.

6.42 If the patient and physician want to continue with the active agent, or if on placebo, begin the active agent, fax (507-284-0885) a completed continuation phase eligibility checklist to the Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.43 Treatment cannot begin prior to registering to the continuation phase and will ideally begin ≤ 7 days after registration.

7.0 Protocol Treatment

7.1 Treatment Schedule-Double Blind Phase and Cross-Over Phase

Agent	Dose	Route	Dose
doxepin	10 mg/mL x 2.5 mL = 25 mg, Dilute to 5 mL with 2.5 mL of Sterile Water for Irrigation, or Sterile Water for Injection, or distilled water**	Oral swish and gargle for 1 minute then spit	Dose 1 or 2* for one dose only (cross-over)
placebo	2.5 mL. Dilute to 5 mL with 2.5 mL of Sterile Water for Irrigation, or Sterile Water for Injection, or distilled water**	Oral swish and gargle for 1 minute then spit	Dose 1 or 2* for one dose only (cross-over)

Add 2

Add 2

* Dose 2 cross-over patients will receive the opposite treatment

Add 2

** Sterile Water for Irrigation, Sterile Water for Injection, and/or distilled water will be provided by the treating location.

7.2 Treatment Schedule-Optional Continuation Phase

Agent	Dose	Route	ReRx
doxepin	10 mg/mL x 2.5 mL = 25 mg mixed with 2.5 mL of distilled water or tap water= 5 mL total*	Oral swish and gargle for 1 minute then spit	Every 4 hours as needed for OM pain during radiation treatment.

Add 1

Add 1

* The study subject will use distilled water or tap water to dilute the doxepin solution during the continuation phase.

7.3 The care provider or nurse will confirm that oral pain is ≥4 out of 10 severity level prior to dose one and dose two at the time of the rinse. While it is anticipated that the majority of patients who undergo RT to the oral mucosa experience OM pain, enrollment will only be allowed at the time of OM pain development at a level of ≥4 out of 10 in severity. If the pain score is < 4 prior to administration of doxepin/placebo, administration should be held off until pain is ≥ 4.

7.4 The study dose(s) will be prepared just prior to administration. The patient will remain at the treating location for the first hour and complete questionnaires at time zero (prior to the oral swish, gargle and spit), 5, 15, 30 and 60 minutes post-administration. The patient will then be allowed to leave the treating location and will be instructed on timing of questionnaire completion at two and four hours post-administration. **If possible**, the patient will receive a phone call reminder from the care provider's assistant at two and four hours post-administration.

7.5 After dose 2, patients will be unblinded and given the option to continue doxepin as part of the optional continuation phase. The code should be broken only after receipt of all patient materials and assessments. If the patient elects to participate in the continuation phase, the investigator will prescribe one-120mL bottle of doxepin hydrochloride oral solution. This bottle will be provided to the treating location by the NCCTG research base pharmacy. This should supply approximately 50 extra doses. If the patient elects to continue receiving doxepin solution after the first bottle has been used, the patient must obtain a prescription from a licensed prescriber. Patients will be responsible to pay for this additional supply.

7.6 In the event of an emergency, call the Registration Office at (507) 284-4130 to break the code on Monday through Friday, 8:00 a.m. to 4:30 p.m. Central Time. If the code must be broken after hours, assume the patient was assigned to active treatment and treat accordingly. Place a call to the Registration Office and leave a message informing them of the need to un-blind a patient. Provide your contact information so that Registration Office personnel can return the call the next business day.

8.0 Dosage Modification Based on Adverse Events: None.

9.0 Ancillary Treatment

9.1 Patients should receive full supportive care while on this study **(during blinded and cross-over s phase only) except for the followings:**

9.11 No analgesics should be given for mucositis pain for 60 minutes prior to and after the study doses. 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.

9.12 No viscous lidocaine, 'magic mouthwash', benzocaine, diphenhydramine or other medicated oral rinse (except 0.9 normal saline or baking soda rinse) should be used within 4 hours prior to or after the study medication.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

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).

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial.

First, identify and grade the severity of the event using the CTCAE v4.0. Next, determine whether the event is expected or unexpected (see Section 10.12) and if the adverse event is related to the medical treatment or procedure (see Section 10.13). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.2). Important: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.3 and 18.0).

Expedited adverse event reporting requires submission of an Adverse Event Expedited Reporting System (AdEERS) report(s). Other expedited reporting requirements and systems may also apply. Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.2 and 10.3. All expedited AE reports must also be sent to the local Institutional Review Board (IRB) according to local IRB's policies and procedures.

10.12 Expected vs. Unexpected

- The determination of whether an AE is expected is based on the agent-specific information provided in Section 15.0 of this protocol.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of this protocol.

10.13 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

10.2 Expedited Adverse Event Reporting Requirements

10.21 Standard Expedited Reporting for Commercial Agents or IND Exempt Agents

	Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite	Increased Incidence of an Expected AE[1]
Submit a full expedited commercial report via AdEERS within 7 working days[2]	X	X

1. An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.

Add 2

2. In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP web site and will NO LONGER be accepted.

10.22 Other Required Expedited Reporting

EVENT TYPE	**REPORTING PROCEDURE**
Secondary AML/MDS	Reporting for this event required during and after completion of study treatment via AdEERS. Report these events using "Neoplasms benign, malignant and unspecified (incl., cysts and polyps)" and including the appropriate adverse event: - Leukemia secondary to oncology chemotherapy OR - Myelodysplastic syndrome OR - Treatment related secondary malignancy
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form electronically via the NCCTG Remote Data Entry System within 5 working days of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form. If an AdEERS report has been submitted, this form does not need to be submitted.

Add 2

10.3 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per CTCAE v4.0 grading unless otherwise stated in the table below:

Category (CTCAE SOC)	Adverse event/Symptoms	Baseline	Each evaluation	Grading scale (if not CTCAE)
	None expected			

10.31 Submit via appropriate North Central Cancer Treatment Group (NCCTG) Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.3:

10.311 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.312 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.313 Grade 5 AEs (Deaths)

10.3131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.3132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.32 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation

11.1 Patients will complete a baseline questionnaire just prior to their first dose of the study drug. They will then complete questionnaires at 5 minutes, 15 minutes, 30 minutes, 1 hour and then at 2 and 4 hours (see Appendix V and VI).

11.2 Patients will also complete questionnaires just prior to their second dose of the study drug and then at the same intervals with the second study compound (doxepin or placebo), just as they did the first time.

11.3 Patients who choose to continue with doxepin rinses after completing blinded and cross-over phase doses will complete a weekly questionnaire until their OM pain resolves or they choose to discontinue doxepin or they complete radiotherapy treatments (see Appendix VII).

12.0 Descriptive Factors: None.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 A patient is deemed *ineligible* if at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted.

- If the patient never received treatment, on-study material must be submitted.

13.2 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are so severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly

registered.

13.3 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted.

13.4 When a patient ends radiation therapy, they will go off study.

14.0 Body Fluid Biospecimens: None

15.0 Drug Information

IND exempt

15.1 Doxepin HCl or Placebo Oral Solution

15.11 **Background**: Doxepin hydrochloride is in a class of psychotherapeutic agents known as dibenzoxepin tricyclic compounds. The agent has antipruritic and antidepressant effects. The mechanism of action of doxepin hydrochloride is not known.

Its antidepressant effect is believed to be partly due to its influences on the adrenergic activity at the synapses where it prevents norepinephrine deactivation through reuptake into the nerve terminals. It is also known to have anticholinergic, antiserotonin and antihistamine effects.

15.12 **Doxepin Formulation**: Doxepin hydrochloride oral solution is available in 120mL bottles. Each mL of solution contains doxepin hydrochloride equivalent to 10 mg doxepin. Inactive ingredients are glycerin, methylparaben, propylparaben, flavoring agent, and purified water.

Placebo 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 473mL (one pint) bottles. The product contains glycerin, sorbitol, sodium saccharin, xanthan gum, flavoring agent, and purified water. The solution is buffered with citric acid and sodium citrate and preserved with methylparaben, propylparaben, and potassium sorbate.

15.13 **Doxepin** P**reparation and Storage**: Store at 20° to 25°C (68° to 77°F). A 120 mL bottle is to be retained for the preparation of multiple doses in the double blind phase of the trial. After a 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.

Add 2

The designated unblinded nurse or pharmacy staff at the patient's institution will add 2.5 mL of the doxepin HCl oral solution to 2.5 mL of Sterile Water for Irrigation, or Sterile Water for Injection, or distilled water just prior to the patient's treatment. The 5 mL total dose will contain 25 mg of doxepin.

Placebo preparation and storage: Store at controlled room temperature (15° to 30°C) (59° to 86°F). A 473 mL bottle is to be retained for the preparation of multiple doses in the double blind phase of the trial. . After a 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.

Add 2

The designated unblinded nurse or pharmacy staff at the patient's institution will add 2.5 mL of the Ora-Sweet SF oral solution to 2.5 mL of Sterile Water for Irrigation, or Sterile Water for Injection, or distilled water just prior to the patient's treatment. The total dose will be 5 mL.

15.14 **Administration:** Study subjects will use the doxepin HCl or placebo solution as an oral rinse for one minute, then will expectorate the rinse. Patients should not eat or drink anything for 15 minutes after taking the medication.

15.15 **Potential Interactions**: The doxepin solution is not physically compatible with a number of carbonated beverages.

15.16 **Doxepin Known Potential Toxicities**: Side effects are expected to be minimal. Based on experience in previous clinical trials, mild burning or stinging discomfort, unacceptable 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,

Add 2

blurred vision, urinary retention, upper respiratory infection, low blood pressure, decreased production of blood cells, and suicidal thoughts.

15.17 **Doxepin Procurement:** The doxepin hydrochloride oral solution will be purchased by NCCTG research base pharmacy personnel. Each bottle will contain 120 mL (4 fluid ounces).

Placebo Procurement: The Ora-Sweet SF syrup will be purchased by NCCTG research base pharmacy personnel. Each bottle will contain 473 mL (one pint).

Add 1,2

Each participating NCCTG main membership will order a starter supply of one bottle of doxepin HCl solution, and one bottle of Ora-Sweet SF placebo from the NCCTG research base pharmacist. Fax or mail the NCCTG Clinical Drug Order/Return Form request to:

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

Add 1,2 Update 1

One bottle of doxepin HCl solution and one bottle of Ora-Sweet SF are each considered to be a "bulk supply" and are to be reserved for use for the preparation of doses used in the double-blind phase of the trial. If a site is in the process of enrolling a patient in the trial, they may order a bottle of doxepin HCI solution for use by the first patient who elects to participate in the optional continuation phase of the trial. Each site is responsible to monitor their supplies and order additional bottles of doxepin HCL solution and Ora-Sweet SF as/if required. A site may order additional bottles of doxepin HCl solution in advance of patient participation in the optional continuation phase.

Add 1

Each treating location will provide their own supply of Sterile Water for Irrigation, Sterile Water for Injection, or distilled water used to dilute the doxepin or placebo doses.

Add 2

The study subject will use distilled water or tap water to dilute the doxepin solution during the continuation phase.

Add 2

Outdated or remaining doxepin, and Ora-Sweet SF placebo, are to be destroyed on-site as per procedures in place at each institution.

15.18 **Nursing Guidelines:**

15.181 If solution needs to be diluted, use only water. Doxepin is not compatible with numerous carbonated beverages.

15.182 Patients may experience a mild burning or stinging sensation after use.

15.183 Patients may experience taste alterations.

15.19 Information for patients opting to continue open label drug: Patients will be instructed to mix 2.5 mL of doxepin with 2.5 mL of distilled water or tap water for a total amount of mixed solution = 5 mL. The patient will swish and gargle the mixture for 1 minute and spit it out. The patient will be supplied with oral syringes and/or other device(s) deemed to be suitable for accurately measuring 2.5 mL of fluid. These measuring devices will be provided by the treating institution.

Add 1

16.0 Statistical Considerations and Methodology

This is a randomized, double-blind, placebo-controlled, phase III trial with a cross-over phase and subsequent continued active agent usage, designed to assess the efficacy of doxepin oral rinse versus placebo for the treatment of cancer therapy-related OM. Primary and secondary data will be obtained from the first phase after randomization. Tertiary data will be obtained in a second phase in the AB/BA cross-over manner [49, 50], in which doxepin and placebo rinse are two treatments in reverse sequence for the two treatment arms, separated by a wash-out period of at least 12 hours. Further tertiary data will be gathered from patients who choose to continue subsequent use of the active agent of doxepin oral rinse.

16.1 Primary Endpoint: 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 doxepin/placebo rinse in the first phase (Dose 1).

16.2 Secondary Endpoints:

16.21 The total taste of the oral rinse as measured by the numerical analogue scale of taste of the oral rinse in the questionnaires.

16.22 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.

16.23 The total drowsiness increase as measured by the numerical analogue scale of drowsiness questionnaires.

16.24 The incidence of using alternative analgesics before 4 hours, between the doxepin oral rinse and placebo arms.

16.25 Patient preference for continued therapy with oral rinse after initial test rinse or after the cross-over phase, as measured by item 8 in the patient-reported questionnaire at 4 hours and the actual participation rate.

16.3 Tertiary Endpoints: (applies to patients during the blinded cross-over phase or the optional continuation of doxepin oral rinse after the first two phases).

16.31 Pain reduction and other adverse event profile in the blinded cross-over phase using the same patient reported questionnaire for testing of a second rinse with the agent they did not receive at first testing (either doxepin or placebo).

16.32 The long-term outcome of doxepin oral rinse for patient continued therapy after cross-over phases as measured by weekly patient questionnaires.

16.4 Analysis Plans

16.41 Primary Analysis

16.411 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 1,2,3,4,5,6. 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 calculated by proration when there are terminal missing data. If the missing data are intermittent, simple imputation 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.

16.412 The primary analysis of the total pain reduction will only use primary data from the first phase. The baseline-adjusted AUC between two treatment arms (doxepin-placebo and placebo-doxepin) will be compared using the two-sample *t* test or the Wilcoxon rank-sum test as appropriate. The 95% confidence intervals will be constructed for the mean

differences of treatment effect.

16.413 Supplementary analyses will analyze these repeated measurements of mouth pain longitudinally with or without incorporation of additional covariates of baseline characteristics using the generalized linear mixed model (GLMM).

16.414 Graphical procedures will include stream plots of individual patient mouth pain scales and plots of average values over time for each treatment arms.

16.42 Secondary Analyses

16.421 The total stinging or burning from the oral rinse will be calculated by the AUC, with time scale replaced by a numerical scale of 1,2,3,4,5,6. The statistical analysis will be the same as the primary analysis.

16.422 The total taste of the oral rinse will be calculated by the AUC, with time scale replaced by a numerical scale of 1,2,3,4,5,6. The statistical analysis will be the same as the primary analysis.

16.423 The total drowsiness increase will be calculated by the AUC adjusting for baseline, with time scale replaced by a numerical scale of 1,2,3,4,5,6. The statistical analysis will be the same as the primary analysis.

16.424 The incidence of utilizing additional analgesics between 1-4 hours after the initial mouthwash will be compared between the arms by the Chi-square test or Fisher's exact test.

16.425 Descriptive statistics and graphical procedures will be used to summarize patient preference for continued therapy.

16.5 Tertiary Analyses

16.51 The intra-patient change (doxepin vs placebo treatment effect) of AUC between two arms (doxepin-placebo and placebo-doxepin) will be compared using the two-sample *t*-test or the Wilcoxon rank-sum test. The CROS procedure [51] with an assumption of no carry-over effect after the wash-out period is highly recommended and preferred over the traditional two-stage (TS) procedure [49, 50]. The 95% confidence intervals will be constructed for the mean differences in the intra-patient change, i.e. treatment effect.

16.52 Descriptive statistics and graphical procedures will be used to summarize the results from the weekly questionnaires from the patients who continued therapy of doxepin oral rinse.

16.6 Sample size and Power Calculations

16.61 Epstein and colleagues reported maximum pain reduction seen at 5 and/or 15 minutes in their research, but we have little preliminary information about the likely variability of total oral pain reduction in AUC. In such circumstances, we have pioneered a sample size estimation process known as the empirical rule effect size (ERES) procedure [52-54]. We define a clinically meaningful effect size as roughly equivalent to one half of the standard deviation.

16.62 At the 5% significance level, we will have 80% power to detect a clinically meaningful standardized effect size of 0.5 with 128 patients (64 patients for each arm) based on the two-sample t-test with equal-variance assumption. This sample size will be further inflated by 15% to account for patient ineligibility, cancellation, or missing data. Hence, the total number of patients will be targeted at 148 patients (74 patients per arm).

16.63 There will be a supplementary process aimed specifically to accrue 25 patients from minority populations for each of the two study arms. To do this, the protocol will remain open for up to an additional 12 months after the main study accrual goal has been met--to accrue additional minority patients, up to a total of 50 additional patients. This additional accrual is not to hold up the primary analysis of this study and/or release of data to the study team for reporting the primary analysis. The additional minority accrual may be contingent on the result of primary analysis, if that analysis is finished prior to the planned completion of the minority accrual. If doxepin is found to be clearly beneficial or has little benefit, the study team will discuss with the NCI whether to close minority accrual.

The total sample size for this trial is hence 148 initial patients and 50 additional minority patients, for an overall total of 198 patients.

16.7 Accrual rate and time to completion: We anticipate accruing approximately 10 patients per month, based on our previous experience in clinical practice. This would mean completing the primary accrual within 15 months from study initiation and completing double-blind data collection in about 16 months from study initiation.

16.8 Missing data: Previous experience with imputation in NCCTG clinical trials have demonstrated that the use of various imputation methods compared to analysis of all available data provides evidence of the degree of robustness of the results relative to the assumptions of the analytical procedure. We expect the amount of missing data to be about 15% and, therefore, will adjust the accrual accordingly. We will examine the data for any influence that would be likely to cause data to be missing for any other reason than simple random chance. In other words, we will explore the data for evidence to suggest that any concomitant influence may cause the data to not be missing completely at random.

16.9a Monitoring: This study will be monitored by the NCCTG External Data Monitoring Committee (DMC), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DMC every six months as per NCI guidelines.

This study will be monitored by the Clinical Data Update System (CDUS) version 2.0. An abbreviated report containing cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

16.9b 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.

16.9b1 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:

- If 6 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 non-hematologic adverse event rate is higher in the active treatment arm as compared to the placebo arm.

16.9b2 We will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.9b3 Unblinding: It is recommended by the protocol investigators that it is reasonable for the study team to be unblinded and allowed to see the data for analysis 3 months following the entry of the last patient onto the study.

16.9c Minority accrual: This study will be available to all eligible patients, regardless of race or ethnic origin. There is no information currently available regarding differential effects of doxepin rinse in subsets defined by race or ethnicity, and there is no reason to expect such differences to exist.

Based on prior NCCTG neuropathy studies and national cancer statistics [55], we expect, for the main accrual, about 10% of patients will be classified as minorities by race and about 30% of patients will be women. The supplementary accrual described above will increase the minority accrual.

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	3	7	0	10
Not Hispanic or Latino	57	131	0	188
Ethnic Category: Total of all subjects*	60	138	0	198
Racial Category				
American Indian or Alaskan Native	4	8	0	12
Asian	3	7	0	10
Black or African American	9	16	0	25
Native Hawaiian or other Pacific Islander	1	2	0	3
White	43	105	0	148
Racial Category: Total of all subjects*	60	138	0	198

These totals must agree. Enter actual estimates (not percentages**)*

Ethnic Categories:	**Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino." **Not Hispanic or Latino**

17.0 Pathology Considerations/Tissue Biospecimens: None.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Forms	Active-Monitoring Phase (Compliance with Test Schedule)				At each occurrence	
	Initial Material	Follow-up Material				
	≤2 weeks after registration	At each evaluation	Optional Continuation Phase	At end of treatment	Grade 4 or 5 Non-AER Reportable Events/ Hospitalization	ADR/ AER
On-Study Form	X					
Provider Assessment Form (Appendix.III)	X					
Evaluation/Treatment Form		X		X		
End of All Treatment/Cancel Notification Form	X[3]			X		
End of Initial (Dose 2) Treatment Form				X[4]		
Adverse Event Form		X	X	X		
Patient Questionnaire Booklet[1]		X	X	X		
Patient Questionnaire Booklet Compliance Form[2]		X	X			
ADR/AER (see Section 10.0)						X
Notification Form Grade 4 or 5 Non-AER Reportable Events/ Hospitalization Form					X	

1. Patient questionnaire booklets **must** be used; copies are not acceptable for this submission.
2. This form must be completed **only** if the patient questionnaire booklet contains absolutely **NO** patient provided assessment information.
3. Submit this form only if withdrawal/refusal prior to beginning protocol therapy occurs.
4. Complete for Optional Continuation Phase patients only.

19.0 Budget

19.1 Costs charged to patient: Routine clinical care

19.2 Tests to be research funded: None

Add 2

19.3 Other budget concerns: NCCTG Research Base will provide the doxepin and Ora-Sweet SF placebo for the double blind phase, and the doxepin for the optional continuation phase.

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NCI Informed Consent Template for Cancer Treatment Trials (English Language)

***NOTES FOR LOCAL INVESTIGATORS:** **[NOTE: Retain this section and asterisk item below for NCCTG model consents]**

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs/* or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

N09C6, Randomized Double-Blind Study of Doxepin Rinse versus Placebo in the Treatment of Acute Oral Mucositis Pain in Patients Receiving Radiotherapy with or without Chemotherapy

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

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 area.

Why is this research study being done?

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. In some patients, radiation therapy has to be stopped because of these symptoms.

The purpose of this research study is to…

- Learn if taking the study drug, doxepin, which is a mouth rinse, is effective in reducing mouth pain in patients undergoing radiation therapy to the head and neck.
- Compare the effects, good and/or bad, of taking doxepin compared to a placebo (inactive agent) while you are receiving radiation therapy to the head and neck.

Doxepin is FDA-approved in the United States for treatment of depression, anxiety and topically for short-term management of rash as well as long term pain management.

How many people will take part in the research study?

About 198 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history
- Oral exam
- Pregnancy test if you are a woman of childbearing potential and if your doctor feels this is needed

You will also complete a questionnaire booklet about your mouth pain just before you begin treatment with doxepin or placebo. The questionnaire should take about 5-10 minutes to complete.

During the study…

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Medical history
- Oral exam

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance as in a roll of the dice. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in any group. Neither you nor your doctor will know the group which you have been placed.

If you are in Group 1 You will receive a one-time single dose of the doxepin rinse to swish, gargle and spit.You will swish and gargle about 1 teaspoon of the rinse in your mouth for 1 minute and then spit it out. You will then come back to see your doctor again the next day, or another day, and will be given a placebo rinse (a placebo is an inactive agent) if you are still having pain at that time. You will swish, gargle and spit, just like you did the day before.

If you are in Group 2 You will receive a one-time single dose of the placebo rinse (a placebo is an inactive agent) to swish, gargle and spit. You will swish and gargle about 1 teaspoon of the rinse in your mouth for 1 minute and then spit it out. You will then come back to see your doctor again the next day, or another day and will be given the doxepin rinse, if you are still having pain at that time. You will swish, gargle and spit, just like you did the day before.

We want to find out if the doxepin oral rinse will lessen mouth pain from radiation therapy to the head and neck area. 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 again 5, 15, 30 and 60 minutes after you use the doxepin/placebo oral rinse. You will then be able to leave the study doctor's office and will be given directions on filling out the questionnaires 2 and 4 hours after the doxepin/placebo oral rinse. You may receive a phone call reminder to fill out the questionnaire at 2 and 4 hours.

If possible, you should avoid taking medication for mucositis (mouth) pain for 60 minutes prior to and after the study medication. You will be allowed to 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 a questionnaire.

No viscous lidocaine, 'magic mouthwash', benzocaine, diphenhydramine or other medicated oral rinse (except saline or baking soda rinse) should be used within 4 hours prior to or after the study medication.

When I am finished taking doxepin/placebo rinse.

After you have finished taking doxepin and placebo rinse, and have completed and returned your questionnaire, you will be told by your study doctor which group you were in and will be given the option to continue using doxepin every 4 hours as needed for mouth pain during your radiation therapy. If you choose to continue taking the doxepin, you will be asked to complete questionnaires weekly during your radiation therapy appointments.

How long will I be in the research study?

You will be asked to take doxepin/placebo rinse for one day, and then be asked to take the doxepin/placebo rinse a second day. This second day you will receive whichever agent (doxepin or placebo) you did not receive on the first day. As described above, you will come back to see

your doctor again on another day when your pain score is at least 4 out of 10 and will be given the doxepin/placebo rinse. You will swish, gargle and spit, just like you did the day before. Just as on the first day, you will be asked to fill out seven questionnaires about changes in your daily life and your feelings of well-being, and about your mouth pain. You will fill out the questionnaires in your study doctor's office 5, 15, 30 and 60 minutes after you use the doxepin/placebo oral rinse. You will then be able to leave the study's doctor's office and will be given directions on filling out the questionnaires 2 and 4 hours after the doxepin/placebo oral rinse. You may receive a phone call reminder to fill out the questionnaire at 2 and 4 hours. You will then be given the option of taking doxepin on an as-needed basis until you are finished with your radiation therapy. You will also be asked to complete a questionnaire on a weekly basis for as long as you continue using the doxepin rinse.

Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the doxepin/placebo rinse can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what followup care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the research study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the doxepin rinse. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Add 2

The following are side effects that have been reported with oral doxepin that has been swallowed. The side effects from topical doxepin that is taken as a rinse that is swished in the mouth and spit out may be less likely to happen.

Risks and side effects related to the doxepin rinse include those which are:

Likely

- Mild burning in your mouth
- Stinging discomfort in your mouth
- Unacceptable taste
- Feeling tired (Fatigue)

Add 2

Less Likely

- Constipation
- Mouth dryness due to lack of saliva
- Dizziness
- Sleepiness
- Difficulty urinating
- Upper respiratory infection
- Weight gain
- Nausea

Add 2

- Blurred vision

Rare but serious

- Low blood pressure
- Decreased production of blood cells
- Suicidal thoughts

As with any medication, allergic reactions are a possibility.

For more information about risks and side effects, ask your study doctor.

Add 2

Reproductive risks: You should not become pregnant while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important that you understand that you may need to use birth control while on this study. Check with your health care provider about what kind of birth control methods to use and how long to use them.

Are there benefits to taking part in the research study?

Taking part in this study may or may not make your health better. While doctors hope doxepin rinse will be effective in reducing mouth related pain in patients undergoing radiation therapy to the head and neck compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about preventing the side effect of mouth pain for patients receiving radiation therapy to the head and neck area.This information could help future cancer patients.

What other choices do I have if I do not take part in this research study?

You do not have to be in this study to receive treatment or care for your radiation therapy induced mouth pain.

Your other choices may include:

- Getting treatment or care for your radiation induced oral mucositis related mouth pain without being in a study
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Institutional Review Board
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The North Central Cancer Treatment Group

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this research study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Add 2

The doxepin or placebo rinse will be given to you free of charge. After you have completed Dose 1 and 2, you will be unblended and given the option to continue doxepin as part of the optional continuation phase. If you participate in this phase, NCCTG will provide one bottle of the doxepin for you to use until the doxepin is gone/or you complete radiation therapy. You will not need to pay for the study drug. However, you or your health plan might also have to pay for other drugs or treatments which are given to help you control possible side effects from the study drug.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the doxepin for some reason. If this would occur, other possible options are:

- You might be able to get the doxepin from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no doxepin available at all, no one will be able to get more and the study would close.

If a problem with getting doxepin occurs, your study doctor will talk to you about these options. You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at *http://cancer.gov/clinicaltrials/understanding/insurance-coverage* . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

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

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this research study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

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

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the research study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

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

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- **For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/**
- **For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/**
- **For NCI's general information about cancer in Spanish, go to http://www.cancer.gov/espanol**

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* **pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.**

Printed Participant Name: _____

Participant Signature: _____

Date: _____

Printed name of person obtaining informed consent:

_____

Signature of person obtaining informed consent:

_____

Date _____

Local IRB changes to this document are allowed. Sections "What are the risks of the research study" or "What other choices do I have if I don't take part in this research study?" should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.

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 and two booklets on the second day you are on the study.

2. For each day you are on the study, the first booklet will be filled out 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.

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.

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 and two booklets on the second day you are on the study.

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 on the top 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.

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

You have been given a booklet to complete for this study. The booklet contains some 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. During this optional continuation phase you will continue to utilize the same dose of doxepin rinse every 4 hours as you feel you need it for your mouth and/or throat pain due to your radiation treatments. You do not need a certain level of mouth pain to take the rinse. **You will mix 2.5 mL of doxepin with 2.5 mL of water (total amount of mixed solution = 5 mL), swish and gargle the mixture for 1 minute and spit it out**.

2. You will be given a new booklet to complete for every week you continue the doxepin oral rinse.

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

4. Please complete the booklet and return it to your nurse or your physician at your next visit or mail it back in the provided envelope.

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

6. You may discontinue doxepin whenever your symptoms no longer require it or when you feel that it is no longer helpful.

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

Thank you for taking the time to help us.

Provider Assessment Form
Oral Mucositis Assessment Scale and WHO Mucositis Grade

Patient ID:
NCCTG Site: _____
Patient Initials: ____ _____ _____
First **Middle** **Last**
Date: _ _/_ _/_ _ _ _ (MM/DD/YYYY)

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

[ ] : [ ] AM / PM

Location	Ulceration/ Pseudomembrane* (circle)				Erythema** (circle)		
Upper lip	0	1	2	3	0	1	2
Lower lip	0	1	2	3	0	1	2
Right cheek	0	1	2	3	0	1	2
Left cheek	0	1	2	3	0	1	2
Right ventral and lateral tongue	0	1	2	3	0	1	2
Left ventral and lateral tongue	0	1	2	3	0	1	2
Floor of mouth	0	1	2	3	0	1	2
Soft palate/fauces	0	1	2	3	0	1	2
Hard palate	0	1	2	3	0	1	2

***Ulceration/Pseudomembrane**
0 = No lesion
1 = < 1 cm^2
2 = 1 cm^2 – 3 cm^2
3 = > 3 cm^2

****Erythema**
0 = None
1 = Not severe
2 = Severe

Presence of infection *: (circle)** **Yes** **No**
If yes, circle: **Local** **Non-oral** **Systemic**

WHO Mucositis Grade: (circle)
1 **= Erythema and soreness**
2 **= Ulcers, able to eat solids**
3 **= Ulcers, requires liquid diet**
4 **= Ulcers, alimentation not possible**

Evaluator Signature: _____

***** Culture if clinically indicated**

Eligibility screening question

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

Questionnaire Dose 1 and Dose 2
Baseline

Before rinsing your mouth with the oral solution, please complete these two pages.

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

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

We hope you will feel better soon. In 5 minutes, please complete the next questionnaire page.

Questionnaire after 5 minutes, Dose 1 and Dose 2

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, Dose 1 and Dose 2

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, Dose 1 and Dose 2

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, Dose 1 and Dose 2

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

_____

_____

_____

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

Questionnaire after 120 minutes, Dose 1 and Dose 2

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 medication(s) over the last hour? (circle 'Yes' or 'No') Yes No

If yes, please list the medication(s) that you took:

Name	**Strength**	**When**
For example ***Oxycodone***	***5 mg***	***2 hours 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, Dose 1 and Dose 2

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 medication(s) over the last 2 hours? (circle 'Yes' or 'No') Yes No

If yes, please list the medication(s) that you took:

Name	**Strength**	**When**
For example *Oxycodone*	***5 mg***	***4 hours ago or within the last 60 minutes***

_____

_____

_____

_____

8. Based on the 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 no, please explain

_____

_____

_____

9. Were the study medication rinses helpful in alleviating your mouth/throat pain? (circle 'Yes' or 'No')Yes No

Other comments:

_____

_____

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

Weekly Questionnaire for Patients Who Continue with Doxepin Rinses

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

1. Did you discontinue the doxepin rinses entirely this week? (circle 'Yes' or 'No') Yes (If yes, go to question 2) No (If no, go to question 4)

2. If yes, on what date did you discontinue doxepin? __ __ / __ __ / __ __ __ __ (MM/DD/YYYY)

3. Please state why you discontinued the doxepin rinse by checking one or more of the following:

_ Pain got better

_Medication did not work

_Didn't like side effects, which ones _____

_Other, please explain_____

4. Are the doxepin rinses 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 your MOUTH PAIN due to your radiation treatment during the past week, with the use of whatever medications that you are taking for it? (circle one number)

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

6. Did your MOUTH and THROAT PAIN due to your radiation treatments resolve entirely during the past week (i.e. pain is now 0 out of 10)? (circle 'Yes' or 'No') Yes No

7. If yes, on what date did this occur? __ __ / __ __ / __ __ __ __ (MM/DD/YYYY)

<u>Only answer the remaining questions if you continued to use the doxepin rinse</u>

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

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

9. 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

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

Yes No

If yes, please explain

_____

_____

_____

Other comments:

_____

_____

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