

**A221304**

# **A Phase III Placebo-Controlled, Randomized Three-Arm Study of Doxepin and a Topical Rinse in the Treatment of Acute Oral Mucositis Pain in Patients Receiving Radiotherapy With or Without Chemotherapy**

ClinicalTrial.gov Identifier: NCT02229539

## **Study Background**

### **Trial Description**

The purpose of this study is to test whether a mouthwash made with a drug called doxepin can reduce the pain caused by mouth sores resulting from radiation therapy. A number of mouth rinse preparations exist for patients with treatment-related oral mucositis pain such as the DLA rinse, an over-the-counter medication. This study will evaluate the effects of doxepin compared to DLA (diphenhydramine, lidocaine and antacids) and placebo. Doxepin is approved by the Food and Drug Administration (FDA) for the treatment of depression, anxiety, long-term pain management, as well as management of rash.

### **Arms:**

Doxepin rinse: (Experimental): Patients receive 2.5 mL (25 mg) doxepin and 2.5 mL water orally, swish and gargle for 1 minute then spit. Doxepin rinse is administered in the clinic on Day 1 (Cycle 1). The patient will remain at the treating location for the first hour and complete the Oral Symptoms booklet at time zero (prior to the oral swish, gargle and spit), and at 5, 15, 30 and 60 minutes post-administration. After completing the booklet at 60 minutes, patients may then leave the clinic and complete the 2- and 4-hour assessments at home. There is an optional continuation phase within seven days following Day 1 (Cycle 1), patients will be encouraged to continue treatment with the study agent for an additional week (Cycle 2) where the patient takes the rinse at home every 4 hours. Chemotherapy is allowed during the continuation phase. Patients randomized to doxepin or placebo, they and their caregivers will continue to be blinded to the treatment. Patients will complete the Oral Symptoms booklet per the protocol.

DLA (diphenhydramine, lidocaine and antacid) rinse: (Active Comparator): Patients receive 5.0 mL DLA orally, swish and gargle for 1 minute then spit. DLA is administered in the clinic on Day 1 (Cycle 1). The patient will remain at the treating location for the first hour and complete the Oral Symptoms booklet at time zero (prior to the oral swish, gargle and spit), and at 5, 15, 30 and 60 minutes post-administration. After completing the booklet at 60 minutes, patients may then leave

the clinic and complete the 2- and 4-hour assessments at home. There is an optional continuation phase within seven days following Day 1 (Cycle 1), patients will be encouraged to continue treatment with the study agent for an additional week (Cycle 2) where the patient takes the rinse at home every 4 hours. Chemotherapy is allowed during the continuation phase. Patients receiving DLA during the continuation phase of the study, they and/or caregivers may be aware that they are receiving DLA. Patients will complete the Oral Symptoms booklet per the protocol.

Placebo rinse: (Placebo Comparator): Patients receive 2.5 mL placebo and 2.5 mL water orally, swish and gargle for 1 minute then spit. The placebo rinse is administered in the clinic on Day 1 (Cycle 1). The patient will remain at the treating location for the first hour and complete the Oral Symptoms booklet at time zero (prior to the oral swish, gargle and spit), and at 5, 15, 30 and 60 minutes post-administration. After completing the booklet at 60 minutes, patients may then leave the clinic and complete the 2- and 4-hour assessments at home. There is an optional continuation phase within seven days following Day 1 (Cycle 1), patients will be encouraged to continue treatment with the study agent for an additional week (Cycle 2) where the patient takes the rinse at home every 4 hours. Chemotherapy is allowed during the continuation phase. Patients randomized to doxepin or placebo, they and their caregivers will continue to be blinded to the treatment. Patients will complete the Oral Symptoms booklet per the protocol.

### **Objectives:**

Patients are stratified according to sex (male vs. female), concurrent use of chemotherapy (no vs. yes), patient age at registration (< 60 years old vs. ≥ 60 years old and RTOG acute radiation morbidity criteria (1 vs. 2 vs 3 or more). Protocol therapy will consist of 2 cycles. Patients are randomized to one of three treatment regimens, which include doxepin, DLA and placebo. Cycle One will consist of one day. The care provider or nurse will confirm that the oral pain is at least 4 out of 10 severity level at the time of the rinse on the first day of the study. If the pain score is less than 4 then administration will be delayed until the pain is at least 4. Patient will be asked to complete the Oral Symptoms booklet at baseline (prior to the oral swish, gargle and spit), and at 5, 15, 30 and 60 minutes post-administration. After completing the booklet at 60 minutes, patients may then leave the clinic and complete the 2- and 4-hour assessments at home. Cycle Two will consist of an optional continuation phase lasting up to 7 days. Initiation of the Cycle 2/Continuation Phase may be delayed up to one week after Cycle 1/Day 1.

### **Primary Objective:**

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

## **Secondary Objectives:**

1. Assess the adverse event profile of the doxepin rinse, the DLA rinse agent, and the placebo using a patient-reported questionnaire at 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours for domains of unpleasant taste, burning or stinging discomfort, and drowsiness.
2. Compare the incidence of using additional analgesics between 1 and 4 hours after the initial mouthwash, between the doxepin oral rinse, the DLA rinse agent, and the placebo arms.
3. Compare the length of time that each study product is used by patients in the one-week continuation phase.
4. Compare the daily pain scores in the one-week continuation phase for the three study arms.
5. Compare the 24-hour morphine equivalent dose used in the continuation phase for the three study arms.

## **Study Milestones:**

Start date: November 2014

Primary Completion Date: May 2016

## **Publication Information:**

Analysis Type: Primary

Pubmed ID: 30990550

Citation: JAMA. 2019 Apr 16;321(15):1481-1490. doi: 10.1001/jama.2019.3504.

Associated Datasets: NCT02229539-D1.csv (Fig1\_allptchar), NCT02229539-D2.csv (Anlypt), NCT02229539-D3.csv (c1ctcae), NCT02229539-D4.csv (c2ctcae)

## **Dataset Information:**

Dataset Name: NCT02229539-D3.csv (c1ctcae)

Description: Dataset NCT02229539-D3.csv (c1ctcae) is one of 4 datasets associated with PubMed ID 30990550. This dataset contains cycle 1 adverse event information.

## **NCT02229539-D3.csv (c1ctcae) Data Dictionary:**

LABEL	NAME	elements	comments
Patient Reference	patref		
Arm	ARM	Doxepin, Placebo, DLA	
Cycle 1: Maximum Adverse Event Grade	c1_maxaegrade	0, 2, 1, 3	NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0
Cycle 1: Fatigue Grade	c1_fatigue_grade	0, 1, 3, 2	<p>NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0</p> <p>Due to data cleaning efforts subsequent to the abstract submission, data may contain slight discrepancies from that reported in the following section in the publication:</p> <ul style="list-style-type: none"><li>- Last sentence of Results paragraph in the abstract (pg. 1481): "Fatigue was reported by 5 patients (6%) in the doxepin mouthwash group and no patients in the diphenhydraminelidocaine-antacid-mouthwash group."</li><li>- First paragraph (pg. 1487): "fatigue during cycle 1, whereas no fatigue was reported in the diphenhydramine-lidocaine-antacid mouthwash group or the placebo mouthwash group."</li></ul>