RANDOMIZED PHASE III, DOUBLE BLIND, PLACEBO CONTROLLED STUDY OF PROPHYLACTIC GABAPENTIN FOR THE REDUCTION OF RADIATION THERAPY INDUCED PAIN DURING THE TREATMENT OF OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

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Protocol Version 1.0 1/6/2017

Randomized Phase III, Double-Blind, Placebo Controlled Study of Prophylactic Gabapentin for the Reduction of Radiation Therapy Induced Pain During the Treatment of Oropharyngeal Squamous Cell Carcinoma

SCHEMA

Pre-study: Determine eligibility

▼

Signed Informed consent

▼

S		**R**	**Arm 1: (control):** Standard supportive care during
T		**A**	definitive treatment plus placebo
R		**N**	
A	**Smoking History:**	**D**	**Arm 2:** 600 mg of gabapentin TID (1800 mg daily
T	Current smoker	**O**	total) during definitive treatment
I	Ex-smoker or non-smoker	**M**	Plus standard supportive care
F		**I**	
Y		**Z**	
		E	

Patient population: Patients being treated with radiation and concurrent chemotherapy for Stage III and IV (non-metastatic) squamous cell carcinoma of the oropharynx

Required Sample Size: 60

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1.1 INTRODUCTION

1.1.1 Specific Aims

Strategies to minimize and mitigate external beam radiation therapy related mucositis and pain during the treatment of head and neck cancer remain limited. We hypothesize that gabapentin could be used to delay or reduce treatment-related pain, reliance on opioid medication, and improve the quality of life for these patients. The specific aims of this proposed study include the following:

- Evaluate the reduction or delay of mucositis related pain and morbidity with the use of gabapentin in patients with stage III or IV oropharyngeal squamous cell carcinoma undergoing definitive radiation with concurrent chemotherapy as part of their cancer management, compared to standard supportive side effect mitigation – using patient reported quality of life endpoints such as the Patient-Reported Oral Mucositis Symptoms (PROMS) scale.
- Assess morphine-equivalent opioid use in both treatment arms by collecting the patient's narcotic use in the previous 24-hour period at each weekly evaluation during radiation treatment.
- Report on change in Speech and swallow performance, as measured by the Performance Status Scale (PSS) for Head and Neck Cancer Patients.
- Evaluate changes in weight from baseline throughout treatment between the two arms.
- Calculate the proportion of patients who end up requiring a feeding tube by the end of treatment in both arms.
- Evaluate changes in patient-report quality of life using the Functional Assessment of Cancer Therapy Head &Neck (FACT-HN) and PRO-CTCAE metrics.
- Evaluate the adverse events associated with gabapentin.
- Evaluate the severity of radiation mucositis (grade 3-4, CTCAE, v. 4).

1.2 Background and Significance

1.2.1 Head and Neck Cancer/ Treatment Related Morbidity

There are an estimated 55,070 patients with head and neck cancer in the United States, with an estimated 12,000 deaths annually and a rising incidence of Human Papilloma Virus-related oropharyngeal cancer. [1, 2] Unfortunately, a large portion of these patients present with locally advanced disease. [3] Definitive radiation with concurrent platinum-based chemotherapy is the primary treatment for stage III and IV oropharyngeal carcinoma.

Chemotherapy has been evaluated in multiple trials in conjunction with radiation therapy to treat a variety of head and neck cancers. A comprehensive meta-analysis revealed an overall survival

benefit of 7% at 2 years and 8% at 5 years with the concurrent use of cisplatin-based chemotherapy. [4] This, however, has not come without major treatment related toxicity and morbidity. The addition of chemotherapy to radiation has been shown to potentially increase short-term toxicity burden by 300% (increased relative risk). [5]

Strategies to minimize and mitigate treatment related mucositis and pain remain limited. Most practitioners utilize a combination of oral anesthetic mouthwashes, opioid medication, infection control, and lifestyle modification. [6]

1.2.2 Gabapentin

Gabapentin is an anticonvulsant and has been used to manage neuropathic pain and is FDA-approved for the treatment of post-herpetic neuralgia and partial onset seizures. While opioids are effective in treating nociceptive pain, head and neck patients experience both neuropathic (burning, aching, stabbing) and nociceptive (dull, sore, tender) pain. [7] Opioid medications have adverse effects including constipation, nausea, vomiting, sedation, impaired psychomotor function, urinary retention, hyperalgesia, as well as the potential for dependence. [8] Gabapentin is thought to provide neuropathic relief of pain by inhibition of alpha-2-delta-1 receptor upregulation in the dorsal horn, reversing pain mediated regulators of pain. [9] It is generally well tolerated, although common adverse effects include somnolence, dizziness, peripheral edema, and fatigue. [10]

Gabapentin has evolved as a strategy to reduce morbidity in patients undergoing radiation treatment. Bar-Ad et al. retrospectively evaluated their experience using gabapentin and found less opioid use and less treatment breaks when using this strategy for patients undergoing chemoradiation treatment to the head and neck. Similar findings were reported for patients undergoing post-operative radiation therapy without chemotherapy. [11] Similarly, Starmer et al retrospectively analyzed 23 patients with oropharyngeal SCC treated with chemoradiation and found that patients used their PEG tubes later, had their PEG tubes removed earlier, and reported less pain and duration of pain in those that used gabapentin. [1] Lastly, Yang et al in their retrospective analysis of their head and neck database found gabapentin use to be associated with reduced PEG tube dependence. [12]

All of these reports are small, single institution, retrospective experiences and are subject to patient selection biases. Given the advantages of gabapentin use during chemoradiation in reducing treatment related pain and PEG tube dependence, we seek to prospectively evaluate this drug in a randomized, blinded setting. This will validate these findings with a greater level of evidence.

1.2.3 Summary and Rationale for This Study:

Given the lack of effective strategies to mitigate treatment related pain from mucositis during head and neck cancer treatment as well as lack of randomized, prospectively evaluated evidence

supporting gabapentin use in this setting, we hereby propose this randomized clinical trial to evaluate the effectiveness of gabapentin in delaying or reducing treatment-related pain, reliance on opioid medication, and improving the quality of life for these patients.

2. PATIENT SELECTION

2.1 Conditions for Patient Eligibility:

2.1.1 Patients being treated with combination radiation and chemotherapy (definitive) therapy for locally advanced (Stage III and IV) squamous cell carcinoma of the oropharynx.
2.1.2 Age ≥ 18.
2.1.3 ECOG performance status 0-1.
2.1.4 Patients must provide study specific informed consent prior to study entry and be able to fill out toxicity and quality of life related questionnaires.
2.1.5 Patients should be concurrently treated with any of the following chemotherapy regimens: high-dose every three week cisplatin, low dose weekly cisplatin, or weekly carboplatin.

2.2 **Conditions for Patient Ineligibility:**

2.2.1 Patients may not be receiving gabapentin, any other investigational agents, or other anticonvulsants.
2.2.2 Patients with metastatic disease are excluded from this clinical trial.
2.2.3 Patient with allergies or hypersensitivity to gabapentin.
2.2.4 Patients receiving surgery as part of their definitive management.
2.2.5 Patients who have received prior chemotherapy or radiation therapy for head and neck cancer.
2.2.6 Patients unable to complete the required forms; however, verbal completion is adequate if recorded on the form daily.
2.2.7 Uncontrolled serious illness including, but not limited to, ongoing or serious active infection requiring IV antibiotics for over 30 days, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia other than chronic, stable atrial fibrillation, immunocompromised state, significant hepatic insufficiency, significant hematological disease, and any serious or unstable psychological condition.
2.2.8 Patients on any of the following medication that cannot find a suitable substitute during the study period: azelastine, orphenadrine, paraldehyde, thalidomide.
2.2.9 Patients with severe renal insufficiency (creatinine clearance of < 60 ml/minute)

2.3 **Required laboratory data (to be done at time of enrollement):**

2.3.1 Creatinine

2.4 Inclusion of Women and Minorities: Both men and women and members of all races and ethnic groups are eligible for this trial.

3. REGISTRATION PROCEDURES

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site has Institutional Review Board approval. Patients must have signed and dated all applicable consents and authorization forms. To register a patient to this study, the signed and dated eligibility checklist, along with any necessary supporting documentation, and the signed patient consent form will be forwarded to the responsible data manager. To complete the registration process, the data manager will assign a patient study number, in sequential order of consent, register the patient to the study, and contact the treating investigator and responsible research nurse to confirm registration.

4. TREATMENT PLAN

4.1 Chemotherapeutic Agent Administration

Chemotherapy, delivered concurrently with radiation therapy, will ultimately be determined by the treating medical oncologist. Patients receiving any of the following regimens will be eligible:

High-dose cisplatin - Cisplatin: 100 mg/m^2/day, every 3 weeks during radiation treatment, for a maximum of 3 doses.

Carboplatin - Carboplatin: Target area under curve (AUC) 2 once weekly for a maximum of 6 doses.

Weekly cisplatin - Cisplatin: 40 mg/m^2/day, weekly during radiation treatment for a maximum of 6 doses.

4.2 Radiation Therapy

Radiation therapy, delivered concurrently with chemotherapy, will ultimately be determined by the treating radiation oncologist. The following guidelines should be followed:

4.2.1 Dose specifications:

Volumes and Lymph node levels should be defined as per the RTOG Head and Neck atlas http://www.rtog.org/CoreLab/ContouringAtlases/HN.aspx.

Definitive treatment (all primary treatment should be delivered with concurrent chemotherapy as per the treating medical oncologist) will be done with simultaneous integrated dosing (SID) in 35 fractions to a total dose of 70 Gy, 63 Gy and 56 Gy to the high-risk, intermediate-risk and low-risk CTVs, respectively.

4.2.2 Physical Factors:

All subjects will undergo radiographic imaging required for radiation treatment planning purposes using a CT scanner. Digitally reconstructed radiographs from the CT will simulate the patient geometry during radiation treatment, including the localization and immobilization methods. A virtual treatment planning procedure is used to design treatment fields mathematically from the CT images.

4.2.3 Target Volumes

The GTV will be treated as the PTV70 (CTV 70+margin) will receive 70 Gy in 35 fractions (2 Gy per fraction)

Creation of the PTV70 is as follows: GTV70 defined from CT-sim and diagnostic CT fusion. GTV-p (primary tumor) and GTV-n (positive lymph nodes) are to be delineated.

CTV70-p=GTV-p with 1 cm expansion, except when the GTV-p is at the base of tongue, then the CTV70-p will be the GTVp with a 1.5 cm expansion.

CTV70-n will be created using the GTV-n with a 1 cm expansion.

CTV70 will then be defined using the CTV70p+ CTV70n. The CTV70 should be modified so as not to cross fascial plains or vertebral bodies.

PTV70 will be defined as the CTV70 with a 0.5 cm expansion. PTV70 should be modified to be cropped 3 mm from the skin surface.

High risk PTV63 (CTV63+margin) areas will receive 63 Gy in 35 fractions (1.8 Gy per fraction)

The CTV63 delineated to include the involved lymph node level, and any adjacent lymph node levels. For example for a right sided level 2 lymph node, CTV63 will include right sided level-2, level-3, level-5, and level-1b. Level-2 should be defined to the base of skull on the involved side (sacrificing parotid on involved side).

PTV63 will be defined as CTV63 with a 0.5 cm expansion.

Low risk PTV56 (CTV56+ margin) regions will receive 56 Gy in 35 fractions (1.6 Gy per fraction)

The CTV56 will include the uninvolved neck, if clinically indicated to be treated. Level-2 in the uninvolved neck should be treated to the level of C1, allowing for parotid sparing. Also included

in the CTV56 is any lymph node level on the involved side that is not included in the CTV63, and is still at low risk of tumor involvement. Such that if right side level-2 LN is involved, then right sided level-4 would be defined as CTV 56. Right sided Level-1a would be included only if clinically indicated.

PTV56 will be defined as CTV56 with a 0.5 cm expansion.

4.2.4 Field Arrangement:

IMRT will be used to cover the primary or planning target volume (PTV), provided that the normal tissue constraints described below are met.

4.2.5 Beam Shaping:

A multileaf collimation system will be used to comply with field margin and normal tissue dose requirements.

4.2.6 Treatment Equipment:

Treatment will be administered on an isocentrically mounted megavoltage linear accelerator with photon energy ≥ 6 MV. Typically, the source-to-axis distance (SAD) will be 100 cm. IMRT will be delivered using volumetric modulated arc therapy (VMAT) technique.

4.2.7 Beam Verification:

Standard IMRT QA procedures developed at our institution will be performed, including monitor units verification, intensity map verification, as well as point dose measurements. Cone beam CT scans will be obtained daily prior to radiation delivery to ensure proper patient positioning.

4.2.8 Dosimetry:

The uniformity requirement will be +/- 5% of the total dose at the prescription point within the planning target volume.

4.2.9 Critical Normal Structures:

QUANTEC Dose Constraint Parameters will be used. Modifications to allow for adequate tumor coverage are allowed at the discretion of the treating physician.

4.2.10 Radiation Therapy Adverse Events and Treatment Modifications

Grade 3-4 (CTCAE, v. 4) therapy-induced mucositis and/or dysphagia, which are enhanced by cisplatin, are expected to develop in about two thirds of patients. Nutritional evaluation prior to the initiation of therapy is highly recommended. Placement of a feeding tube should be recorded, as should use of a feeding tube during and after treatment . Other common radiation adverse

events include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, and skin erythema and desquamation within the treatment fields.

Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis. Much less common radiation adverse events include: mandibular osteoradionecrosis (< 5% incidence with attention to the dental recommendations), and cervical myelopathy (< 1% with restriction of spinal cord dose to ≤ 45 Gy).

4.3 Protocol Treatment

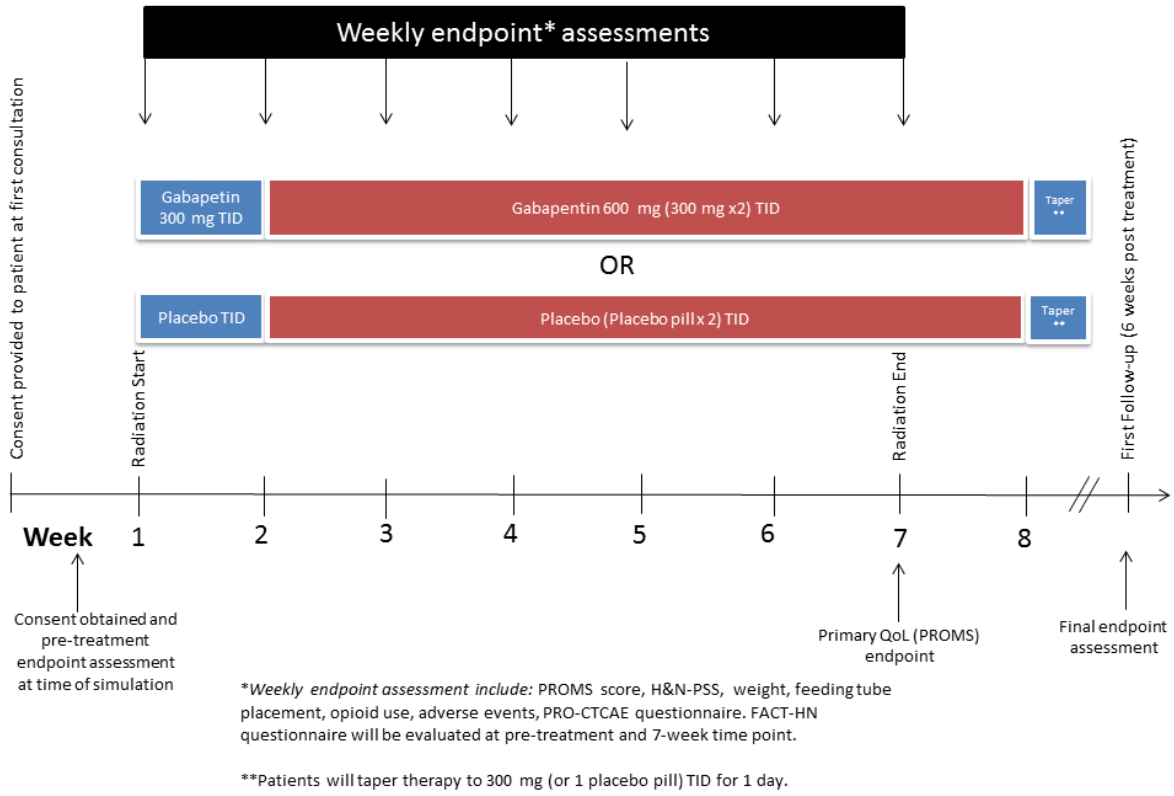

Figure 1: Treatment schema, as described below.

4.3.1 Arm 1

Patients will receive a placebo along the same dosing schedule as the experimental arm (patients randomized to placebo will take the same number of capsules as those assigned to gabapentin).

This will also include standard supportive care for treatment-related pain and mucositis as needed during concurrent chemotherapy and radiation treatment, consisting of the following:

• Viscous lidocaine 2% oral solution

• Oral liquid or solid opioid medications- e.g., morphine, oxycodone. These will be introduced and titrated at the discretion of the treating physician when the patient-reported pain score is ≥ 4 on a 0-10 scale.

4.3.2 Arm 2

Gabapentin will be initiated at a dose of 300 mg to be taken at bedtime of the night prior to the first radiation treatment. During week 1, the dose will be 300 mg three times a day for a total daily dose of 900 mg. Starting week 2, the dose will be 600 mg taken 3 times per day for a total daily dose of 1800 mg. This will continue until one week after the end radiation treatment (week 8). Therapy will then be titrated down to 300 mg three times a day for 1 day, and then discontinued all together. The standard supporting care for treatment-related pain and mucositis described above will also be included.

4.3.3 Adverse Events

Side effects of gabapentin include somnolence, dizziness, peripheral edema, and fatigue. Rarely, patients experience changes in behavior or suicidal ideation. These effects will be evaluated on a weekly basis.

4.3.4 Study medication accountability

Patient compliance with be evaluated weekly during clinic visits. Patients are expected to receive 3 doses per day (21 per week), 7 days a week during radiation. Patients who take at least 12 doses a week will be considered compliant. Patients that do not begin gabapentin or require a feeding tube will be followed for the endpoints measured in the protocol for an intent-to-treat analysis.

The investigator is required to maintain adequate records of the disposition of the investigational products. Participants will be asked to return unused tablets at the end of radiation treatment and at first follow-up. The unused tablets will be counted by pharmacy.

4.4 Duration of Follow Up

Patients will be followed for 6 weeks after completion of definitive treatment or until removal (or) termination from study, or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Toxicity notations, quality of life information, and disease status will be recorded. If it is not possible to coordinate a follow-up evaluation at 2 ± 1 months, then a follow-up phone call will

be made to the patient by the treating physician, or clinical trials office designee, in lieu of a visit.

4.5 Assignment of interventions

4.5.1 Allocation sequence generation

Separate randomization lists will be produced by a statistician for current smokers as well as for former/ non-smokers with a goal of 1:1 allocation to both treatment arms.

4.5.2 Allocation concealment mechanism

The sequence of the randomization numbers is kept in sealed envelopes independent of the investigators.

4.5.3 Implementation

The Henry Ford Research Pharmacy will label the tablet packages according to the randomization list. Single sealed envelopes containing the participants' randomization code will be located and the Radiation Oncology Clinic.

4.5.4 Unblinding

Blinding of the investigators, outcome assessors, pharmacists, data analysts and trial participants will be maintained throughout the study. Adverse events (AEs) that are considered serious, unexpected and at least possibly related to the medication would have to be unblinded. The study will be unblinded by the trial statistician after the final visit of the primary endpoint assessment.

4.5.5 Withdrawal of participants/stopping rules and urgent safety

Participants have a right to withdraw at any time and may be withdrawn at the investigator's discretion. Reasonable effort should be made to contact any participant lost to follow-up. The information collected before the withdrawal will be included in analysis. Participants will not be replaced. The PI will have the authority to deviate from the protocol if doing so relates to the immediate safety of a participant, where continuing to follow protocol would put that participant at risk. If any of the following criteria are met, study enrolment and study therapy will be suspended: death in any participant, where death is attributed in any way to study therapy or intervention; grade 4 anaphylaxis as defined by the World Allergy Organization (WAO).

Study therapies will be discontinued for any of the following reasons: two or more occurrences of grade 3 or above systemic allergic reactions as defined by the WAO; any AE that presents an unacceptable consequence to the participant; an illness that requires treatment not consistent with protocol requirements; inability to comply with the study protocol and pregnancy.

An internal data safety committee will be formed through the Clinical Trials Office and will meet quarterly to review potential adverse effects from the study medication.

5. DOSING DELAYS/DOSE MODIFICATIONS

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) version 4.0 for toxicity and Serious Adverse Event (SAE) reporting.

5.1 General Considerations

5.1.1 Dose Modifications for Gabapentin

If patient cannot tolerate gabapentin at the dose specified in this protocol, dose can be reduced in 300 mg (or 1 pill) decrements until side effects subside. If intolerance continues, therapy should be discontinued. Patients who are unable to tolerate the medication will be withdrawn from the study. Patient should be continued to be followed as specified on the protocol, however, for intent-to-treat analysis purposes.

6. ADVERSE EVENT REPORTING:

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for reporting of adverse events (AEs).

Serious Adverse Events (SAE) and adverse events will be carefully recorded, and SAEs will be reported to Henry Ford Hospital's IRB if they meet the IRB's SAE reporting criteria.

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

 Death;

 A life-threatening adverse drug experience;

 Inpatient hospitalization or prolongation of existing hospitalization;

 A persistent or significant disability/incapacity;

 Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy, including a male patient's impregnation of his partner, occurring on study must be reported to the IRB as a medically significant event. SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported to the IRB if the reporting criteria is met.

7. PHARMACEUTICAL INFORMATION

7.1 Gabapentin

Please refer to the FDA-approved package insert for additional information.
a. Description – Anticonvulsant, Miscellaneous; GABA Analog
b. Pharmaceutical Data (as taken from UpToDate) –
Absorption: Variable, from proximal small bowel by L-amino transport system; saturable process; dose-dependent
Distribution: Vd: 58 ± 6 L; CSF concentrations are ~20% of plasma concentrations
Protein binding: <3%
Metabolism: Not metabolized
Bioavailability: Inversely proportional to dose due to saturable absorption:
Immediate release:
900 mg/day: 60%
1,200 mg/day: 47%
2,400 mg/day: 34%
3,600 mg/day: 33%
4,800 mg/day: 27%
Half-life elimination:
Adults, normal: 5 to 7 hours; increased half-life with decreased renal function; anuric adult patients: 132 hours; adults during hemodialysis: 3.8 hours
Time to peak: Adults: 2 to 4 hours.
Excretion: Proportional to renal function; urine (as unchanged drug)
Clearance: Apparent oral clearance is directly proportional to CrCl.
c. Administration – Orally
d. Storage and Stability - : Store vials at room temperature and protect from light.
e. Supplier – Gabapentin is commercially available.

8. STUDY CALENDAR

The institutional review board (IRB) approval process is expected to be completed by March of 2017. The trial will start accrual of patients subsequently. Given the typical volume of patients treated at our institution, it is expected to take 1-1.5 years to accrue the required 60 patients to complete this study. Patients will be followed up until the first follow-up after completion of radiation treatment (6 weeks). The trial is expected to conclude January of 2019 with data analysis and reporting to take place subsequently.

9. STATISTICAL CONSIDERATIONS

9.1 Study Endpoints/ Analysis Plan

9.1.1 Primary endpoint

The primary endpoint is change in quality of life and pain, as measured by the Patient-Reported Oral Mucositis Symptoms (PROMS) scale over the entire study period. This will be measured at baseline and weekly during clinic visits. Additional measurements will be obtained at 6-weeks (first follow-up) from the time of radiation treatment completion.

The PROMS scale consists of 10 questions on a visual analogue scale of 100-mm lines addressing oral functions affected by oral mucositis.[13] This questionnaire has been validated in patients undergoing radiation treatment for head and neck cancers and correlates well with clinician determined scores of mucositis.[14]

Repeated measures analysis of variance (ANOVA) will be used to determine if there was a significant difference between the mean PROMS scores of the two groups over the entire study period, and t-tests will be used to examine if there was a difference in the PROMS scores for the two groups at each week of the study period.

9.1.2 Sample size/ Justification of Number of Subjects

Based on reported means and standard deviation of PROMS scores of patients undergoing radiation treatment, a total of 60 patients will be required to evaluate a 16% reduction in PROMS score at week 7 (final week) of radiation treatment, with $\alpha = 0.05$ and power = 80%. This assumes a 10% dropout rate.

9.2.1 Secondary Endpoints

9.2.2 Speech and Swallow Function:

Report on change in Speech and swallow performance, as measured by the Performance Status Scale (PSS) for Head and Neck Cancer Patients (see appendix). This will completed by the treating physician/ speech-language pathologist during the same time points as the primary endpoint.

9.2.3 Weight Loss and Feeding Tube use

Patient weight loss will be evaluated by comparing the percent weight change per patient from baseline to 6 weeks post-treatment between treatment arms using the Wilcoxon-rank sum test at the significance level of 0.05. The feeding tube placement and use will also be documented.

9.2.4 Opioid Use

Patients with at least 1 reported administration of opioid analgesic will be considered to have received opioid analgesics. The total dose of opioid analgesics will be the sum of all opioid analgesic administrations that have been converted to morphine equivalents (see Appendix II). Use of opioid analgesics will be assessed for a 24-hour period before completing the assessment weekly during radiation. The relationship between analgesic use and treatment-related pain will be evaluated using the general linear model with (at minimum) stratification, treatment arm, and compliance.

9.2.5 Adverse Events (CTCAE, v. 4)

Adverse events related to gabapentin will be reported. Additionally, the incidence of grade 3-4 radiation induced mucositis during treatment will be compared between treatment arms using Fisher's exact test at the significance level of 0.05.

9.2.6 Other Quality of Life Metrics

Patients will be asked to complete the FACT-HN and PRO-CTCAE quality of life forms (see Appendix). The FACT-HN will be assessed at baseline and at the 7-week (final week) of radiation. The PRO-CTCAE will be assessed at baseline and weekly with the PROMS scale.

The change in scores from baseline to the 6-week follow-up timepoint will be used for analysis.

All assessments are summarized in Table 1.

Table 1. Subject assessments.

Parameters	Prior to Study Therapy	Weekly During Radiation Therapy	At First Follow-up (6-weeks post completion)
History and Physical [a]	X		X
Performance status [a]	X		X
Creatinine	X		
PROMS Score [b]	X	X	X
HN-PSS Score [a]	X	X	X
FACT H&N [b]	X		X
Weight	X	X	X
Daily opioid use (in morphine equivalents) [a]	X	X	X
Assess if feeding tube has been placed [a]	X	X	X
CTCAE and other adverse events [a]	X	X	X
PRO-CTCAE questionnaire [b]	X	X	X

[a] Physician or evaluator reported.

[b] Patient reported.

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APPENDIX I

ZUBROD PERFORMANCE SCALE

0 Fully active, able to carry on all predisease activities without restriction

1 Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours

4 Completely disabled. Cannot carry on self-care. Totally confined to bed

5 Death

APPENDIX II

Analgesic Conversion Tables

EQUIANALGESIC POTENCY CONVERSION	
Name	Equianalgesic Dose *(mg)* po
Morphine	60
Hydromorphone *(Dilaudid)*	7.5
Methadone *(Dolophine)*	20
Oxycodone	30
Levorphanol *(Levo-Dromoran)*	4
Codeine	200
TRANSDERMAL FENTANYL *(DURAGESIC)* DOSE PRESCRIPTION BASED UPON DAILY MORPHINE EQUIVALENCE	
Oral 24-hour morphine *(mg/day)*	Duragesic Dose *(ug/h)* 45-134
	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275

NARCOTIC EQUIVALENCY INDEX

NARCOTIC	ROUTE	CONVERSION FACTOR
Morphine	IM/IV	1.00
0.17 for single dose trial; 0.33 for chronic administration		
Hydromorphone	IM	6.67
(Dilaudid)	po	1.33
Codeine	IM	0.08
po		0.05
Oxycodone*	IM	0.67
po		0.33
Levorphanol	IM	6.25
(Levodromoran)	po	3.13
Meperidine	IM	0.10
(Demerol)	po	0.03
Methadone	IM	1.38
(Dolophine)	po	0.69

* 1 tablet of Tylox, Percocet, or Percodan contains 5 mg of oxycodone.

APPENDIX III

Weekly Patient and Clinician Reported Questionnaires

Patient Reported Oral Mucositis Symptom (PROMS) Scale

1. Mouth* pain - *Mouth encompass also lips, cheeks, tongue, gums, palate and throat

no pain _____ worst possible pain

2. Difficulty speaking because of mouth* sores

no trouble speaking _____ impossible to speak

3. Restriction of speech because of mouth* sores

no restriction of speech _____ complete restriction of speech

4. Difficulty eating hard foods (hard bread, potato chips etc) because of mouth* sores

no trouble eating hard foods _____ impossible to eat hard foods

5. Difficulty eating soft foods (Jello, pudding etc) because of mouth* sores

no trouble eating soft foods _____ impossible to eat soft foods

6. Restriction of eating because of mouth* sores

no restriction of eating _____ complete restriction of eating

7. Difficulty drinking because of mouth* sores

no trouble drinking _____ impossible to drink

8. Restriction of drinking because of mouth* sores

no restriction of drinking _____ complete restriction of drinking

9. Difficulty swallowing because of mouth* sores

not difficult to swallow _____ impossible to swallow

10. Change in taste

no change in taste _____ complete change in taste

I have taken pain medication today. Yes No

The name of your pain medication: _____

What is the dose you are taking? _____

How do you take your pain medication? (for example, by mouth, by patch, by injection) _____

How often do you take your pain medication? (for example, once a day, twice a day)

PERFORMANCE STATUS SCALE FOR HEAD AND NECK CANCER PATIENTS: PSS-HN

Patient Name _____ ID# /__/__/__/__/__/__/__/__/ Date /__/__/__/__/__/__/

NORMALCY OF DIET /__/__/__/

100	Full diet (no restrictions)
90	Full diet (liquid assist)
80	All meat
70	Raw carrots, celery
60	Dry bread and crackers
50	Soft chewable foods (e.g., macaroni, canned/soft fruits, cooked vegetables, fish, hamburger, small pieces of meat)
40	Soft foods requiring no chewing (e.g., mashed potatoes, apple sauce, pudding)
30	Pureed foods (in blender)
20	Warm liquids
10	Cold liquids
0	Non-oral feeding (tube fed)

PUBLIC EATING /__/__/__/

100	No restriction of place, food or companion (eats out at any opportunity)
75	No restriction of place, but restricts diet when in public (eats anywhere, but may limit intake to less "messy" foods (e.g., liquids)
50	Eats only in presence of selected persons in selected places
25	Eats only at home in presence of selected persons
0	Always eats alone
999	Inpatient

UNDERSTANDABILITY OF SPEECH /__/__/__/

100	Always understandable
75	Understandable most of the time; occasional repetition necessary
50	Usually understandable; face-to-face contact necessary
25	Difficult to understand
0	Never understandable; may use written communication

List MA, Ritter-Sterr C, Lansky SB. A Performance Status Scale for Head and Neck Cancer Patients. Cancer. 66:564-569, 1990

NCI CTCAE v4.0 mucositis oral

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Oral mucositis	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain, not interfering with oral intake; modified diet indicated	Severe pain, interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death

Oral mucositis is characterized by inflammation of the oral mucosa.

NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

Reproduced from: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, June 2010, National Institutes of Health, National Cancer Institute. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (Accessed October 22, 2013).

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, what was the SEVERITY of your DIFFICULTY SWALLOWING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

2.	In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

3.	In the last 7 days, what was the SEVERITY of SKIN CRACKING AT THE CORNERS OF YOUR MOUTH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

4.	In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

5.	In the last 7 days, how OFTEN did you have PAIN?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

Do you have any other symptoms that you wish to report?	
○ Yes	○ No

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

Please list any other symptoms:

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe