CLINICAL STUDY PROTOCOL

Protocol No.	**PR-001**
Product	RRx-001
Title:	PREVLAR: A Phase 2a Randomized, Parallel Group, Open-Label, Multicenter Study to Assess the Safety and Efficacy of Different Schedules of RRx-001 in the Attenuation of Oral Mucositis in Patients Receiving Concomitant Chemoradiation for the Treatment of Locally Advanced Squamous Cell Carcinomas of the Oral Cavity or Oropharynx
Development Phase	Phase 2a
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Amendment No.	Amendment 01
Sponsor:	EpicentRx, Inc. 11099 North Torrey Pines Road, Suite 160 La Jolla, CA 92037
Sponsor's Medical Contact:	Bryan Oronsky, MD Chief Medical Officer Email: boronsky@epicentrx.com Phone: 408-569-3202

INVESTIGATOR AGREEMENT PAGE

EpicentRx, Inc.

Protocol No. PR-001,
PREVLAR: A Phase 2a Randomized, Parallel Group, Open-Label, Multicenter Study to Assess the Safety and Efficacy of Different Schedules of RRx-001 in the Attenuation of Oral Mucositis in Patients Receiving Concomitant Chemoradiation for the Treatment of Locally Advanced Squamous Cell Carcinomas of the Oral Cavity or Oropharynx

June 04, 2018

I will provide copies of the protocol, any subsequent protocol amendments and access to all information provided by the Sponsor to the study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational drug and the study protocol.

I agree to conduct this clinical trial according to the attached protocol, except when mutually agreed to in writing. I also agree to conduct this study in compliance with all federal, state and local regulations, as well as with the requirements of the appropriate Institutional Review Board and any other institutional requirements.

_____ _____

Principal Investigator **Date**

Printed Name: _____

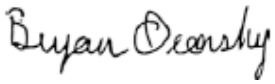
Institution: _____

PROTOCOL APPROVAL PAGE

TITLE: PREVLAR: A Phase 2a Randomized, Parallel Group, Open-Label, Multicenter Study to Assess the Safety and Efficacy of Different Schedules of RRx-001 in the Attenuation of Oral Mucositis in Patients Receiving Concomitant Chemoradiation for the Treatment of Locally Advanced Squamous Cell Carcinomas of the Oral Cavity or Oropharynx

SPONSOR:

EpicentRx, Inc.
11099 North Torrey Pines Road, Suite 160
La Jolla, CA 92037



Bryan Oronsky, M.D. **Date** 04 June 2018

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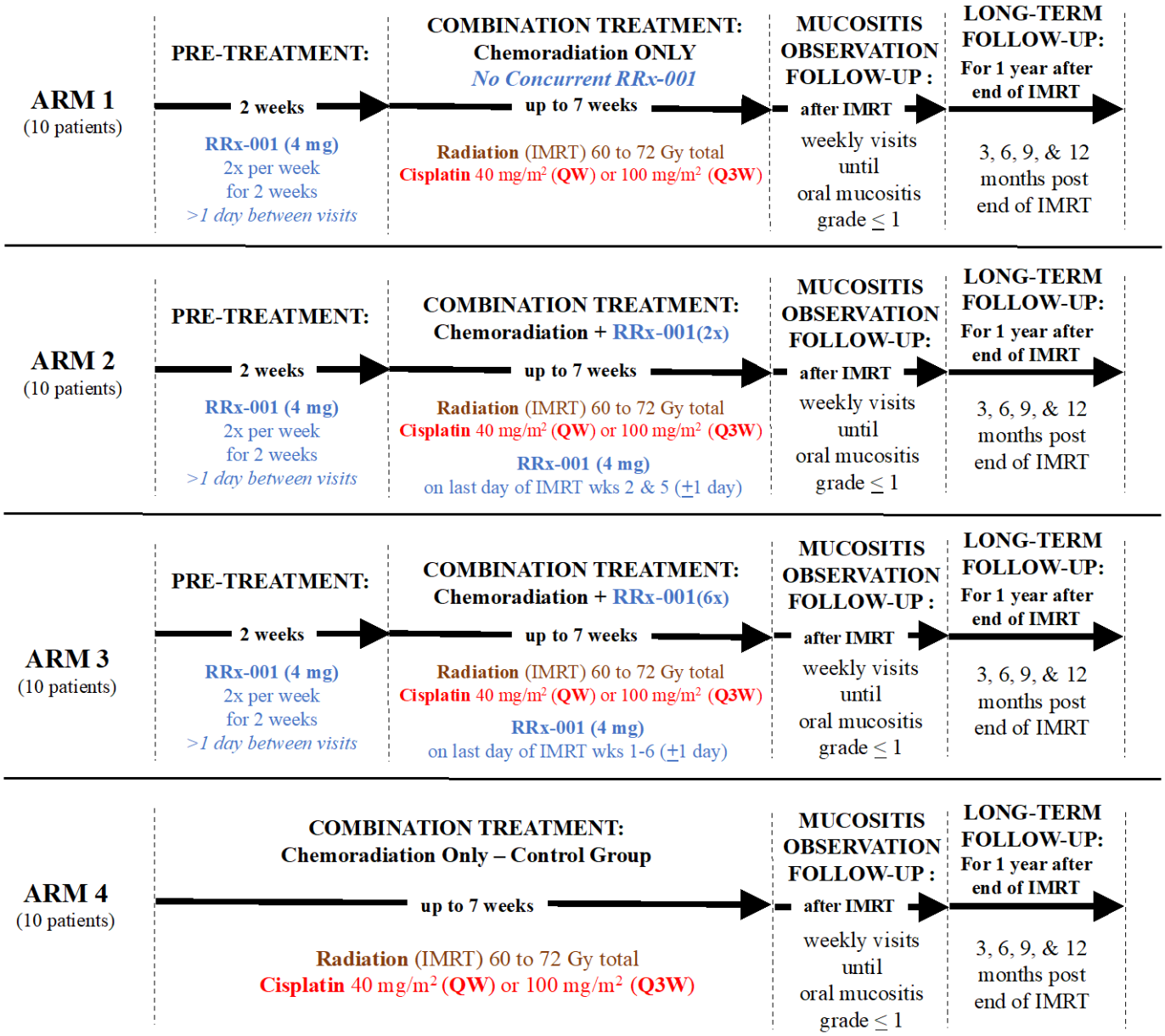
LIST OF ABBREVIATIONS

AABB	American Association of Blood Banks
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BID	Twice a day
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CRT	Chemo-Radiation Therapy
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DDP	Cis-diamminedichloridoplatinum (cisplatin)
DLT	Dose Limiting Toxicity
DMA	N, N-Dimethylacetamide
ECOG	Eastern Cooperative Oncology Group
HNC	Head and Neck Cancer
HRPP	Human Research Protections Program
IMRT	Intensity-Modulated Radiation Therapy
IRB	Institutional Review Board
NCCN	National Comprehensive Cancer Network
NYHA	New York Heart Association
OM	Oral Mucositis
OS	Overall Survival
PET	Positron Emission Tomography
POC	Proof-of-Concept
q.d.	quaque die/every day
RBC	Red Blood Cell
SAE	Serious Adverse Event
SD	Standard Deviation
SOM	Severe Oral Mucositis
TEAE	Treatment Emergent Adverse Events
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO	World Health Organization

1 STUDY SCHEMA AND ASSESSMENTS

1.1 Treatment Schemas



1.2 Schedule of Assessments Table

Procedures	Screening	Pre-Treatment		Combination Treatment							Mucositis Observation Follow-up	28 Day Post IMRT Safety Visit[17]	Long-Term Follow-Up[18]			
		Wk -2	Wk -1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7[16]	weekly (until OM grade ≤ 1)		3 mo post RT	6 mo post RT	9 mo post RT	12 mo post RT
	≤ 28 Days of Tx Start	D1 ±2d	D8 ±2d	D15 ±2d	D22 ±2d	D29 ±2d	D36 ±2d	D43 ±2d	D50 ±2d	D57 ±2d	following end of IMRT	28 days post end of IMRT +5 days	± 7 days	± 14 days	± 14 days	± 14 days
Informed Consent	X															
Demographics	X															
Medical & Onc History[1]	X															
Dental Assessment[2]	X															
Laryngopharyngoscopy[3]	X										X	X	X	X	X	X
Audiogram[4]	X															
Physical Exam[5]	X	X	X	X	X	X	X	X	X	X	X	X				
Oral Mucositis Assessment (WHO, CTCAE)[6]	X	X		X	X	X	X	X	X	X	X	X				
Oral Mucositis Daily Questionnaire (OMDQ)[7]	X			X	X	X	X	X	X	X	X	X				
Oral Routine Assessment[8]			X													
Vital Signs	X	X	X	X	X	X	X	X	X	X						
ECOG Status	X	X	X	X	X	X	X	X	X	X	X	X				
Lab Assessments[9]	X	X	X	X	X	X	X	X	X	X		X				
Pregnancy Test[10]	X															
Adverse Events		X	X	X	X	X	X	X	X	X	X	X				
Concomitant Medications & Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest CT or PET/CT[11]	X										X[11]					
CT, MRI, or PET/CT of tumor site & neck nodes[12]	X										X[12]					
RRx-001 Administration[13]		X[13]														
Cisplatin Administration[14]				X	X	X	X	X	X	X						
Radiation Therapy (IMRT)[15]				X	X	X	X	X	X	X						

Schedule of Assessments Table Footnotes

1. Record patient cancer and medical history as well as previous oral history (i.e. previous occurrences of oral mucositis, history of smoking, alcohol consumption, dry mouth (xerostomia), chewing tobacco usage, and dental history).
2. Dental Assessment: ENT examination recommended during screening to perform dental assessment.
3. Laryngopharyngoscopy: mirror (indirect laryngopharyngoscopy) and/or fiberoptic (direct laryngopharyngoscopy) procedure is recommended at these time points but is not required (at discretion of treating physician).
4. Audiogram: Recommended within 84 days of starting treatment but is not required.
5. Physical Exams:
   - A *full* physical exam must be performed during screening (including: ECOG status, swallowing assessment and assessment for PEG Tube), and during Combination Treatment week 1 and at the 28 Day Safety Visit (post treatment).
   - A *brief* physical exam, to include ECOG status, by a Radiation Oncologist and/or Medical Oncologist and/or ENT or Head & Neck Surgeon must be done weekly during Pre-Treatment, Combination Treatment, and during the Mucositis Observation Follow-up until OM grade ≤ 1 is achieved.
6. Oral Mucositis Assessment will be performed by a trained on-site assessor at screening, day 1 prior to start of RRx-001 pretreatment, day 15 prior to the start of Combination Treatment (chemoradiation), twice a week (no less than 48 hours apart) during Combination Treatment (weeks 1 - 7), and once each week on the same day (±1 day) during the Mucositis Observation Follow-up until an OM grade ≤ 1 is achieved. Lesions will be scored by a central assessor according to WHO (Appendix C) and WHO grade assessment will be communicated back to site study team by the central assessor.
7. Oral Mucositis Daily Questionnaire (OMDQ) to be completed in clinic at screening and then daily in the provided OMQD Booklet starting Week 1 (protocol Day 15) of combination treatment, continuing through the Mucositis Observation Follow-up until an OM grade ≤ 1 is achieved. See Appendix D.
8. Record current oral routines (i.e. smoking and chewing tobacco) at screening. If oral routines change, please update oral assessment accordingly. Review patient oral care instructions (Appendix G) and dispense oral hygiene kit following enrollment and prior to start of chemoradiation.
9. Lab Assessments include a Complete Blood Count (CBC) with differential, a Complete Metabolic Panel (CMP), magnesium and phosphate: to be performed at screening, weekly during Pre-Treatment, Combination Treatment, 28 Day Safety Visit, and as clinically indicated per institutional guidelines. CMP to include: sodium, potassium, glucose, calcium, albumin, bilirubin, ALT, AST, and Alk Phos.
10. Negative serum or urine pregnancy test required within 14 calendar days prior to start of treatment for women of childbearing potential.
11. Chest CT scan, or PET/CT scan, must be done within 42 calendar days prior to starting treatment to rule out metastatic disease. Chest CT scan, or PET/CT scan, imaging during Long-Term Follow-Up to be performed per institutional standards and assessed via RECIST v1.1 until progression (PD) or start of next cancer directed therapy or 12 month post RT visit, whichever occurs first. When measurable disease is not present (e.g. post-operative patients), RECIST v1.1 assessment is not performed until measurable disease presents (considered PD) or start of next cancer directed therapy.
12. CT scan, MRI, or PET/CT scan of the tumor site and neck nodes must be done within 42 calendar days prior to starting treatment. Note: The CT scan of the neck and/or PET/CT performed for radiation planning may serve as both staging and planning tools. Imaging evaluations of the primary tumor and neck should be performed via institutional standards and assessed via RECIST v1.1 until progression or start of next therapy. When measurable disease is not present (e.g. post-operative patients), RECIST v1.1 assessment is not performed until measurable disease presents (considered PD) or start of next cancer directed therapy. The post-radiation imaging can be contrast enhanced CT, MRI, or PET/CT of the head and neck, or whole body PET/CT (minimum neck and chest), based on the preference of the treating clinician.
13. Administration of RRx-001 to be performed according to the schema Section 1.1 and Section 8.1.2, with pre-medications as described in the pre-medications Section 8.1.5.
14. For Cisplatin dosage, refer to Section 8.2.
15. Radiation Therapy (IMRT) will consist of single daily fractions of 2.0 to 2.2 Gy with a cumulative radiation dose between 60 Gy and 72 Gy, lasting 6 to 7 weeks in duration.
16. Combination Treatment will be a duration of 6 to 7 weeks depending on IMRT fractionated scheduling. The Mucositis Observation Follow-up day 1 is the day following the last dose of IMRT.
17. A 28 Day Safety Visit will occur 4 weeks (28 days) post last dose of radiation treatment (+5 day window). If the patient has an OM grade ≥ 2, patient will continue with the Mucositis Observation Follow-up weekly visits until an OM grade of ≤ 1 is achieved. If the patient finished Combination Treatment with an OM grade ≤ 1, the patient will return to clinic 28 days post IMRT (+ 5 days) for this 28 Day Safety Visit. Once the patient is assigned an OM grade ≤ 1 and has completed the 28 Day Safety Visit, the patient will proceed into Long Term Follow Up.
18. Long-Term Follow-Up may be performed via chart review. All procedures performed during the follow-up period should be recorded as Concomitant Procedures. Patients should continue to be followed monthly if experiencing an adverse event related to the investigational agent of RRx-001 until resolution, or event is assessed as a grade ≤ 2.

2 STUDY SUMMARY

Title	PREVLAR: A Phase 2a Randomized, Parallel Group, Open-Label, Multicenter Study to Assess the Safety and Efficacy of Different Schedules of RRx-001 in the Attenuation of Oral Mucositis in Patients Receiving Concomitant Chemoradiation for the Treatment of Locally Advanced Squamous Cell Carcinomas of the Oral Cavity or Oropharynx
Phase	Phase 2a
Patient Population	Pathologically-confirmed diagnosis of squamous cell carcinoma (SCC) of the oral cavity or oropharynx planned to be treated with cisplatin plus concurrent IMRT Note: Patients with unknown HPV positive primary tumors (SCC) whose treatment plan matches the requirements specified in Inclusion Criteria #2 below are eligible for the trial
Objectives	Safety: To assess the safety and tolerability of varying dosing schedules of RRx-001 during treatment and for 28 days following end of IMRT. To assess the long-term effect of RRx-001 on tumor response to standard concomitant chemoradiation. Efficacy: To assess the efficacy of RRx-001 in the attenuation of severe oral mucositis (SOM) in patients receiving cisplatin and radiation therapy for the treatment cancers of the oral cavity or oropharynx.
Number of Patients	Approximately 40 evaluable patients
Study Design	This is a Phase 2a, randomized, open-label, parallel group trial to assess the safety and efficacy of three schedules of RRx-001 compared to standard of care in patients receiving a standard regimen of tri-weekly cisplatin plus concomitant IMRT in patients being treated for cancers of the oral cavity or oropharynx. Patients meeting the eligibility criteria and consenting to participate will be randomized 1:1:1:1 to one of the three regimens of RRx-001 or a control (~10 patients per arm) with 1 stratification factor (two levels: oral cavity or oropharynx): Arm 1: "RRx-001 Pre-Treatment + SOC Chemoradiation" Two infusions of RRx-001 will be given each week during the two weeks prior to the start of chemoradiation (four doses total). No additional RRx-001 will be given during chemoradiation. Arm 2: "RRx-001 Pre-Treatment + 2 Concurrent Doses + SOC Chemoradiation" Two infusions of RRx-001 will be given each week during the two weeks prior to the start of chemoradiation. In addition, one dose of RRx-001 will be given on the last radiation day in each of weeks 2 and 5 during chemoradiation Arm 3: "RRx-001 Pre-Treatment + 6 Concurrent Doses + SOC Chemoradiation" Two infusions of RRx-001 will be given each week during the two weeks prior to the start of chemoradiation. In addition, one dose of RRx-001 will be given on the last radiation day of each of the first 6 weeks during chemoradiation Arm 4: "SOC Chemoradiation Only (Control)" No doses of RRx-001 will be administered. Patients assigned to this arm will receive only standard of care chemoradiation

	All patients will receive standard of care (SOC) chemoradiation in the form of a 7-week course of fractionated radiation therapy concurrent with a QW or Q3W cisplatin regimen. Cisplatin should not be given within 24 hours of RRx-001 administrations. All doses of RRx-001 will be given at 4 mg per infusion. Administration of RRx-001 will not be blinded, so patient and study staff may be aware of the treatment assignment. The study will be performed in four stages: 1. Screening phase (≤ 4 weeks before randomization). Patients assessed for eligibility. 2. Pre-Treatment and Combination Treatment dosing periods. This will consist of the time beginning two weeks prior to the start of chemoradiation (Pre-Treatment) and ending on the last day of radiation therapy (LDRT). A baseline assessment will be performed on the first day of RRx-001 administration. 3. Post Treatment "Mucositis Observation Follow-up". This will consist of the time from the end of IMRT until ulcerative oral mucositis grade is ≤ 1 (WHO scale) 4. Long-term follow-up will consist of the 12 months from the LDRT. Patients will be followed for safety endpoints throughout the study. Patients will be evaluated for the presence and severity of oral mucositis during the course of chemoradiation and following end of treatment until oral mucositis grade is ≤ 1. During the combination treatment period (until end of radiotherapy), mucositis severity will be assessed twice weekly by trained evaluators. Following the end of radiotherapy (known as the "Mucositis Observation Follow-up"), mucositis will be assessed once weekly until resolution (WHO grade 0 or 1) of ulcerative mucositis. Patients in the study will be followed for one year following radiotherapy (IMRT), in order to evaluate long-term safety and tumor outcomes.
Eligibility Criteria (Inclusion and Exclusion)	Inclusion Criteria 1. Pathologically confirmed diagnosis of squamous cell carcinoma (SCC) of the oral cavity and oropharynx Note: Patients with unknown primary tumors whose treatment plan matches the requirements specified in Inclusion Criterion #2 below are eligible for the trial 2. Treatment planned to include standard cisplatin monotherapy administered either every three weeks (100 mg/m^2 for 3 doses) or weekly (40 mg/m^2 for 7 doses) with concomitant radiation delivered as a continuous course of IMRT with single daily fractions of 2.0 to 2.2 Gy with a cumulative radiation dose between 60 Gy and 72 Gy. Planned radiation treatment fields must include at least two oral sites (buccal mucosa, floor of mouth, tongue, soft palate) that are each planned to receive a total of > 55 Gy. Patients who have had prior surgery are eligible, provided they have fully recovered from surgery, and patients who may have surgery in the future are eligible. 3. ECOG performance status ≤ 2. 4. Participants must have adequate organ and marrow function as defined below: A. Absolute neutrophil count (ANC) ≥ 1,500 / mm^3 B. Platelets ≥ 100,000 / mm^3 C. Hemoglobin ≥ 9.0 g/dL 5. Adequate renal and liver function as indicated by: A. Serum creatinine acceptable for treatment with cisplatin per institutional guidelines) B. Total bilirubin ≤ 1.5 x upper-normal limit (ULN) C. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN D. Alkaline phosphatase ≤ 2.5 x ULN

	6. Human papilloma virus (HPV) status in tumor has been documented using tumor immunohistochemistry for HPV-p16 or other accepted test for patients with cancers of the oropharynx, base of tongue, or unknown primary. 7. Age 18 years or older 8. Patient must consent to the access, review and analysis of previous medical and cancer history, including imaging data by the sponsor or a third party nominated by the sponsor. 9. Ability to understand and sign a written informed consent document. 10. Women of child-bearing potential and men with partners of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 90 days following completion of therapy. Note: A woman of child-bearing potential is any female (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria: • Has not undergone a hysterectomy or bilateral oophorectomy; or • Has not been postmenopausal for at least 12 consecutive months 11. Adequate visual access to permit examination of the following oral cavity sites: lips, buccal mucosa, floor of mouth, ventral and lateral tongue and soft palate. <u>Exclusion Criteria</u> 1. Prior radiation to the head and neck 2. Prior induction chemotherapy 3. Tumor of the lips, nasopharynx, hypopharynx, larynx, or salivary glands 4. Patients with simultaneous primaries 5. Stage IV, M1 (distant metastasis) 6. Malignant tumors other than HNC within the last 5 years, unless treated definitively and with low risk of recurrence in the judgment of the treating investigator 7. Presence of oral mucositis (WHO Score ≥ Grade 1) or other oral mucosal ulceration at study entry 8. Grade 3 or 4 dysphagia or odynophagia (National Cancer Institute Common Toxicity Criteria, version 5.0) or inability to eat a normal diet 9. Requirement at baseline for parenteral or gastrointestinal tube-delivered nutrition for any reason. Prophylactic placement is allowed. 10. Known history of HIV or active hepatitis B/C (patients who have been vaccinated for hepatitis B and do not have a history of infection are eligible) 11. Any significant medical diseases or conditions, as assessed by the investigators and sponsor that would substantially increase the medical risks of participating in this study (i.e., uncontrolled diabetes, NYHA II-IV congestive heart failure, myocardial infarction within 6 months of study, severe chronic pulmonary disease or active uncontrolled infection, uncontrolled or clinically relevant pulmonary edema). 12. Pregnant or nursing 13. Untreated active oral or dental infection 14. Known allergies or intolerance to cisplatin and similar platinum-containing compounds 15. Evidence of immediate life-threatening disease or a life expectancy of less than 3 months 16. Receipt of unapproved or off-label medication within 30 days prior to start of study treatment, including use of an investigational agent 17. Sjogren syndrome

Statistical Methods	Safety Endpoints: • Incidence of adverse events, including serious adverse events (SAEs) and clinically significant laboratory abnormalities. • Overall tumor response to treatment using RECIST or site preference criteria. Efficacy Endpoints: • Duration (in days) of severe oral mucositis (SOM, WHO grades 3 or 4) • Time (in days) to onset of SOM • Incidence of SOM • Incidence and duration of ulcerative mucositis (WHO grades 2, 3, 4) • Patient-reported mucositis pain as measured by question 2 of the Oral Mucositis Daily Questionnaire Design: This is a randomized, open-label, parallel group, Phase 2 study to assess the safety and radioprotective potential of RRx-001 in patients undergoing chemoradiation therapy for locally advanced head and neck cancer. A total of approximately 40 patients will participate in this study. All patients will receive standard chemoradiation therapy consisting of cisplatin either every three weeks (100 mg/m^2 for 3 doses) or weekly (40 mg/m^2 for 7 doses) + radiotherapy (IMRT) administered daily (except weekends) for 7 weeks. In conjunction with this "standard of care" (SOC), patients will be randomly assigned to receive one of 3 regimens of RRx-001 or a control (no treatment). Sample Size: A sample size of approximately 40 patients (~10 per group) is considered adequate for this proof-of-concept (POC) study to explore the radioprotective potential of RRx-001 and identify a safe regimen for further development. Statistical Methods: Efficacy and safety data will be summarized using descriptive statistics, including the mean, standard deviations, median, minimum and maximum for continuous endpoints and frequency tables for categorical data. Efficacy Analysis: Hypothesis testing of efficacy endpoints will be performed for exploratory purposes only. For continuous efficacy endpoints, non-parametric methods will be used to compare each RRx-001 group to the untreated control group (Wilcoxon rank-sum tests). Fisher's exact test will be used to evaluate treatment differences for binary outcomes. Two-sided 95% confidence intervals will be calculated for proportions using the Clopper-Pearson method. Safety Analysis: Safety data, including adverse events (AEs), serious adverse events (SAEs), ECOG performance status, clinical laboratory tests, vital signs and physical examination results will be listed and summarized descriptively by treatment group. Adverse events will be coded by system organ class (SOC) and preferred term using MedDRA (Version 18.1), and severity will be based on NCI CTCAE Grade criterion (Version 5.0). Descriptive statistics (sample size, mean, median, standard deviation, quartiles and range) and graphical methods (longitudinal plots) will be used to present change from pre-treatment values in laboratory parameters during the treatment period. The incidence of febrile neutropenia, bacterial infections, grade 3 or 4 cervicofacial dermatitis, and other toxicities of clinical interest (xerostomia, trismus, fatigue, weight loss, radiation dermatitis, and dysgeusia) will be tabulated by treatment arm.

3 INTRODUCTION AND RATIONALE

3.1 Mucositis in Head and Neck Cancer Patients Treated with Radiotherapy and Systemic Chemotherapy

Worldwide, head and neck cancer is the sixth most common form of the disease with over 500,000 new cases this year. In the United States, head and cancers account for approximately 3% of all cancers with over 60,000 new cases anticipated this year. Of those, the overwhelming majority will be tumors of the mouth and oropharynx. Historically, tobacco and alcohol use is the major risk factor for the most common histologic subtype (90%), squamous cell carcinoma (HNSCC). However, over recent decades the predominant pathoetiology of HNC has shifted from carcinogen-induced mucosal transformation to HPV-mediated cancer. This shift has impacted the clinical presentation, epidemiology, management and prognosis of the disease. Firstly, unlike tobacco-related HNSCC, which presents in the oral cavity (tongue/floor of mouth), HPV-related cancers mainly develop from the oropharynx. Secondly, HPV-driven tumors tend to affect a significantly younger patient population with less extensive tobacco exposure and a better performance status compared to HPV-negative tumors, thereby incentivizing more aggressive "curative" treatment. Thirdly, HPV-related cancers are significantly more treatment-responsive than tobacco-associated squamous cell cancers of the head and neck, which may tip the balance in favor of non-surgical management. And, finally, HPV imparts a better prognosis in terms of tumor control and survival.

Regardless of the etiology, the vast majority of patients with locally invasive cancers of the mouth or oropharynx are treated with concomitant chemoradiation, a combination that is superior to radiation alone since chemotherapy increases the susceptibility of the tumor cell to radiation-induced lysis. For locally advanced disease (Stages II-IVB), the standard of care is concurrent chemoradiation therapy in lieu of or in addition to surgery. Conventional fractionation for concurrent chemoradiation is up to 70 Gy (2.0 Gy/fraction; daily Monday-Friday in 7wk). Cisplatin, given as a radiosensitizer, is typically administered in one of two regimens: either every three weeks during radiation (100 mg/m^2) or weekly as a lower dose (40 mg/m^2). Recent data suggests that the higher dose regimen has better survival benefit.

Oral mucositis is among the most common and devastating acute toxicities associated with radiation therapy to the head and neck. The characteristic ulcerative lesions, which occur on the oropharyngeal mucosa included in the radiation fields are associated with progressive, unrelenting pain that profoundly impacts quality of life in multiple dimensions. As a case in point, the poem below, written by a patient with mucositis, vividly and graphically communicates the extreme suffering due to mucositis, forcing the reader to vicariously experience the horribly sadistic details through the writer's pain-distorted perceptions of teeth, touch and taste:

A fish hook lodges in my throat.
Spittle, kindergarten paste, thickens everything – even vision.
Mouth, pocked with sores & blisters, swollen ulcerated tongue.
Topside, sandpapered with number 7 coarsest grade.

Taste buds, saliva glands, seared.
Cool water, corrosive acid now.
The tongue rests; teeth become enemies.
Coiled steel razored wire atop dentate prison walls.
Only moans escape my lips. I cannot eat or speak.
Inside a howl festers.
Pain lengthens time.

Anita Hart Balter (NEJM 1990)

Due to the severe oral morbidity, mucositis may impact the ability to eat normally. Consequently, changes to liquid-based diets are common and, in about a quarter of cases, percutaneous feeding via a gastrostomy feeding tube and/or parenteral nutrition is required. Ulcerative mucositis is a significant cause of unscheduled chemoradiation treatment breaks, typically lasting a week, which may improve palliation at the expense of survival. In granulocytopenic patients, oral mucositis is a potential site of secondary infection and portal of entry for the indigenous oral flora, often leading to bacteremia and sepsis. Finally, mucositis drives healthcare resource use and costs through emergency room visits, surgical insertion of feeding tubes and hospitalizations. It is not surprising that the incremental cost of mucositis exceeds $17,000 per patient. Despite its high clinical and economic burden, an approved interventional agent for radiation-induced mucositis is not yet available.

Patients with radiation-induced mucositis generally show highly consistent clinical courses. Concomitant chemotherapy increases both the risk and severity of mucositis. Signs and symptoms typically begin by the completion of the first week of treatment (cumulative radiation dose of 10 Gy) and consist primarily of mucosal erythema and symptoms akin to a burned mouth from hot food or drink that are easily controlled with standard OTC pain medications. At cumulative radiation doses of 20 Gy to 30 Gy, the integrity of the mucosa breaks down and mucosal ulcerations that are usually limited to the movable mucosa (the more keratinized epithelium of the hard palate, dorsal tongue and gingiva are unaffected), occur. Unlike common oral ulcers like aphthous stomatitis, the ulcers associated with mucositis are irregular, deep and disproportionately painful, requiring more aggressive symptom management such as the use of narcotic analgesia. Ulceration severity usually peaks at radiation doses of around 50 Gy (end of week 5). The lesions expand and become confluent. Breakthrough pain, even with morphine or fentanyl is not uncommon. Lesions typically heal spontaneously after 2-4 weeks following the cessation of radiation therapy.

A variety of scales are used to assess mucositis severity, of these, the WHO scale is the most consistent and widely used. This scale, which has been effectively used in clinical trials, is based on a combination of functional (ability to eat) and objective (presence of ulceration or erythema) criteria. WHO scores correlate with patient-reported outcomes, analgesic use and resource use. Other available scales include RTOG and NCI-CTCv5, which have evolved to contain elements that are similar to WHO criteria.

Concepts of the pathogenesis of mucositis have undergone dramatic revisions from Sonis' original hypothesis in 1998 of epithelial injury due to direct clonogenic cell death of epithelial

stem cells to a complex biologic process involving oxidative stress and immune activation that culminates in epithelial apoptosis, atrophy, ulceration and healing [Sonis 1998].

To date, palifermin (KGF1), a pleiotropic growth factor, is the only agent approved for mucositis and its use is limited to patients receiving stomatotoxic conditioning regimens prior to hematologic stem cell transplant. Despite an active developmental pipeline of compounds to prevent and/or treat OM, which includes dusquetide, an immunomodulatory peptide, GC4419, a dismutase mimetic, brilacidin, a defensin mimetic, current treatment options are mainly limited to topical barrier devices for symptom management, opioid and NSAID analgesics, ice chips (cryotherapy) and oral rinses such as "magic mouthwashes" that vary in composition depending on institutional folklore. None of these approaches has adequately mitigated the clinical development of mucositis or its symptoms. Thus, the degree of the unmet need in mucositis is related to the severity of symptoms and the lack of an approved treatment regimen, which, if addressed, would substantially improve quality of life and treatment outcomes for head & neck cancer patients.

The rationale for this trial is that RRx-001, as a systemically non-toxic putative dual radiochemoprotector/sensitizer with activity in multiple tumors types including small cell carcinoma of the oral cavity, will protect the normal mucosa but not the tumor and delay the duration of oral toxicity.

3.2 Nonclinical Studies

3.2.1 RRx-001 Antitumor Activity

RRx-001 is a novel anticancer agent of the dinitroazetidine class that has demonstrated selectivity of action in tumor cells versus normal tissues, and inhibition of tumor growth *in vivo* with minimal toxicity [Das 2016; Ning 2012]. The activity of RRx-001 is thought to be associated with a nucleophilic substitution by circulating thiol compounds and covalent binding of RRx-001 to cysteinyl residues in red blood cell hemoglobin. This binding event is responsible for the autooxidation of hemoglobin and the generation of reactive oxygen and nitrogen species (RONS) inside red blood cells (RBCs) [Reid 2015]. Nitro-oxidative stress leads to plasma membrane translocation of phosphatidylserine (PS), which in turn is involved in PS-mediated erythrocyte adhesion to the hypoxic tumor vasculature. Allosteric modification of hemoglobin by the RRx-001 adduct catalyzes the reduction of nitrite to nitric oxide under these hypoxic conditions and normalizes the tumor vasculature, resulting in improved tumor oxygenation and response to radiation treatment [Brouse 2015]. Endocytosis of RRx-001-adducted red blood cells by tumor associated macrophages induces polarization to the M1 phenotype and immunosensitization via release of inflammatory chemokines and cytokines [Oronsky 2017a].

3.2.2 RRx-001 Combination with Cisplatin

The effects of combined treatment of RRx-001 and cisplatin were evaluated. Mice received vehicle or RRx-001 via intravenous injection at 5 mg/kg for 3 times, once every 48 hours prior to receiving intraperitoneal injection of cisplatin 2 mg/kg for 5 times, once every other day. Pretreatment with RRx-001 significantly attenuated the cisplatin-induced reduction in hematological parameters (hemoglobin concentration, leukocyte count and platelet count) indicative of protection against these toxic effects in bone marrow. In addition, there was a trend

toward reduction in cisplatin-induced renal toxicity with apparent attenuation of increases in serum creatinine and blood urea nitrogen levels. When the combination was tested in mice bearing sarcoma 180 tumors, RRx-001 treatment appeared to attenuate the body weight loss caused by cisplatin but did not diminish antitumor efficacy [Oronsky 2017b].

3.2.3 RRx-001 Radiosensitization of Tumor Cells

When combined *in vitro* with radiation, RRx-001 (1 μM) shifted the radiation survival curves of tumor cell lines downward. The radiation survival at 2Gy was decreased from 72% to 12% in HT29 cells and from 89% to 1.4% in SCC VII cells. At 10Gy, RRx-001 further decreased the radiation survival from 1.3% to 0.07% for HT29 cells and from 3.3% to 0.03% in SCC VII cells. The radiation dose modifying factors (DMFs) of RRx-001 were 1.7 and 1.6 at 10% survival for HT29 and SCC VII cells, respectively. The *in vivo* radiosensitizing properties of RRx-001 were demonstrated in mice bearing SCC VII tumor xenografts. Tumor-bearing mice were treated with either 5 mg/kg RRx-001 i.p. daily for 5 days or local tumor irradiation of 250 cGy for 5 days or both. Either radiation alone or RRx-001 alone inhibited tumor growth and produced tumor growth delay (TGD) times of 3.2 ± 1.8 days and 1.8 ± 0.6 days, respectively. The combination of radiation and RRx-001 resulted in a statistically significant lengthening TGD time of 7.0 ± 2.1 days. Higher daily doses of radiation (400 cGy) and RRx-001 (6 mg/kg) enhanced the therapeutic efficacy of radiotherapy and prolonged the TGD time from 7.9 ± 2.4 days for radiation alone to 13.9 ± 1.9 days for combination therapy. Each combination regimen did not cause a significant decrease in animal body weight compared with untreated control mice or radiation-treated mice [Ning 2012].

3.2.4 RRx-001 Radioprotection of Normal Cells

Mice were treated with vehicle or RRx-001 10 mg/kg i.p. 24 hours prior to irradiation (9.35 Gy delivered at 0.6 Gy/min). Survival was evaluated over 30 days post-exposure and was significantly increased in the RRx-001-treated mice, 67% compared to 33% in vehicle-treated mice ($p<0.005$). In addition, RRx-001-treated mice showed accelerated recovery of bone marrow cellularity and Colony Forming Units compared to vehicle-treated mice after a sublethal total body radiation exposure (7 Gy delivered at 0.6 Gy/min) (Jurgensen et al., 2017 Radiation Research Society). In another study, RRx-001 treatment enhanced intestinal stem cell (crypt cell) survival and regeneration in mice that were exposed to total body irradiation of 10-15 Gy in combination with RRx-001 (10 mg/kg i.p.) as compared to mice treated with radiation alone [Scicinski 2015].

3.2.5 RRx-001 Toxicology

Repeated-dose toxicity studies of RRx-001 (3 times/week up to 4 weeks in duration) were conducted in rats at dose levels of 12, 20.1 and 30 mg/kg per day and in dogs at dose levels of 4, 8 and 12 mg/kg per day (due to clinical signs the 8 and 12 mg/kg doses were reduced to 3 and 5 mg/kg on Day 4). The no observed adverse effect level (NOAEL) was < 12 mg/kg in rats and 5 mg/kg in dogs. Target organs of RRx-001 in rats were spleen and lungs. Effects on lungs were observed in dogs. RRx-001 was genotoxic in the *in vitro* bacterial reverse mutation assay.

3.3 Clinical Experience with RRx-001

3.3.1 Safety

To date, based on the sum of the data from 9 total Phase 1 and Phase 2 trials, RRx-001 is well tolerated over time with a consistently favorable safety profile in which the majority of serious adverse events are cancer-related. The two main (and arguably the only) RRx-001 related adverse events are: 1) non-dangerous infusion site reactions and 2) immune-mediated pseudoprogression or tumor flare, which is generally a favorable sign despite the potential for transient tumor enlargement. A total of approximately 220 patients with cancer have been treated with RRx-001 either alone or in combination with chemotherapy, radiotherapy or chemoradiotherapy over a timespan of approximately 6 years.

As a single agent, the majority of treatment-emergent adverse events, besides local infusion pain, which has since largely resolved with co-infusion of autologous blood, have resulted from disease progression or intercurrent illness. No evidence of drug-related organ damage (hepatotoxicity, cardiotoxicity, renal toxicity, pulmonary toxicity or bone marrow suppression) or clinically relevant changes in physical examination, vital signs, EKG, and hematology or clinical chemistry parameters have been observed over time.

In concurrent combination with radiation, chemotherapy (temozolomide and irinotecan) and immunotherapy (nivolumab), the serious adverse events that have been observed are consistent with the known toxicity profiles of these other agents.

When dosed as a single agent until progression followed sequentially with chemotherapy, RRx-001 may partially protect normal tissues from the cytotoxicities of chemotherapy, resulting in an increased relative dose intensity (RDI) of chemotherapy.

Overall RRx-001 has been well tolerated (especially when co-infused with autologous blood) both alone and in combination with minimal to no evidence of systemic toxicity. Two serious adverse events (SAEs) have been attributed by Principal Investigators to single agent RRx-001:

1. Rectal bleeding in a colorectal patient with an elevated INR and daily aspirin use
2. Ischemic stroke in a patient with brain metastases and multiple vascular risk factors including morbid obesity, untreated hypercholesterolemia and a previous history of hypercoagulability

No SAEs have been attributed to RRx-001 in combination with radiation or chemoradiation.

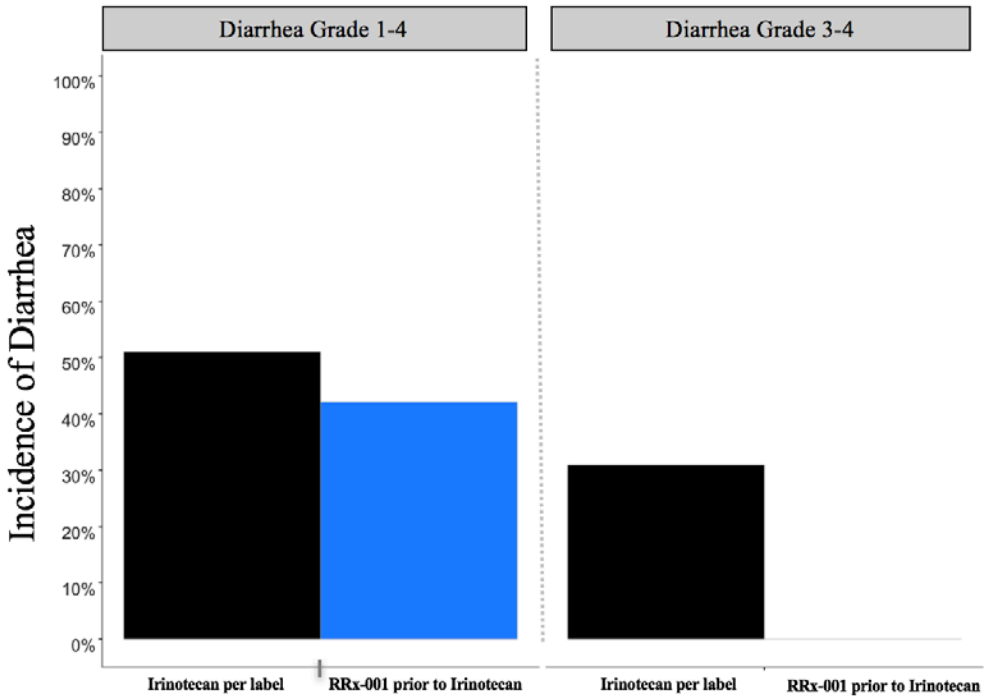
3.3.2 Activity

3.3.2.1 Clinical Chemoprotection Data

Data from two trials, ROCKET and QUADRUPLE THREAT in colorectal cancer and lung and ovarian cancer, respectively, suggest attenuation of the bone marrow and GI toxicities of sequentially administered chemotherapy, in which irinotecan and cisplatin/etoposide, respectively, were administered after discontinuation of RRx-001 treatment. The topoisomerase I inhibitor, irinotecan, is associated with significant toxicity, particularly diarrhea and

neutropenia with Grade 3 or 4 diarrhea reported in up to 34% of patients even with anti-diarrheal treatment and Grade 3 or 4 neutropenia reported in 23–44% of patients [Vanhoefer 2001]. In the ROCKET colorectal trial, of the 19 patients that were rechallenged with irinotecan after RRx-001 treatment, *Grades 3-4 diarrhea and neutropenia were not observed in any patients*.

Figure 1: Incidence of Diarrhea During Irinotecan Treatment After Exposure to RRx-001



For the platinum agents, cisplatin and carboplatin, the incidence of Grade 3-4 bone marrow toxicities are as follows according to the Carboplatin package insert:

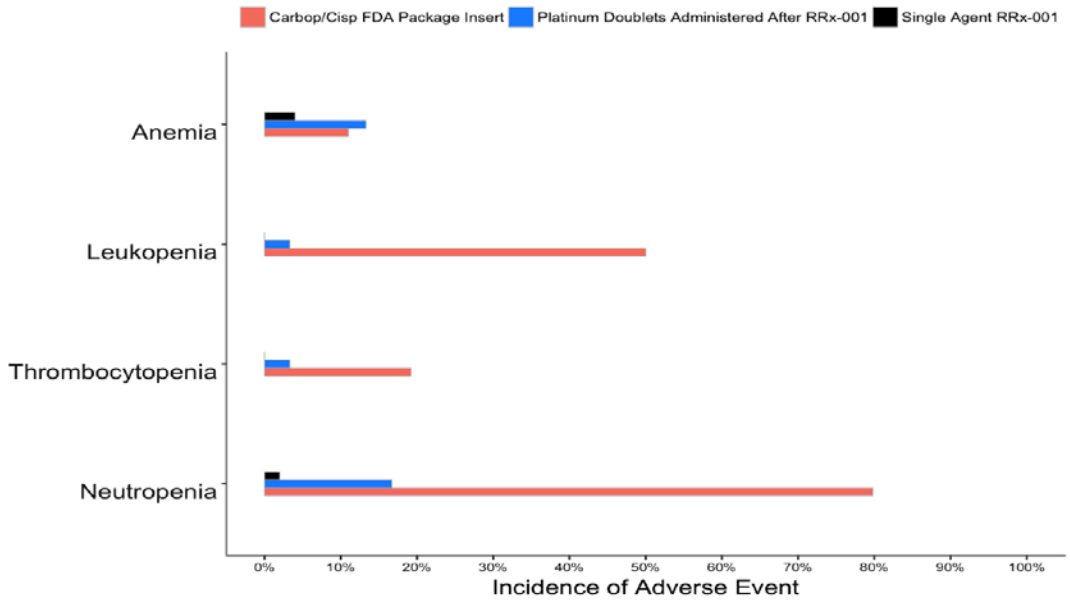
Table 1: Carboplatin vs. Cisplatin Incidence of > Grade 3 Cytopenias from a Meta-Analysis in SCLC

	Carboplatin	Cisplatin
Thrombocytopenia	41	6
Neutropenia	81	79
Leukopenia	68	52
Anemia	18	12

By contrast, in an analysis of 50 patients with safety data from the QUADRUPLE THREAT trial, 30 of whom to date have received platinum (either cisplatin or carboplatin) after RRx-001, the incidence of bone marrow toxicities is dramatically less as shown below:

- thrombocytopenia 3.3%
- neutropenia 30%
- leukopenia 3.3%
- anemia 16.7%

Figure 2: Bar Graph Showing Comparative Incidences of Myelotoxicity from Platinum on an Ovarian Cancer NCIC Study (Source FDA Package Insert) vs. Platinum Administered After RRx-001



3.3.2.2 Clinical Radioprotection Data

Evidence of clinical radioprotection is also potentially present in the Phase 1 BRAINSTORM trial in which 31 patients (22 evaluable) with brain metastases received concurrent whole brain radiotherapy (WBRT) and RRx-001 up to a dose of 33 mg. In this trial the intracranial response rate was 50% and the intracranial disease control rate in evaluable patients (stable disease or better) was 100%. No grade 3 or 4 neurotoxicities were reported, potentially indicative of neuroprotection.

3.3.3 Metabolism

In blood, RRx-001 reacts non-enzymatically and covalently with reduced glutathione (GSH), and with the beta93Cys residue of hemoglobin (Hb), forming RRx-001-GSH and RRx-001-Hb metabolites, respectively. Pharmacokinetics given the rapid conversion of the RRx-001 parent molecule to its glutathione (GSH) and hemoglobin conjugates, RRx-001-GSH, as the predominant measurable metabolite in the plasma, was chosen as a surrogate for drug exposure. Terminal half-life of RRx-001-GSH was calculated as approximately 30 minutes. AUC and C_{max} were mostly dose proportional for doses up to 55 mg/m^2 in Phase 1. Unfortunately, since the red blood cell is the main intermediary of RRx-001 activity (and local toxicity), the absorption, distribution, metabolism and excretion profile of the GSH conjugate is not a useful or relevant measure of the pharmacology and safety of RRx-001.

3.4 Dose and Dose Schedule of RRx-001

The 4 mg dose has been chosen on the basis of previous experience in two chemoradiation trials for brain metastases and primary GBM, as well as a lower incidence of infusion reactions and a hypothesized lower incidence of pseudoprogression.

Based on clinically observed blood flow changes in the tumor, which last for at least 7 days, the optimal frequency of dosing was determined to be once weekly, although twice weekly has also been tried in clinical studies.

4 PROPOSED MECHANISMS OF RADIOPROTECTION

RRx-001 bound to hemoglobin in red blood cells produces reactive oxygen and nitrogen species, which leads to compensatory anti-inflammatory gene expression in tissues from upregulation of Nrf2 (nuclear factor erythroid 2-related factor 2), a regulatory transcription factor with a critical role in the antioxidant response pathway. The protective role of Nrf2 was evaluated in mice bearing SSC VII tumor xenografts that received a single intravenous dose of RRx-001 (10 mg/kg). Histological examination of the tumors demonstrated that the intensity of Nrf2 (nuclear factor erythroid 2-related factor 2) cytoplasmic and nuclear proteins was dramatically higher in RRx-001-treated tumors compared to that in control tumors. This higher nuclear expression of Nrf2 suggests that after RRx-001 treatment Nrf2 translocates to the nucleus and induces antioxidant gene expression. The downstream expression of Nrf2-activated antioxidant enzymes, heme oxygenase 1 and NAD(P)H dehydrogenase quinone, was assessed both *in vitro* and *in vivo* in SCC VII tumor cells following RRx-001 treatment and showed a time-dependent increase of expression [Ning 2015]. Hence, it is hypothesized that RRx-001 protects tissues from radiation injury via Nrf2 nuclear translocation and upregulation of multiple antioxidant pathways, which minimizes oxidative stress and maintains the redox status.

5 STUDY OBJECTIVES

This is an exploratory, open-label study, which is intended to examine varying dosing schedules of RRx-001 in combination with standard of care for cancers of the oral cavity and oropharynx.

The study seeks to assess the safety and tolerability of varying dosing schedules of RRx-001 during treatment and for 28 days following end of treatment and to assess the long-term effect of RRx-001 on tumor response to standard concomitant chemoradiation.

It is also the objective of the study to assess the efficacy of RRx-001 in the attenuation of severe oral mucositis (SOM) in patients receiving cisplatin and radiation therapy for the treatment cancers of the oral cavity or oropharynx.

6 STUDY DESIGN

6.1 Description of the Study

The purpose of this proof-of-concept study is to determine whether RRx-001 has the potential to reduce the severity and duration of oral mucositis, an acute inflammatory condition, which generally peaks within 3 weeks after the start of chemoradiation therapy and, in the majority of cases, subsides shortly after the cessation of therapy.

This is a 4-arm Phase 2 exploratory proof-of-concept trial in which patients requiring standard chemoradiation therapy (concomitant cisplatin and radiation therapy) are randomized to receive one of three different regimens of RRx-001 (experimental groups) or standard care alone (control group). Approximately 40 patients will be randomized to 1 of the following 4 arms with 1 stratification factor (two levels: oral cavity or oropharynx):

Arm 1: "RRx-001 Pre-Treatment + SOC Chemoradiation (IMRT + Cisplatin)"

Two infusions of RRx-001 4 mg with 10 mg dexamethasone as a premedication will be given each week during the two weeks prior to the start of chemoradiation SOC followed by cisplatin either every three weeks (100 mg/m^2 for 3 doses) or weekly (40 mg/m^2 for 7 doses) and IMRT administered daily (excepting weekends) for 7 weeks. No additional RRx-001 will be given during the course of chemoradiation.

Arm 2: "RRx-001 Pre-Treatment + 2 Concurrent Doses + SOC Chemoradiation (IMRT + Cisplatin)"

Two infusions of RRx-001 4 mg with 10 mg dexamethasone as a premedication will be given each week during the two weeks prior to the start of chemoradiation SOC, followed by cisplatin either every three weeks (100 mg/m^2 for 3 doses) or weekly (40 mg/m^2 for 7 doses) and IMRT administered daily (excepting weekends) for 7 weeks. In addition, one dose of RRx-001 4 mg with 10 mg dexamethasone as a premedication will be given in each of weeks 2 and 5 of the course of chemoradiation.

Arm 3: "RRx-001 Pre-Treatment + 6 Concurrent Doses + SOC Chemoradiation (IMRT + Cisplatin)"

Two infusions of RRx-001 4 mg with 10 mg dexamethasone as a premedication will be given each week during the two weeks prior to the start of SOC chemoradiation, followed by cisplatin either every three weeks (100 mg/m^2 for 3 doses) or weekly (40 mg/m^2 for 7 doses) and IMRT administered daily (excepting weekends) for 7 weeks. In addition, one dose of RRx-001 4 mg with 10 mg dexamethasone as a premedication will be given in each of the first 6 weeks of the course of chemoradiation.

Arm 4: "SOC Chemoradiation Only (Control)"

No doses of RRx-001 will be administered. Patients assigned to this arm will receive only standard of care (SOC) chemoradiation in the form of cisplatin either every three weeks (100 mg/m^2 for 3 doses) or weekly (40 mg/m^2 for 7 doses) and IMRT administered daily (excepting weekends) for 7 weeks.

Administration of RRx-001 will not be blinded, so patient and study staff may be aware of the treatment assignment.

Patients will be followed for safety endpoints throughout the study. Patients will be evaluated for the presence and severity of oral mucositis during the course of chemoradiation and for up to 6 weeks following the cessation of RT.

Oral mucositis (OM) will be evaluated according to Section 11.1.

Patients in the study will be followed up to one year following the end of radiotherapy, in order to evaluate safety and tumor outcomes.

7 STUDY POPULATION

7.1 Eligibility Criteria

Patients must meet all of the Inclusion Criteria to participate in this study.

Patients meeting any of the Exclusion Criteria at baseline will be excluded from study participation.

8 DRUG TREATMENT

8.1 RRx-001 Drug Treatment

See Section 1.1 Treatment Schemas for treatment schedule.

8.1.1 RRx-001 Formulation

RRx-001 Drug Product and diluent product: RRx-001 Drug Product is supplied as a sterile solution in PEG-400. Prior to administration, DMA will be added to RRx-001 Drug Product, using aseptic techniques, to yield a solution containing 66% PEG-400 and 33% DMA. This solution will then be diluted, using aseptic techniques, to 2.0 mg/mL with Water for injection (WFI). Please refer to pharmacy manual for drug storage conditions and drug preparation instructions.

8.1.2 RRx-001 Administration

RRx-001 treatment will be administered on an outpatient basis. Patients will receive 4 mg of RRx-001, premixed with the patient's blood prior to reinfusion, per the schedule outlined in the study schema (Section 1.1).

The administration procedure of RRx-001 incorporates the use of an in-line filter 'device' as an added patient safety element; though likely unnecessary, given the patient's own blood is being drawn into a syringe containing anticoagulant, where the study drug (RRx-001) is subsequently transferred to mix with the blood, followed by the treated blood being reinfused back into the patient, within approximately 15 minutes from start of blood draw, all inside a closed sterile assembly.

The filter 'device' is a clinical use in-line blood filter and is part of an FDA approved Neonatal Syringe Set that is used to deliver small aliquots of whole blood. Modification was made for our use by the manufacturer, both to the tubing length (adding approximately 3") and tubing ends (changing the previously female luer connector to a male luer connector on 1 end, and a removing an IV bag spike and replacing it with a male luer connector on the opposite end), thus making this technically 'off label' use.

Appropriate in-use studies have been conducted with this filter 'device' and these results along with the following device labeling: 'CAUTION—Investigational device for use with RRx-001. Limited by Federal law to investigational use under IND 107,674' have been shared with the FDA by way of an information amendment submission, dated December 14, 2017.

RRx-001 Therapy Handling:

RRx-001 doses will be prepared by the pharmacy for the clinic, where the patient administration procedure takes place. For details of the pharmacy procedure, please refer to the latest version of the pharmacy manual.

The methodology for administering the RRx-001 dose by premixing with the patient's blood that has been anticoagulated with Acid-Citrate-Dextrose Formula A (ACD-A) is based on procedures used in blood product transfusions. Standard procedures for avoiding hemolysis will be followed. These include the use of large gauge IV needles (19g or larger preferred) and slow consistent rate during blood draw to avoid undue mechanical shear stress to red blood cells.

Whenever blood is present during the administration procedure, handle with care and do not shake. Avoid excessive temperatures, (both high and low temperatures can cause hemolysis). Avoid conditions that create high turbulence or trauma to the red blood cells.

RRx-001 Therapy Administration Procedure in the Clinic:

The RRx-001 and ACD-A anticoagulant doses should be properly labeled per institutional standards and in accordance with the latest pharmacy manual guidelines.

Ensure that the RRx-001 and anticoagulant doses, both provided from pharmacy, are for the correct patient (using patient identifiers noted on labeling); that the RRx-001 and anticoagulant are mixed with the patient's autologous blood; and that the mixture is re-infused back to the correct patient. DO NOT proceed with administration if any discrepancies are noted.

Administration procedure steps should be followed carefully and can be found in the latest version of the 'Blood Administration Best Practices & Guidelines for IV Infusion of RRx-001 + Blood Mix'. Safety guidelines are based on procedures used in blood product transfusions. **It is important each step is followed in the order outlined in the guide to maintain sterility at all times.**

8.1.3 Storage and Stability

RRx-001 is not light sensitive. The product should be used within 30 minutes after dilution. RRx-001 solutions diluted with saline are not stable and saline should not be used. The osmolality of the 2.0 mg/mL dosing solution was determined to be 614 mOsm/kg. The study product is to be stored in a secured site with restricted access.

8.1.4 Supply

RRx-001 will be supplied by the Sponsor.

8.1.5 Pre-Medications

Corticosteroids are required as a premedication: Dexamethasone (10 mg, IV or PO) or an equivalent dosage of another steroid.

Table 2: RRx-001 Regimen Premedication Description

Premedication RRx-001	Route	Schedule
10 mg Dexamethasone (or equivalent dose of another corticosteroid)	IV or PO	Same day prior to dosing

8.1.6 Prohibited Medications / Supplements

Contraindications

Due to their antioxidant properties (and in the case of alpha lipoic acid iron chelating properties), which are presumed to counteract the free radical generation of radiation therapy, the following

are contraindicated: alpha lipoic acid, Vitamin E, N-acetylcysteine and omega 3 fatty acid supplements.

8.2 Cisplatin Drug Treatment

Combination Treatment: Patients will receive cisplatin per Investigators Discretion:

- Option 1: 3 doses at 100 mg/m^2 on Day 1 (± 2 Days) of Weeks 1, 4, and 7
- Option 2: 7 doses at 40 mg/m^2 on Day 1 (± 2 Days) of Weeks 1, 2, 3, 4, 5, 6, and 7
- Note: Cisplatin should not be given within 24 hours of RRx-001

Patients will receive cisplatin in accordance with applicable guidelines such as NCCN and/or the package insert; however, these guidelines are not intended to supersede or replace institutional guidelines with respect to appropriate and necessary care for individual patients [Ang 2010].

8.2.1 Supply

Cisplatin is commercially available.

8.2.2 Pre-Medications

Cisplatin premedication should be provided via institutional guidelines.

8.3 Dose Modifications

8.3.1 Dosing Delays/Dosing Modifications: RRx-001 Therapy

The starting 4 mg dose has been chosen on the basis of previous experience in two chemoradiation trials for brain metastases and primary GBM, as well as a lower incidence of infusion reactions and hypothesized lower incidence of pseudoprogression. The most common toxicity of RRx-001 is mild or moderate infusion-related reactions. Dose modification or drug discontinuation for toxicity may take place at the discretion of the Investigator and will be reported. If a grade 3 or 4 study drug-related adverse event occurs after a dose reduction, RRx-001 will be discontinued. The dose modifications are listed below in the table below.

Table 3: Dose Modifications for RRx-001 Administration

Sequential Dose Modifications	RRx-001 Dose (mg)	RRx-001 Dose (mg/m^2)	mL	Infusion Time	Frequency
Initial	4	2.3	2.0	Not to exceed 4 hours from extraction of blood	Per SOA
Dose reduction	2	1.15	1.0	Not to exceed 4 hours from extraction of blood	Per SOA
Dose reduction	0.5	0.29	0.25	Not to exceed 4 hours from extraction of blood	Per SOA

8.3.2 Dosing Delays/Dosing Modifications: Cisplatin

- Neutropenia: If on the day of scheduled treatment with cisplatin the absolute neutrophil count (ANC) is < 1200, hold treatment until ANC ≥ 1200, then treat at 100% dose. Neutropenic fever will require permanent 25% dose reduction. Per CTCAE, v. 5.0, febrile neutropenia is described as ANC < 1000/mm^3 with a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than 1 hour.
- Thrombocytopenia: If on the day of scheduled treatment with cisplatin the platelet count is < 75,000, hold treatment until platelets are ≥ 75,000, then treat at 100% dose. Thrombocytopenia that results in bleeding will require a 25% dose reduction
- Neurotoxicity: If any signs of grade 3 or greater neurotoxicity occur, discontinue cisplatin. Continue radiation therapy (RT).
- Renal Adverse Events: Cisplatin should be administered on the scheduled day of treatment using the following guidelines. Note: If creatinine is > 1.2 mg/dL, clearance must be calculated (Cockcroft-Gault) in order to make dose adjustment. If the calculated nomogram is 50 mL/min or above, a 24-hour urine collection is not needed, but if the calculation is less than 50 mL/min, a 24-hour urine collection is mandated.

Creatinine Clearance	Cisplatin Dose 100 mg/m^2	Cisplatin Dose 40 mg/m^2
> 50 mL/min	100 mg/m^2	40 mg/m^2
40-50 mL/min	50 mg/m^2	20 mg/m^2
< 40 mL/min	Hold drug*	Hold drug*

*Cisplatin should be held (but RT continued), and the creatinine measured weekly. If creatinine clearance is > 50 mL/min, then the second dose of cisplatin can be given at the reduced dose of 50 mg/m^{2}or 20 mg/m^2. Also see Section 8.4.2 below.

- *Other Adverse Events*
    - Mucositis: Significant mucositis from radiation and cisplatin is expected and will not be an indication for cisplatin dose modification. No cisplatin dose reductions will be made.
    - Ototoxicity: For new clinical hearing loss not requiring a hearing aid or for tinnitus that interferes with activities of daily living, treat at 50% dose reduction. For hearing loss requiring a hearing aid, discontinue cisplatin. Continue RT and RRx-001. If the physician is unsure about the severity of the hearing loss, an audiogram is encouraged.

8.4 Missed or Omitted Doses and Alternative Treatment Schedules

8.4.1 Missed Doses: RRx-001

If doses of RRx-001 doses are missed those doses will be skipped. If all the doses of RRx-001 are missed that patient may be considered non-evaluable. The missed or omitted dose(s) and the reason for omission should be recorded.

8.4.2 Missed or Omitted Doses: Cisplatin

In the event of any grade 3 or 4 event, treatment will be delayed. If the delay is more than 21 days because of hematologic or renal adverse events, that dose will be omitted. If a dose of cisplatin is missed or omitted, it will not be made up or added to the end of treatment.
If radiotherapy is held, cisplatin should similarly be held and resumed when radiation resumes. In this case, the cisplatin dose is not considered skipped or omitted, but delayed.

9 RADIATION THERAPY

Intensity Modulated Radiation Therapy (IMRT) in accordance with the American College of Radiology (ACR) and American Society for Radiation Oncology (ASTRO) Practice Guideline for IMRT) is mandatory for this study [Hartford 2012].

10 OTHER THERAPY

10.1 Permitted Concomitant Supportive Therapy

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, antifungal treatment, and treatment of other newly diagnosed or concurrent medical conditions. All supportive care should be listed as a concomitant medication.

Patients will conform to a standard oral care regimen consistent with national/international guidelines and will be provided instructions and supplies to assure adherence (Appendix F & Appendix G).

10.2 Non-permitted Concomitant Supportive Therapy

- Amifostine
- Topical antibiotic rinses, creams or troches
- Benzydamine hydrochloride
- Caphosol
- Glutamine (topically applied)
- GM-CSF (Leukine)
- IL-11
- Magic mouthwash or Miracle mouthwashes are allowed as long they do not contain any of the following:

- Chlorhexidine
- Diphenhydramine
- Tetracycline or other antibiotic
- Hydrogen peroxide

- Other disallowed medications:
  - Herbal, alternative remedies, other natural product (i.e. honey) and alcohol-containing mouthrinses.
  - MuGard
  - GelClair
  - Episil
  - Prothelial
  - Palifermin or other growth factors
  - Povidone-iodine rinses
  - Prevention mouth rinse
  - ReBalance
  - Steroid rinses or gels
  - Sucralfate suspension for topical use (oral formulations, i.e., tablets are allowed).
  - Other biologic modifiers. Hematopoietic growth factors such as GCSF are allowed.
  - Other investigational agents.

If non-permitted concomitant supportive therapies are used (Section 10.2) the data may be censored and the patient may be replaced.

11 EFFICACY ASSESSMENTS

11.1 Oral Mucositis (OM) Assessments

Mucositis assessments will be completed at the screening visit, day 1 of pretreatment prior to administration of RRx-001, twice weekly (no less than 48 hours apart) within each 5-day radiation week during the combination treatment phase, at the end of the combination treatment phase (last day of radiation) and the same day each week (± 1 day) during the Mucositis Observation Follow-up until resolution of ulcerative mucositis occurs (WHO grade 0 or 1).

Oral mucositis will be assessed by a trained evaluator using a standard oral mucositis assessment instrument. If a patient withdraws prior to the end of the combination treatment phase, an oral assessment must be completed on the day of withdrawal, and it is suggested that patients be assessed weekly until resolution of ulcerative mucositis occurs (WHO grade 0 or 1). Patients will be instructed not to discuss their treatment regimens with the assessor. Additionally, the assessor will be provided training to assure uniform interactions with patients to limit bias in the assessment.

Specific training and instructions are required for all individuals who perform mucositis assessments. Such training will be provided by the sponsor or its designee. Site study staff

designated as oral evaluators must be licensed professionals and properly delegated such tasks (on DOA log). Oral evaluators will conduct all assessments using a standardized and consistent method. To reduce inter-observer variability, as few oral evaluators as possible should be involved in the assessments of an individual patient. Ideally, the same assessor will evaluate a single patient throughout the combination treatment and mucositis observation follow-up. All efforts to maintain uniformity should be used.

The study's efficacy endpoints will be based on WHO mucositis criteria. Since patients' ability to eat is a component of the WHO scale, standardization of the assessment of food intake and, particularly, the definition of solids, liquids and "nothing by mouth" is critical.

- A normal solid diet is defined as firm, shaped food that does not flow or conform to the shape of its container and requires chewing. Examples include rice, meat including fish, poultry, bread, rolls, toast, salad, cereal.
- A modified soft solid diet consists of foods that do not conform to the shape of its container, still require minimal chewing, but are less dense than standard solids. Examples include eggs, pasta, fruit or soup.
- For the purposes of the clinical trial mucositis assessment, liquids are defined as foods that take the shape of their container and which don't require chewing. In addition to things we typically think of as pure liquids like juice, milk shakes, smoothies or frappes, also heavily pureed foods, yogurt, oatmeal and jello fall into this category.
- The "nothing by mouth" category is appropriate for patients who can't eat or swallow EXCEPT for medication. Please note that sips of water used to help aid in swallowing medication still constitute a "nothing by mouth" selection. This would also be the best option for patients who require the assistance of a feeding tube.

11.2 Pain Assessments

Pain will be assessed with the OMDQ Question 2 (mouth and throat soreness or MTS), which will be completed daily from baseline until oral mucositis assessment grade 0 or 1. The OMDQ is provided in Appendix D. The OMDQ will be provided in booklets for patient distribution during Combination Treatment and Mucositis Observation Follow-up.

11.3 Analgesic Use

Patients often require analgesics, including opioids for pain control. Patients will record any analgesic use, including name, dose, and frequency of dose, in the OMDQ Booklet. Information from the source documents and the diary will be recorded into the EDC system as a concomitant medication. Analgesics will be converted to morphine equivalents at the time of data analysis.

11.4 Other Assessments

Frequency and duration of interruptions in radiation therapy will be recorded.

11.5 Tumor Assessments

Tumor assessments will be performed according to the schedule of assessments. The patient's tumor response will be assessed using RECIST v1.1 [Eisenhauer et al. 2009] until progression, start of next therapy or until end of Long Term Follow-up, whichever comes first [Appendix B]. When measurable disease is not present (e.g. post-operative patients), RECIST v1.1 assessment is not performed until measurable disease presents (this is considered progression and no further assessments will be done) or start of next therapy. Tumor status information will be collected and will include disease progression, and survival. During the follow up period, data will be collected at standard of care intervals, i.e., month 3 (± 7 days) and also at months 6, 9 and 12 (each ± 14 days) following the last day of combination therapy to document start date of subsequent therapies.

12 ASSESSMENT OF SAFETY

The safety of RRx-001 will be assessed through collection and analyses of adverse events (AEs) and laboratory tests.

12.1 Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to RRx-001, cisplatin or radiation therapy, all events of death, and any study specific issue of concern.

12.1.1 Adverse Events

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation patient administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (including abnormal laboratory finding, for example), symptom or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol specified AE reporting period, including signs or symptoms associated with SCC that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies).
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.
- Clinical progression of SCC should not be reported as an AE.

12.1.2 Serious Adverse Events

An AE should be classified as an SAE if:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

All AEs that do not meet any of the criteria for serious should be regarded as non-serious AEs.

The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of a specific AE, e.g., mild (Grade 1), moderate (Grade 2), or severe (Grade 3) myocardial infarction. "Serious" is a regulatory definition (see previous definition) and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities.

Severity and seriousness should be independently assessed when recording AEs and SAEs into the EDC system.

12.2 Methods and Timing for Assessing and Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, IRB, and EpicentRx, Inc. in accordance with CFR 312.32 (IND Safety reporting).

12.2.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 30 days following the last administration of study treatment (RRx-001, cisplatin and radiation therapy) or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

12.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all patient evaluation time points during the study. All AEs and SAEs whether volunteered by the patient, discovered by study

personnel during questioning, or detected through physical examination, laboratory test, or other means will be recorded in the patient's medical record and into the EDC system.

Each recorded AE or SAE will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria if applicable, suspected relationship to the investigational product (see following guidance), and actions taken.

The AE grading (severity) scale found in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0, will be used for AE reporting.

Table 4: Adverse Event Grading (Severity) Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI-CTCAE grading criteria)	Transient or mild discomfort (< 48 hours); no interference with the patient's daily activities; no medical intervention/therapy required
2	Moderate (apply event-specific NCI-CTCAE grading criteria)	Mild to moderate interference with the patient's daily activities; no or minimal medical intervention/therapy required
3	Severe (apply event-specific NCI-CTCAE grading criteria)	Considerable interference with the patient's daily activities; medical intervention/therapy required; hospitalization possible
4	Very severe, life threatening, or disabling (apply event-specific NCI-CTCAE grading criteria)	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable
5	Death related to AE	

Note: Regardless of severity, some events may also meet regulatory serious criteria. Refer to definitions of an SAE

[a]Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI-CTCAE listing.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

- **YES**

There is a plausible temporal relationship between the onset of the AE and administration of the investigational product (RRx-001), and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the investigational product (RRx-001); and/or the AE abates or resolves upon discontinuation of the investigational product (RRx-001) or dose reduction and, if applicable, reappears upon re-challenge.

- **NO**

Evidence exists that the AE has an etiology other than the investigational product (RRx-001) (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the investigational product (RRx-001) (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Product Label or current Investigator Brochure.

Unexpected adverse events are those not listed in the Product Label or current Investigator Brochure or not identified. This includes adverse events for which the specific or severity is no consistent with the previous description.

12.2.3 Specific Instructions for Recording Adverse Events

Investigators are strongly encouraged to use correct medical terminology/concepts when reporting AEs or SAEs and to avoid colloquialisms and abbreviations.

a. Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

b. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

c. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

d. Pregnancy

If a female patient becomes pregnant while receiving investigational therapy or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to the EpicentRx, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion,

whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female patient exposed to the investigational product should be reported as an SAE.

e. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a patient has completed or discontinued study participation if attributed to prior investigational product exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study, this should be reported as an SAE.

12.3 Reporting Requirements for Adverse Events

12.3.1 Expedited Reporting Requirements for Serious Adverse Events

All SAEs are required to be reported to the Sponsor on the SAE CRF within 24 hours of a site's knowledge of the SAE. Please send all SAE reports to:

Fax Number: (650) 396-4450 or SAEREPORTING@epicentrx.com

The Medical Monitor, Dr. Bryan Oronsky, can be reached at 408-569-3202 (cell) or boronsky@epicentrx.com should any questions arise regarding an SAE or SAE reporting.

Relevant follow-up information should be submitted to EpicentRx's Drug Safety as soon as it becomes available and/or upon request.

Occasionally, EpicentRx may contact the reporter for additional information, clarification or current status of the patient for whom an adverse event was reported. For questions regarding SAE reporting, you may contact the EpicentRx Medical Contact (re: page 1).

12.3.2 Routine Reporting of Adverse Events

- The Institutional Review Board (IRB) should be notified per local guidelines.

12.4 Type and Duration of Follow-Up of Patients After Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period that are considered at least possibly related to the study drug should be followed to their resolutions, or until the investigator assesses them as stable, or the patient is lost to follow-up. Resolution of AEs and SAEs (with dates) should be documented on the appropriate AE CRF page and in the patient's medical record to facilitate source data verification.

For some SAEs, the Sponsor or its designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

13 STATISTICAL METHODS

13.1 Sample Size

A sample size of 40 patients is considered adequate for this POC study to explore the radioprotective potential of RRx-001 and identify a safe regimen for further development.

With 10 patients per group, the study will have approximately 80% power to detect a 75% reduction in the average number of days with severe OM (from 24 to 6 days) at the two-sided 5% significance level; this calculation is based on Student's t-test and assumes the standard deviation for duration of severe OM is 13 days. While not powered for more modest treatment effects, the study will yield important safety information and trends in efficacy data to inform decisions about future study designs.

13.2 Efficacy Analysis

Statistical methods for the calculation and analysis of efficacy endpoints are provided below. Limited hypothesis-testing will be performed, as this is a small POC study. All statistical analyses are exploratory.

Duration of Severe Oral Mucositis (SOM): The duration of SOM (WHO grade 3 or 4) will be calculated as the number of days from the onset of SOM (first time a WHO grade 3 or 4 is observed) to the day when severe OM has resolved (first time WHO grade 2 or less is observed after last WHO grade 3 or 4). Durations of 0 will be assigned to patients who do not experience severe OM. Any patient who dies or withdraws prior to resolution of severe OM will be assumed to have severe OM for the remainder of the observation period. All available OM assessments will be used to derive efficacy endpoints, including WHO grades recorded during the treatment and follow-up period in order to capture resolution of OM.

The duration of SOM will be compared for each of the 3 RRx-001 regimens versus the untreated control group using the Wilcoxon rank-sum test. This rank-based test does not depend on normality assumptions for these small sample sizes. All patients randomized (the intent-to-treat population) will be used for this analysis.

Time to onset of SOM: The number of days from the start of chemotherapy until the date of first OM assessment grade 3 or 4 will be listed and summarized descriptively for each treatment group.

Incidence of SOM: The incidence of SOM (WHO grade 3 or 4) will be calculated as the number of patients with at least one OM WHO grade 3 or 4, divided by the number patients in the treatment group. Patients with no OM assessments will be assumed to have severe scores. Patients who die or withdraw without experiencing OM grade 3 or 4 will also be assumed to have severe scores. The incidence of SOM will be compared between each RRx-001 group and the control arm using Fisher's Exact test. Clopper-Pearson two-sided 95% confidence limits will be calculated for the proportion of patients with SOM in each treatment arm.

Duration and incidence of ulcerative OM: The duration of ulcerative OM (WHO grade 2, 3, and 4) will be calculated in a manner similar to duration of severe OM. That is, the duration of ulcerative OM will be calculated as the number of days from the onset of ulcerative OM (first time a WHO grade 2, 3, or 4 is observed) to the day when ulcerative OM has resolved (first time WHO grade 0 or 1 is observed after last WHO grade 2, 3 or 4). A similar imputation scheme will be used in the event that patients die or withdraw prior to resolution of OM to grade 0 or 1. The Wilcoxon rank-sum tests will be used to compare treatment groups. Incidence of ulcerative OM will be calculated and analyzed as described above for severe OM.

Patient-reported pain: The average of patient-reported mouth and throat soreness (MTS) scores, graded on a scale from 0 (no soreness) to 4 (extreme soreness), will be summarized by treatment group during each study week and displayed graphically. The number of patients with scores of 0 or 1 will be enumerated by time and treatment group.

13.3 Safety Analysis

Safety will be evaluated on the basis of treatment-emergent AEs (TEAEs), vital signs, weight, physical examinations, tumor assessments, and clinical laboratory assessments.

All adverse events will be coded by Preferred Term and System Organ Class using the most recent version of MedDRA. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (Version 5.0) will be used to grade both clinical and laboratory AEs. By-patient listings of deaths, SAEs, and AEs leading to discontinuation will be provided. The by-patient AE data listings will include onset and resolution dates, verbatim term, Preferred Term, treatment, severity (grade), relationship to treatment, action taken for the event, and outcome.

The incidence of treatment-emergent AEs (TEAEs) will be summarized by treatment group and tabulated by System Organ Class (SOC) and Preferred Term (PT). A TEAE is defined as an AE that first occurs or worsens in severity on or after the first dose of the study medication.

Vital signs (systolic and diastolic blood pressure, pulse, and temperature) and body weight will be summarized for each treatment group using descriptive statistics. Summary statistics (n, mean, median, standard deviation, minimum, and maximum) will be calculated for both the actual value and the change from baseline value at each scheduled visit.

Clinical laboratory data will be presented for each treatment group using descriptive statistics based on the observed values and change from baseline values at each scheduled visit. Summary statistics (n, mean, median, SD, minimum, and maximum) will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. Shift tables from baseline to the worst post-baseline values during the treatment period will be provided for chemistry parameters and hematology parameters that have NCI-CTCAE v5.0 toxicity grades. Both scheduled and unscheduled post baseline values during the treatment period will be considered. Additionally, the number and percentage of patients with Grade ≥ 3 will be presented for each CTCAE gradable laboratory test.

All clinical laboratory data will be listed by patient. Values outside the normal ranges will be flagged and toxicity grades will be displayed for relevant parameters.

Pre-study abnormalities and reported abnormalities at the end of study will be tabulated by body system. Changes in physical examinations will be described in the text of the final study report. Tumor response assessments at each follow-up visit will be tabulated by treatment group.

Prior and concomitant medications will be tabulated for each treatment group; details regarding dose regimens and start/stop dates will be presented in by-patient data listings.

Progression Free Survival (PFS) defined from the time of registration to the time of the first radiographic documentation of objective progression (per RECIST v1.1) or the date of death, whichever is earlier, will be evaluated using Kaplan-Meier methods. Subjects still alive without progressive disease at the time of analysis will be censored on the date of the last objective progression-free observation prior to the start of subsequent anti-cancer therapy.

14 SPONSOR AND INVESTIGATOR REQUIREMENTS

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered into the EDC system. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, data entered into the EDC system will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

14.1 Institutional Review Board Approval

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. In addition, any advertising materials must be approved by the IRB. The study will be conducted in accordance with U.S. FDA, applicable national and local health authority, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant adverse events.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the Investigator Brochure and that are considered possibly or probably related to the study drug by the investigator. Investigators must forward to their IRB any written safety report or update provided by EpicentRx (e.g., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

14.2 Study Monitoring Requirements

The Sponsor will designate a Sponsor's Study Monitor (i.e., clinical research associate (CRA)) who will be responsible for monitoring this clinical trial. The Sponsor's Study Monitor will monitor the study conduct; insure the proper completion and retention of source documentation completion and retention, accurate study drug accountability records and prompt data entry to CRF. To this end, the Sponsor's Study Monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. Monitoring will also be carried out remotely using redacted source documents. It is essential that the Sponsor's Study Monitor have access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the Sponsor's Study Monitor will adhere to all requirements for patient confidentiality as outlined in the Informed consent form (ICF). The Investigator(s) or their representative(s) will be expected to cooperate with the Sponsor's Study Monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information. Investigator(s) or their representative(s) are required to respond in writing to any deficiencies or protocol deviations noted by the monitor in the site visit report.

14.3 Data Collection

Study documentation includes all data entered into the EDC system, data correction forms or queries, source documents, correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. All source documents produced in this study will be maintained by the Investigator, and made available for inspection by the Sponsor, regulatory authorities, or both, and redacted copies may be requested by Sponsor.

14.4 Disclosure of Data

Patient medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

In accordance with the Health Information Portability and Accountability Act (HIPAA), patients who have provided written informed consent must also sign a patient authorization to release medical information to his or her personal physician or other appropriate medical personnel responsible for his or her welfare, to EpicentRx and authorized representatives of EpicentRx, upon request, for source verification of study documentation.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, local health authorities, EpicentRx, Inc., and their authorized representative(s), collaborators and licensees, and the HRPP.

14.5 Retention of Records

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including electronic data, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

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16 APPENDICES

Appendix A. ECOG Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix B. RECIST 1.1

Tumor assessments will be made according to the schedule of assessments. Response and progression will be evaluated using RECIST v1.1 [Eisenhauer et al. 2009].

Non-Target Lesion Evaluation

Response	Definition
Complete Response (CR)	■ Disappearance of all extranodal non-target lesions ■ All lymph nodes must be non-pathological in size (<10 mm short axis). ■ Normalization of tumor marker level
Non CR/Non PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. (Subjective judgement by experienced reader)

Target Lesion Evaluation

Response	Definition
Complete Response (CR)	Disappearance of all extranodal target lesions. All pathological lymph nodes must have decreased to <10 mm in short axis.
Partial Response (PR)	At least a 30% decrease in the SLD of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	SLD increased by at least 20% from the smallest value on study (including baseline, if that is the smallest) The SLD must also demonstrate an absolute increase of at least 5 mm. (Two lesions increasing from 2 mm to 3 mm, for example, does not qualify)
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD

Appendix C. Oral Mucositis WHO Grading System

Grade	Description
0 (none)	None
I (mild)	Oral soreness, erythema
II (moderate)	Oral erythema, ulcers, solid diet tolerated
III (severe)	Oral ulcers, liquid diet only
IV (life-threatening)	Oral alimentation impossible

Appendix D. Oral Mucositis Daily Questionnaire (OMDQ)

This questionnaire (see next page) has been used as a tool to assess oral mucositis in patients undergoing hematopoietic stem cell transplantation [Stiff et al., 2006].

Patients should be instructed to complete the OMDQ in its entirety in a comfortable area at about the same time each day. The OMDQ should be completed prior to the oral mucositis assessment on a given study day. For days the patient does not visit the clinic, the patient is to complete it at home.

Oral Mucositis Daily Questionnaire (OMDQ)

1. How would you rate your OVERALL HEALTH during the LAST 24 HOURS? (circle one number)

0	1	2	3	4	5	6	7	8	9	10

Worst possible — Halfway between worst possible and perfect health — Perfect health

2. During the LAST 24 HOURS, how much MOUTH AND THROAT SORENESS did you have? (circle one number)

No soreness	0	→ If you circled 0, please skip to question 5
A little soreness	1	
Moderate soreness	2	
Quite a lot of soreness	3	
Extreme soreness	4	

3. During the LAST 24 HOURS, how much did MOUTH AND THROAT SORENESS limit you in each of the following activities? (circle one number)

	Not limited	Limited a little	Limited some	Limited a lot	Unable to do
A. Swallowing	0	1	2	3	4
B. Drinking	0	1	2	3	4
C. Eating	0	1	2	3	4
D. Talking	0	1	2	3	4
E. Sleeping	0	1	2	3	4

4. On a scale of 1 to 10, how would you rate your OVERALL MOUTH AND THROAT SORENESS during the LAST 24 HOURS? (circle one number)

0	1	2	3	4	5	6	7	8	9	10

No soreness — Halfway between worst possible and perfect health — Worst possible

5. During the LAST 24 HOURS, how much DIARRHEA did you have? (circle one number)

No diarrhea	0	→ If you circled 0, STOP here
A little diarrhea	1	
Moderate diarrhea	2	
Quite a lot of diarrhea	3	
Severe diarrhea	4	

6. On a scale of 1 to 10, how would you rate your OVERALL DIARRHEA during the LAST 24 HOURS? (circle one number)

0	1	2	3	4	5	6	7	8	9	10

No diarrhea — Halfway between worst possible and perfect health — Worst possible diarrhea

Study Day ____ Date: _____

Instructions: Please list all medications you have used or taken today.

Time	Medication Name	Dose per Unit	Number of Units	Reason for Using/Taking Medication
08 : 10 (AM)/PM	Tylenol Extra Strength Gel Capsules	500 mg	2 pills	Jaw Pain
03 : 15 AM(PM)	Oral Anesthetic Paste Maximum Strength	Thin Layer	1 application	Inner Cheek irritation
____:____ AM/PM				
____:____ AM/PM				
____:____ AM/PM				
____:____ AM/PM				
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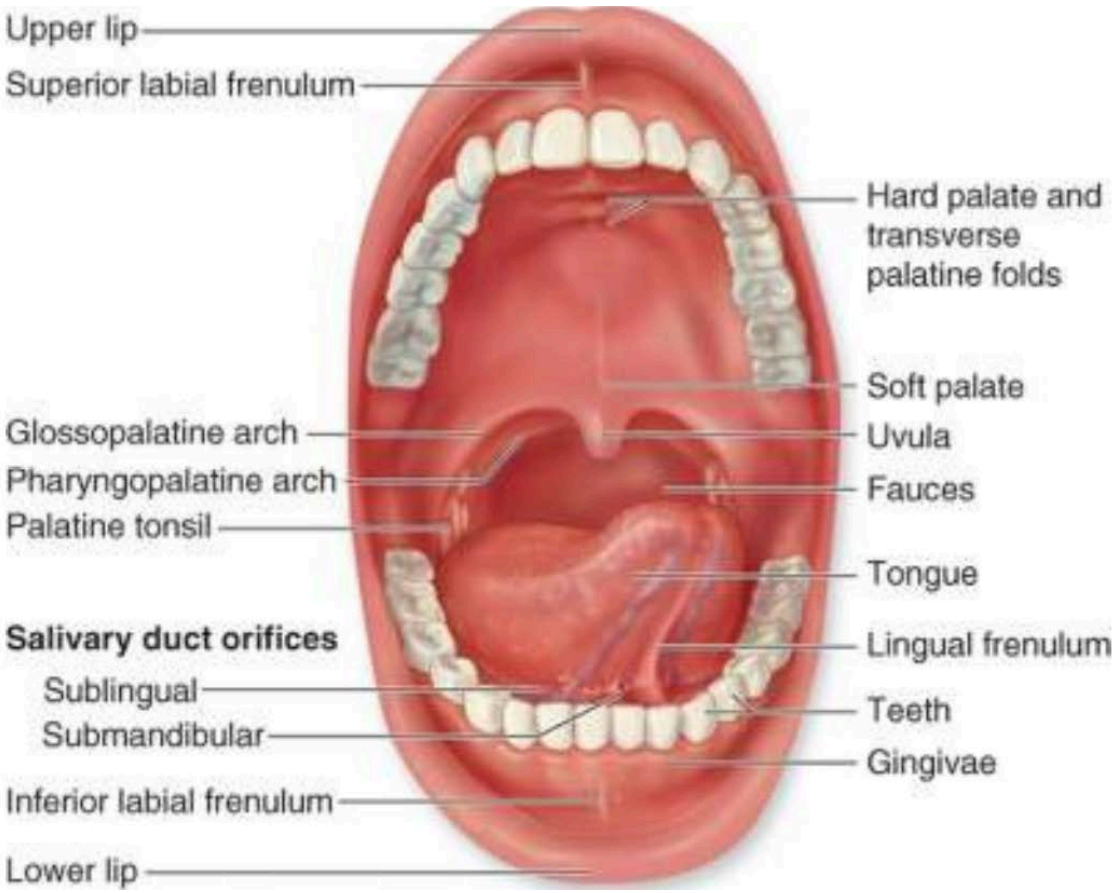
Appendix E. Anatomy of the Mouth



Appendix F. Standard Oral Health Maintenance Regimen

The following protocol is strongly recommended to standardize the maintenance regimen for all dentulous or partially dentulous study participants to optimize oral health during radiation therapy and minimize the risk of post-radiation dental sequelae. As per standard practice, all patients should be instructed on the risks to oral health of concomitant chemoradiation including dental caries, periodontal disease and osteoradionecrosis. The following should be discussed with each patient and written materials (provided in next appendix) should be reviewed. A study-supplied ***Oral Hygiene Kit*** should be dispensed to each patient at study start and renewed as needed.

1. Diet – Minimize foods that contain refined sugars such as cookies, cakes, candy, sugar-containing drinks, etc. Favor fruits and vegetables.
2. Avoid alcohol and tobacco products.
3. Practice scrupulous oral hygiene:
    a. Use the soft toothbrush provided in the oral hygiene kit or an electric toothbrush at least twice daily.
    b. Use the toothpaste provided in the oral hygiene kit or a similar product.
    c. Clean spaces between the teeth using dental floss or similar device.
4. Chew sugarless chewing gum after meals (Xylitol-containing gum is supplied in the oral hygiene kit). Avoid other forms of chewing gum.
5. Brush at bedtime with a 0.4% stannous fluoride gel
6. Rinse twice daily with a fluoride-containing mouthrinse such as CloSYS or similar rinse.

Appendix G. Patient Oral Care Instructions

(to be reviewed with patient during screening)

Dear Patient,

Thank you for participating in this trial. To help minimize your risk of developing oral health-related issues during and after radiation therapy, you'll receive an oral hygiene kit containing a soft toothbrush (AIM), a standard fluoride-containing toothpaste gel (PRO-SYS Flouride Toothgel), xylitol-containing chewing gum (Epic), 0.4% stannous fluoride gel (ESPE OMNI Gel), flossers (DenTek) and a fluoride mouthrinse (CloSYS). Here are some instructions on how best to use them and some strategies to keep your mouth comfortable and healthy.

1. **Keep your mouth moist**
    a. Drink plenty of water.
    b. Suck ice chips.
    c. Use a saliva substitute to help moisten your mouth.

2. **Clean your mouth, tongue, and gums**
    a. Use the soft toothbrush provided in the oral hygiene kit or an electric toothbrush. Brush your teeth and tongue after every meal using the fluoride toothpaste.
    b. Chew the sugarless gum after meals.
    c. At bedtime brush your teeth with the 0.4% stannous fluoride gel (ESPE OMNI Gel).
    d. Rinse twice daily with the fluoride-containing mouthwash such (CloSYS).
    e. Floss your teeth gently every day. If your gums bleed and hurt, avoid the areas that are bleeding or sore, but keep flossing your other teeth.

3. **If your mouth is sore, watch what you eat and drink**
    a. Choose foods that are good for you and easy to chew and swallow.
    b. Take small bites of food, chew slowly, and sip liquids with your meals.
    c. Eat moist, soft foods such as cooked cereals, mashed potatoes, and scrambled eggs.
    d. If you have trouble swallowing, soften your food with gravy, sauces, broth, yogurt, or other liquids.

4. **Remember to stay away from**
    a. Sharp, crunchy foods, like taco chips, that could scrape or cut your mouth.
    b. Spicy or acidic foods, like citrus fruits and juices, which may irritate your mouth.
    c. Sugary foods and drinks, like candy or soda, that could cause cavities.
    d. Toothpicks, because they may cut your mouth.
    e. Tobacco and alcohol products.

If you have any questions, please don't hesitate to ask your study nurse.