RADIATION THERAPY ONCOLOGY GROUP

RTOG 0435

A RANDOMIZED, PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF PALIFERMIN (NSC# 740548; IND #100,192) FOR THE REDUCTION OF ORAL MUCOSITIS IN PATIENTS WITH LOCALLY ADVANCED HEAD AND NECK CANCER RECEIVING RADIATION THERAPY WITH CONCURRENT CHEMOTHERAPY (FOLLOWED BY SURGERY FOR SELECTED PATIENTS)

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 0435

A Randomized, Phase III, Double-Blind, Placebo-Controlled Study To Evaluate The Efficacy And Safety Of Palifermin (NSC# 740548; IND #100,192) For The Reduction Of Oral Mucositis In Patients With Locally Advanced Head And Neck Cancer Receiving Radiation Therapy With Concurrent Chemotherapy (Followed by Surgery For Selected Patients)

SCHEMA (5/23/07)

<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>Both Arms:</th>
<th>8 Weeks</th>
<th>Selected Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>S 1. III</td>
<td>Palifermin/placebo begins on Day –3 (Friday) prior to start of RT/Chemo;</td>
<td>Post-Treatment Reassessment Required Neck Persistent nodal Dissection persistent nodal</td>
<td></td>
</tr>
<tr>
<td>T 2. IVA-B</td>
<td>Required CT/MRI Persistent nodal Disease, but Disease, but</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R N Tumor Site</td>
<td>Concurrent then on next 3 Fridays of RT/chemo, days 5, 12, 19 for all patients</td>
<td>Complete response</td>
<td></td>
</tr>
<tr>
<td>T 1. Oral cavity or oropharynx</td>
<td>O Arm 1: palifermin, Palifermin/placebo given</td>
<td>(total of 4 doses)</td>
<td></td>
</tr>
<tr>
<td>I Oropharynx</td>
<td>E 180 μg/kg on last Friday of RT/Chemo</td>
<td>If suspicion of relapse: Directed biopsy</td>
<td></td>
</tr>
<tr>
<td>F 2. Hypopharynx I</td>
<td>Use of IMRT if oral ulcers are present</td>
<td>for 3 weeks post-</td>
<td></td>
</tr>
<tr>
<td>Y or Larynx Z</td>
<td>Arm 1: palifermin, Palifermin/placebo given</td>
<td>Arm 2: placebo RT/Chemo until mucositis resolves to WHO grade 0-1 (no oral ulcers are present) (for a total of up to 4 doses)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a) See Section 5.1 for pre-registration requirements. NOTE: It is mandatory the treating physician determine the radiation therapy technique (3D-CRT vs. IMRT) to be used prior to the site registering the patient.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) See Sections 6.0, 7.0, and 8.0 for further details of radiation therapy, drug therapy, and surgery; for details of surgery for primary, see Section 8.2.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c) Note: After RT/chemotherapy is completed (last day of RT), palifermin or placebo should be discontinued if no ulcerative lesions in the oral mucosa are present (see Section 7.3 for further details of treatment).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patient Population: (See Section 3.0 for Eligibility) [5/23/07] [8/7/07] Patients with selected Stage III or IVA-B squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx (excluding T1N1M0) who are receiving concurrent radiotherapy and chemotherapy

Required Sample Size: 298
1. Does the patient have a histologically or cytologically proven diagnosis of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx? (Y)

2. Are there at least 2 mucosal subsites (see subsites on QP form) of the oral cavity/oropharynx mucosa assessable by visual transoral inspection that will receive at least 66 Gy? (Y)

3. Is the patient able to eat soft solids and not require a feeding tube for nutrition or hydration? (Y)

4. Is the patient a selected stage III (excluding T1N1M0) or IVA or IVB at study entry? (Y)

5. Did the patient have a thorough physical assessment with documentation of alcohol/tobacco history and current medications (including opioids/dosing) within 8 weeks prior to registration? (Y)

6. Has a chest x-ray or chest CT been done within 6 weeks prior to registration? (Y)

7. Has an MRI or CT scan with contrast of tumor site been done within 6 weeks of registration? (Y)

8. Has the patient had an assessment of mucositis (QP form) and xerostomia (XQ) within 2 weeks prior to registration/start of treatment according to study guidelines? (Y)

9. Is the Zubrod Performance Status 0-1? (Y)

10. Is the patient ≥ 18? (Y)

11. Are all lab parameters (e.g., hematologic, hepatic, metabolic and renal) within the ranges and within the defined time frames specified in Section 3.1? (Y)

12. If the patient is a female of child bearing potential, was a serum pregnancy test done 2 weeks prior to registration? (Y)

13. Has the patient agreed to refrain from using all products listed in Section 9.2, Non- permitted Supportive Therapy? (Y)

14. Was the informed consent signed? (Y)

15. Does patient have prior history of head and neck squamous cancer? (N)

16. Does patient have history of prior invasive malignancy other than head and neck, except non-melanomatous skin cancer? (Y)
   If yes, has the patient been disease free for a period of three years? (Y)

17. Has the patient had systemic chemotherapy for this cancer? (N)

18. Has the patient had prior radiation therapy to the planned treatment site? (N)

19. Has the patient had a surgical resection for this tumor? (N)

20. Does the patient have symptomatic and or uncontrolled cardiac disease (New York Heart Association classification III or IV)? (N)
21. Did patient have a transmural myocardial infarction within the last 6 months?

22. Does the patient have acute bacterial or fungal infection requiring intravenous antibiotics at time of registration?

23. Does the patient have COPD exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at time of registration?

24. Does the patient have hepatic insufficiency resulting in clinical jaundice and/or coagulation defects?

25. Is the patient sero-positive for hepatitis B virus (HBV) or hepatitis C virus (HCV)?

26. Is the patient sero-positive for human immunodeficiency virus (HIV), or does patient have Acquired Immune Deficiency Syndrome (AIDS)?

27. Does the patient have history of pancreatitis?

28. Does the patient have collagen vascular disease, such as scleroderma?

29. Has the patient previously been treated with palifermin or other keratinocyte growth factors, such as velafermin or repifermin?

30. Has the patient ever had prior allergic reaction or known sensitivity to any of the agents administered during dosing, including *E. coli*-derived products, such as Nutropin®, Neupogen®, Humulin®, Roferon®, Neumega®, Neulasta®, IntronA®, Betaseron®?

The following questions will be asked at Study Registration:

**CREDENTIALING FOR 3D-CRT OR IMRT IS REQUIRED BEFORE REGISTRATION.**

1. Name of institutional person registering this case?

2. Has the Eligibility Checklist (above) been completed?

3. Is the patient eligible for this study?

4. Date the study-specific Consent Form was signed? (must be prior to study entry)

5. Patient’s Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]

6. Verifying Physician

7. Patient’s ID Number

8. Date of Birth

9. Race
10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)

11. Gender

12. Patient’s Country of Residence

13. Zip Code (U.S. Residents)

14. Patient’s Insurance Status

15. Will any component of the patient’s care be given at a military or VA facility?

16. Calendar Base Date

17. Randomization date (This date will be populated automatically.)

18. Medical Oncologist’s name

19. Specify disease stage (III vs. IVA-B).

20. Specify tumor site (Oral cavity/oropharynx vs. hypopharynx/larynx).

21. Specify use of IMRT (no vs. yes).

22. Specify patient’s weight in Kg.

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by ____________________________ Date ________________________
1.0 INTRODUCTION

1.1 Radiation-Chemotherapy-Induced Oral Mucositis

Acute oral mucositis (defined to be 105 days [15 weeks] or less from the start of treatment) is the most common dose-delaying toxicity encountered in radiation therapy for head and neck cancer (HNC), and is dose limiting during more intensive altered fractionation and concurrent chemoradiation.1 Mucositis results in submucosal injury and the shedding of cells in the outer epithelium at a rate exceeding their replacement, so that the integrity of the mucosal barrier is interrupted.2 This results in painful erythema and, if severe enough, mucosal ulceration that can be patchy or confluent. Resulting symptoms include pain, dysphagia, odynophagia, dehydration, weight loss, airway obstruction, and aspiration. Mucositis may lead to micronutrient deficiency, dehydration, and negative nitrogen balance that may require intravenous hydration, the placement of a feeding gastrostomy tube acutely, or total peripheral venous hyperalimentation in order to maintain adequate nutrition and hydration. If the mucosal injury is severe enough, it may not heal and take on an ulcerative appearance, termed “a consequential late effect.” Some of these patients will be at risk for permanent gastrostomy feeding tube and tracheotomy dependence. Furthermore, any ulcerated area weakens the mucosal barrier, and may allow infection by resident pathogenic microorganisms of the oral cavity that have the potential to be life-threatening or fatal, especially if the patient is neutropenic as a result of systemic therapies. Other radiation-induced toxicities include hyposalivation with dryness of oral mucosa (xerostomia), loss of taste, and pain with chewing. A wide range of agents and interventions has been described in the literature as attempts to ameliorate mucositis symptoms.3 Currently, there is no FDA-approved intervention for the prevention of radiation-induced mucositis, and there is no standard therapy that reliably prevents mucositis, nor fosters recovery of radiotherapy-induced mucositis. Our current understanding of the pathophysiology of mucositis allows for the investigation of rational interventions at appropriate time in the mucositis process.2 One such approach is the use of epithelial growth factors.

1.2 Recombinant Human Keratinocyte Growth Factor (Palifermin) Background

Keratinocyte growth factor (KGF) is an epithelial-specific growth factor.4 Recombinant human KGF (palifermin) has been found to markedly reduce chemotherapy- and radiation-induced injury to the mucosal lining of the oral cavity and the lower gastrointestinal (GI) tract in a variety of animal models of chemotherapy, radiotherapy, and blood stem cell transplantation.5-6 The action of the drug appears to be bimodal: a growth-enhancing differentiation and a cytoprotective effect throughout the GI tract, both of which result in a thickening of the epithelial tissues (squamous epithelium of the oral cavity, and glandular tissue of the intestinal column). Results from in vivo experiments have been reported characterizing effects of palifermin on tumor response to chemotherapy and to radiotherapy in mouse models.7 Palifermin has demonstrated a clinical effect in reducing the incidence and duration of severe oral mucositis in two different clinical studies in patients with hematologic malignancies undergoing total body irradiation with high-dose chemotherapy and peripheral blood stem cell support leading to its approval by the US Food and Drug Administration (FDA) [Amgen studies 980231 and 20000162].8-9 In addition, a placebo-controlled study of palifermin performed in colorectal cancer patients receiving 5-Fluorouracil chemotherapy with leucovorin showed a reduction of oral mucositis in that disease setting as well10 (Amgen Inc.; Data on file).

There is no current human data demonstrating the efficacy of palifermin to reduce mucositis in patients undergoing chemoradiation. A prior study evaluating palifermin efficacy in reducing the duration of mucositis in patients with locally advanced HNC receiving once-daily or twice-daily radiation therapy (RT) with concurrent cisplatin/5-fluorouracil chemotherapy (phase 2 study 990119) failed to consistently and significantly show a decrease in the severity/duration of mucosal toxicity. It was hypothesized that a lack of palifermin activity in this trial was due to the use of a sub-optimal dose schedule, i.e., weekly 60 μg/kg palifermin (Amgen Inc., Data on file). As a consequence, a dose finding study was performed.

A phase I trial (20010192) was recently conducted in 79 normal volunteers to explore the dose-response (as measured by proliferation of epithelial cells in the buccal mucosa) relationship of single palifermin escalating doses up to 250 μg/kg (Amgen Inc., Data on file). Results of this study: 1) confirmed that the dose of 60 μg/kg/day, when administered as a single dose, is sub-optimal in inducing epithelial cell proliferation as measured by Ki67 staining; and 2) showed a
dose-response curve up to the dose of 250 μg/kg/day with a plateau phase around 160 μg/kg/day for epithelial cell proliferation.

The current study is designed to evaluate the efficacy and safety of multiple weekly administrations of palifermin at doses determined to be effective in this phase I study to patients with advanced HNC receiving standard definitive radiotherapy/chemotherapy. In particular, the study design uses a dose-schedule of palifermin that emphasizes reducing the time to onset and the resolution of mucositis by delivering the agent in the early and post-treatment temporal phases of the chemoradiotherapy schedule.

In a separate study to be conducted by Amgen, weekly dose administration (weeks 1-7) will be compared to placebo in H&N patients receiving chemoradiotherapy with cisplatin. Thus, the current study focuses on lessons directly from preclinical data for dose–schedule design and tests a separate question than the Amgen-sponsored trial.

1.3 Rationale for Palifermin Dose Schedule and Radiotherapy/Chemotherapy Regimens

The main objective of this study is to evaluate the efficacy for mucositis and symptom reduction and the safety of multiple weekly administrations of palifermin at the dose of 180 μg/kg to patients with advanced HNC receiving definitive radiotherapy/chemotherapy.

1.3.1 Selection of Palifermin Dose Schedule

The dose of 180 μg/kg was selected for this study based on the following:

- Preclinical studies with daily exposure 8 to 20 times the intended human dose of 180 μg/kg were well tolerated in animals.
- The concept of collapsing multiple palifermin doses had previously been demonstrated in animal models of gastrointestinal tract mucosal injury, where a three-day (5 mg/kg/day x 3 days) and a one-day (15 mg/kg/day x 1 day) pre-treatment course of palifermin demonstrated equivalent efficacy in reducing chemotherapy-induced mucosal ulceration and weight loss, and in improving overall survival.11-12

For reasons of clinical safety and practicality, a split dose schedule is not feasible for the treatment of patients with head and neck cancer receiving radiotherapy with concurrent chemotherapy, as this requires palifermin dosing overlapping with radio and/or chemotherapy, as well as during weekends. From clinical data in patients with hematological malignancies, it is recommended that palifermin should not be administered within 24 hours of chemotherapy, as this may result in an increased severity and duration of oral mucositis. Therefore, a collapsed dose of 180 μg/kg given on Fridays after completion of radiotherapy is the only possibility to maintain a feasible dosing schedule and to avoid administering palifermin during radiotherapy with concurrent chemotherapy or on Saturdays.

- Comparison of the biologic activity and adverse event profile data from the healthy volunteers study (study 20010192) demonstrated that the dose of 180 μg/kg will likely give the optimum balance between biologic activity (areas of Ki67 staining at 48 hours post-palifermin administration) and the reversible acute adverse events considered related to palifermin (skin and oral reactions).
- More than 780 subjects have been exposed to palifermin in doses ranging from 0.2 μg/kg up to 250 μg/kg during phase I, II, and III clinical trials. Investigational product schedules included daily administration for 1 to 3 consecutive days pre-chemoradiotherapy and pre/post-chemoradiotherapy, and once weekly administration for up to 10 weeks. One hundred thirteen head and neck cancer patients have been exposed to once weekly palifermin administrations up to 10 weeks in a phase I study (970149 – 20 to 80 μg/kg) and a phase II study (990119 – 60 μg/kg).

Experience to date indicates that single daily palifermin doses up to 250 μg/kg and weekly palifermin administrations up to 80 μg/kg are generally well tolerated with a similar adverse event profile observed in palifermin and placebo subjects. Sub-acute skin and oral reactions represent one exception: they have been observed more frequently in cancer patients receiving palifermin than in placebo recipients, and in almost all the volunteers receiving palifermin at doses > 200 μg/kg (Amgen Inc., Data on file). The skin reactions manifested as erythema, flushing, edema and pruritus occurring on all areas of the body. Oral reactions included tingling of lips and mouth, thickening of tongue and oral mucosa, loss of taste, and mucosal erythema. These reactions typically started 12 hours after
palifermin administration, were generally described as mild to moderate in severity, and mostly resolved without intervention within a few days. They appeared to be dose related and are thought to be related to the pharmacological activity of palifermin.

- The dose of 180 μg/kg is the same cumulative dose of palifermin that has shown clinical activity (i.e., reduction in the duration of severe oral mucositis) when administered in phase II and phase III trials to patients with hematologic malignancies (studies 980231 and 20000162) receiving myeloablative therapy with peripheral blood stem cell support. In these studies, 60 μg/kg/day palifermin was administered for 3 consecutive days before conditioning treatment and for 3 days after stem cell infusion, resulting in both a clinically and statistically significant reduction in the duration of severe oral mucositis and related clinical sequelae. Of note, the concept of collapsing multiple palifermin doses has previously been demonstrated in animal models of GI tract mucosal injury where a three-day (5 mg/kg/day x 3d) and a one-day (15 mg/kg/day x 1d) pre-treatment course of palifermin demonstrated equivalent efficacy in reducing chemotherapy-induced mucosal ulceration and weight loss, and in improving overall survival.11

- Results from preclinical experiments indicate that the mucositis protective effect of palifermin was more pronounced if palifermin was given before radiation-induced ulceration became manifest,12 as opposed to its use concurrent with RT after the mucositis injury was manifested.

Therefore, this study is designed to evaluate whether weekly palifermin started prior to chemoradiation and continued until the onset of ulcerative mucositis is more effective than placebo in reducing oral mucositis during treatment. This study also is designed to evaluate if palifermin administered after the completion of chemoradiation is more effective than placebo in reducing the time to recovery from oral mucositis.

1.3.2 Palifermin Safety Data to Date

- The adverse event profile of palifermin, 2 x 180 μg/kg/day, in 12 patients undergoing high-dose myelotoxic therapy (study 20010182 part B) further indicated that single doses of palifermin at this dose level are well tolerated. To date, at total of 65 patients have received the 180 μg/kg dose in clinical studies without any dose limiting toxicities.

- Based on the overall efficacy and safety profile of palifermin available at the time of designing the solid tumor clinical trials program, a weekly dose of 180 μg/kg was initially selected for four Amgen sponsored studies in head and neck cancer or NSCLC. It is noted that prior to the start of the 20040118 study in resected head and neck cancer patients, the weekly palifermin dose of 180 μg/kg weekly had not been administered to patients who had recently undergone surgery for their carcinoma.

- Preliminary safety information from ongoing palifermin clinical studies demonstrate no safety signals observed in non-surgical subjects treated thus far with IP at the 180 μg/kg dose.

1.3.2.1 Palifermin Serious Adverse Events

One recent serious adverse event involving palifermin was reported in April 2005 from a study conducted in Europe (study number 20040118), in which a patient developed respiratory insufficiency and severe tongue edema during head and neck cancer treatment with radiation, chemotherapy, and palifermin post-operatively. This event prompted a review of the available safety data from 10 subjects by the independent Data Monitoring Committee held on May 9, 2005. The DMC recommended reducing the dose to 120 μg/kg weekly for all studies in patients with resected carcinomas based on the following:

- Of the 10 patients reviewed by the DMC from studies 20030185 and 20040118, three patients had discontinued IP:
  1. The first subject (study 20040118) discontinued after 2 doses of IP due to oral and skin adverse events.
  2. The second subject (study 20030185) requested to discontinue IP after 5 doses. This patient experienced pulmonary embolism requiring hospitalization. The patient had prior history of pulmonary embolism and had started the study on Coumadin; however, the INR (international normalized ratio) was suboptimal.
  3. The third patient (study 20040118) requested to discontinue IP after 6 doses due to hypersalivation. This subject also experienced swelling in the area of tracheostoma, skin rash (with pruritus and dysesthesia) in the head, neck and trunk areas, edema of the tongue and oral mucosa, and taste alterations.

- A total of 3 patients with head and neck cancer or non-small cell lung cancer receiving doses of 180 μg/kg IP, experienced a Serious Adverse Event:
(1) Pulmonary embolism (patient mentioned above, study 20030185).
(2) One patient (study 20040118) experienced respiratory insufficiency and edema of the mouth after 3 doses of IP due to swelling of oral structures. The patient required tracheotomy and continued on IP.
(3) One patient (study 20030185) had neutropenic sepsis at week 8, approximately 2 weeks after the last dose of IP and after 1 chemo consolidation cycle.

On the basis of the DMC recommendation, studies in resected patients were amended to be conducted at a reduced dose of IP of 120 μg/kg/week. This amendment included the new safety information as well. However, the DMC specifically recommended continuation of all studies in unresected patients (Head and Neck Cancer Study 20020402 and Non-small Cell Lung Cancer Study 20030185) to be continued at a weekly dose level of 180 μg/kg. Tolerability of palifermin at this dose level is anticipated to be higher in an unresected patient population.

1.3.3 Radiotherapy/Chemotherapy Regimens

Once-daily standard fraction radiotherapy (2 Gy/day x 5 days/week for a total of 70Gy in 7 weeks) with concurrent chemotherapy is considered a standard treatment approach for patients with locally advanced unresected HNC.13-14

A variety of drugs (both as single agent and in combination) have been used concurrently with RT, yet no particular chemotherapy regimen has evolved as the absolute standard of care within the U.S. or globally. Cisplatin is the only chemotherapy drug used concurrently with radiotherapy for HNC, however, that has been shown to improve survival in multiple randomized, prospective clinical trials.14-16 As a result, the RTOG standard treatment for patients with locally advanced HNC is once-daily RT (70Gy in 7 weeks) combined with concurrent cisplatin at 100mg/m² on days 1, 22, and 43. The addition of this chemotherapy may improve survival, but results in an approximate doubling in the rate of severe mucositis.

In conclusion, definitive RT/Chemotherapy treatment is associated with a high incidence of severe oral mucositis and related sequelae. Palifermin, if found safe and effective in reducing the incidence and severity of oral mucositis, could meet a significant unmet medical need, improve patients' well-being, and reduce the use of health resources.

1.3.4 Safety Considerations: Palifermin Tolerability, Lack of Neutralizing Antibody Protection, Lack of Tumor Growth Stimulation

Safety issues arise when considering the use of a non-fully humanized epithelial growth factor during cancer therapy. While the tolerability of palifermin administered weekly at dose levels above 180 μg/kg is not known, based on available pharmacokinetics data, no accumulation of palifermin is expected after once weekly dosing of palifermin.

Antibody formation is a theoretical concern with any protein based therapy, the risk of formation with palifermin is not felt to be significant. A total of the 964 subjects in palifermin clinical trials were tested by an electrochemiluminescence immunoassay, 2% of subjects in each group (12/643 palifermin-treated subjects and 5/321 placebo-treated subjects) tested positive at one or more post-dose time points for anti-palifermin antibodies. All were below the quantitation limit of the confirmatory assay. None of these subjects showed any neutralizing activity in the confirmatory bioassay. Based on these data, routine antibody testing within this study will not be required.

In view of the theoretical risk that palifermin, being an epithelial growth factor, could stimulate the growth of tumors carrying KGF receptors, this study will include long-term follow up of all subjects to monitor loco-regional and distant tumor control, second primary malignancy development, and survival. No evidence has been found to date from palifermin clinical studies to indicate that tumors could be protected by palifermin from treatment efficacy or that patient survival could be impacted negatively. Patients will be followed long term to evaluate these endpoints. Disease outcome and survival data from this trial will be subject to review by an independent data monitoring committee (DMC) that oversees the safety data from several of palifermin studies conducted as part of Amgen’s palifermin clinical development program.

Long-term follow up has been assessed in two previous studies of palifermin in locally advanced head and neck cancer utilizing radiotherapy plus concurrent chemotherapy. Of 159 subjects that received investigational product, 46 received placebo and 113 received
palifermin. Subjects were monitored for disease and survival status every 3 months for the first year and then annually until death or when lost to follow-up. As of August 10, 2004, 11 of 46 subjects (24%) in the placebo group and 31 of 113 (27%) in the palifermin group have died. Overall, rates for survival, disease progression, and progression-free survival for subjects in these studies compare favorably to the rates reported in the literature for similar patient populations (Palifermin Investigator’s Brochure).

Results of long-term follow up in metastatic colorectal cancer also have been assessed. These patients received multiple cycles of chemotherapy without radiation. Of 145 subjects enrolled in the 950225 study, a total of 123 (84% placebo, 85% palifermin) have died. Deaths primarily resulted from disease progression in both treatment groups (Palifermin Investigator’s Brochure).

1.4 Mucositis Assessments (5/23/07)
A standardized grading system and a rigorous mucositis assessment schedule are critical to the reliability of the key endpoints in mucositis trials. Mucositis assessments have been routinely conducted by RTOG investigators for more than 20 years using a standardized grading scale, the RTOG acute mucositis scale. However, this scale was designed for broad toxicity assessment, not for a key mucositis trial endpoint.

RTOG 0435 will utilize the WHO scale for assessment of the primary endpoint. The WHO grade will be calculated at RTOG Headquarters after collection of specific data components by local investigators. The 4 data components are:
1. The presence of mouth or throat pain (and use of opioids);
2. The mode of nutrition (oral vs. non-oral);
3. The form of nutrition (solids vs. liquids);
4. The presence of ulceration.

A computer-based mucositis training program will be used to enhance consistency in mucositis assessments among investigators. This will include specific diagrams of pre-defined mucosal subsites and photos of various mucositis grades. Investigators will be required to register and complete the computer-based training program before enrolling patients to this trial (see Section 5.1.6).

1.5 Functional and Symptom Assessments
It is now well recognized that comprehensive treatment evaluation must include assessment of the patient’s function and symptom burden. In HNSCC, both the disease and its treatment have the potential to significantly impact key functions, such as eating, speaking, and socializing. Most recently, investigators have documented the effects of intensive chemoradiotherapy regimens. While these treatments minimize surgery and consequently disfigurement, they have other significant immediate, delayed and potentially long-term side effects that may profoundly influence symptom burden. Radiotherapy, particularly combined with radiosensitizing chemotherapy, is associated with severe mucositis, sticky saliva, pain, dry mouth, hoarseness, skin irritation and difficulties in swallowing and tasting, with many of these symptoms persisting years after treatment completion. For example, in studies of patients on regimens similar to those used in the current protocol, List and colleagues observed that on-treatment, up to three-quarters of patients reported moderate to severe problems with dry mouth, swallowing, tasting, sticky saliva and hoarse voice. While there was some improvement in most symptoms over 12 months, there was little change in dry mouth and over a third continued to report difficulties with sticky saliva and swallowing. In addition, patients’ diets remained extremely restricted with a half to three-quarters on a soft food diet at 12 months. Longer follow-up (2-4 years post-treatment) of these patients suggested some continued recovery in ability to eat a full range of foods and comfort in eating with others, although a third still had significant restrictions in diet and there was little change in other QOL or symptom domains post 12 months. Recent longer term follow-up of a second cohort of patients treated with intensive chemoradiotherapy has shown virtually no change in any QOL dimension, report of symptoms or performance status from 12 months to 2-4 years post-treatment completion.

There are to date, very few, if any data on the impact of adding novel biologic agents like palifermin, in attempt to reduce toxicities of chemoradiotherapy regimens. While such agents might be expected to add little toxicity themselves, empirical documentation of all relevant effects is critical. As more and more trials are beginning to use, and often times, add these new biologic
agents, it is important to demonstrate that they significantly improve either quality of life or performance/function, or reduce patient symptom burden. As described above, while some small single arm cohort studies have suggested relatively long-term continued impairment (and even worsening) in some areas, examination of the late effects in a large study is warranted. This study will be one of the first to prospectively and systematically assess symptom burden, function and performance up to 5 years or more post-treatment. The current study will employ the M.D. Anderson Symptom Inventory for Head and Neck Cancer (MDASI-HN) and the Brief Pain Inventory (BPI).

1.5.1 The M.D. Anderson Symptom Inventory for Head and Neck Cancer (MDASI-HN)
Symptoms will be systematically assessed using the validated MDASI. The MDASI has been used in Phase I though Phase IV trials in the U.S. and in Europe. This tool can be used in clinical and research settings. The MDASI measures on a numeric rating scale of 0-10 both severity of symptoms and the interference symptoms cause in patients daily activities. The 13 core MDASI symptom items are based on extensive evaluation of symptoms common to cancer and cancer treatment. Symptoms on the core MDASI include pain, fatigue, and appetite changes that the HNC population typically experiences. Patients easily complete it as a self-report tool, or it can be completed with the help of research staff either in the clinic or over the telephone with an interactive voice response system.

The MDASI was developed to add items relevant to specific cancers and cancer treatments to patient-completed modules. Site-specific items for the Head and Neck module (MDASI-HN) were developed through focus groups with head and neck cancer patients, and specialists in surgical, medical, dental, and radiation oncology, and symptom researchers. This instrument includes 12-14 head and neck specific items, including at least 5 that do not appear in the FACT-HN. In fact, many of the most intense symptoms reported do not appear on FACT-HN. The instrument was validated in a cohort of more than 200 patients. The coefficient alpha was highly reliable. The MDASI takes about 5 minutes for patients to complete, and is being validated in several languages.

1.5.2 The Brief Pain Inventory (BPI)
The BPI asks patients to rate their pain for the last week on 0-10 scales at its ‘worst,’ ‘least,’ ‘average,’ and ‘now.’ The scales are presented on a 10 cm line, with each number equidistant from the next. Each scale is bounded by the words ‘no pain’ at the 0 end and ‘pain as bad as you can imagine’ at the other. Using the same type of scales, patients are also asked to rate how their pain interferes with several quality of life domains including activity, walking, mood, sleep, work, and relations with others. These scales are bounded by ‘does not interfere’ at the 0 end and ‘interferes completely’ at the other. Patients also are asked to estimate the pain relief they are receiving from their pain treatment (in percent), to locate areas of pain on a human figure, and to estimate the cause of their pain (cancer disease, cancer treatment, or non-cancer). The patient can complete the BPI in approximately 5 minutes, and the assessment is available in 12 languages.

Issues of the validity and reliability of the BPI have been examined in detail. The BPI’s ease of translation and brief administration have made it a frequently used tool in clinical trials where reduction or prevention of pain are primary or secondary outcome measures, and it is considered as the FDA standard for a pain assessment tool. The typical standard deviation for the item “worst pain” in most cancer populations is 2.4. Therefore, the finding of a one-point difference in the “worst pain” item at different times or between to comparative groups is considered significant. In this setting, narcotic use is not corrected for, but that data is collected and tracked in the form of morphine-equivalents.

1.6 Xerostomia (5/23/07)
Xerostomia is permanent and unrelenting after standard RT for head and neck squamous cell carcinoma (HNSCC), and represents a major distressing symptom for long-term head and neck cancer survivors. Harrison et al reported that all (100%) patients treated for oropharyngeal cancer with standard RT techniques experienced xerostomia. The standard radiation therapy for advanced oropharyngeal tumors typically involves the collateral administration of high radiation dose to the salivary glands bilaterally. In most cases this causes a marked reduction in oral salivary output. Xerostomia, the patient’s perception of decreased salivary output, is the most prevalent late side effect of radiation for head and neck malignancies and is cited by many patients as the major cause of their decreased quality of life. In addition to its effects on subjective well-being, decreased saliva output causes alterations in speech, taste, and difficulties...
with mastication and deglutition that create secondary nutritional deficiencies. Saliva is a complex body fluid; 92% to 98% of its composition is water, and the rest is an array of immunoglobulins, proteins, enzymes, small organic molecules, and other components that protect, repair, and moisturize the oral cavity and hold at bay more pathogenic bacteria, viruses, and fungi. Oral mucosal dryness creates a predisposition to fissures and ulcers; while changes in the composition of the oral flora lead to dental caries and opportunistic infections. While for most toxicities, grade 3 is considered the threshold for being serious, the FDA has also recommended that grade 2 xerostomia be included as having a clinically significant negative impact on patient function and quality of life. Therefore, a reduction in the incidence of grade 2 xerostomia has been accepted as a clinically meaningful endpoint in clinical trials.35

The radiation dose to and its effects on salivary tissue can be reduced by physical or chemical techniques. Physical techniques include submandibular salivary transfer, and the more conformal RT treatment delivery including IMRT for parotid salivary sparing. Chemical techniques include the use of normal tissue cytoprotectants such as amifostine. IMRT leads to a relative but not absolute sparing of parotid function. Studies evaluating post-IMRT xerostomia demonstrated that up to 70% of patients have at least some symptoms of dry mouth,36 and that up to 30% of patients had late grade 2 xerostomia.37 The use of IMRT does not reduce the incidence of severe mucositis or its consequences, including gastrostomy feeding tube placement rates.37

In June 1999, amifostine was approved by the FDA to reduce the incidence of moderate to severe xerostomia in patients undergoing post-operative RT for head and neck cancer, where the radiation port includes a substantial portion of the parotid glands. On an intent-to-treat basis, the incidence of Grade 2 acute xerostomia was significantly reduced in those patients treated with amifostine (51% vs. 78%, p<0.0001), and the mean cumulative radiation dose received at onset of Grade 2 acute xerostomia increased (60 vs. 42 Gy, p=0.0001). Grade 2 late-effect xerostomia occurred in 57% of patients in the control arm and 31% of patients in the amifostine arm (p=0.002). However, no difference was apparent in the incidence of Grade 3 mucositis between the amifostine (35%) and control (38%) arms.35 Amifostine did not reduce the incidence of more severe mucositis in this trial and has done so inconsistently in other trials. There may be a dose-response relationship for amifostine in that it may require a higher than standard dose for mucositis reduction. Neither IMRT nor amifostine use is applicable to all patients undergoing RT for HNSCC, and both are used in a relative minority of patients. Amifostine is proscribed in this trial. There is evidence that palifermin may have the potential to protect salivary tissue from the effects of irradiation (Amgen’s Palifermin Investigator Brochure), and this will be evaluated as a secondary end point in this trial.

The “response definition” for sialometry is the actual volume measured and its function. Unfortunately, there has been no clear clinical benefit from an increase in saliva output. Doubling of saliva output or an increase of 0.5 mL per minute is not always associated with a subjective clinical benefit but does represent an objective surrogate of response. The only endpoint currently accepted is subjective response as it provides an accepted unequivocal clinical benefit. However, there are many subjective criteria and scales used, and there is no single accepted endpoint or instrument. Pilocarpine and cevimeline tested subjective response and used a global questionnaire (different for each) as the primary endpoint.

Patient self-reporting is the most meaningful xerostomia assessment. To facilitate patient self-reporting, a Xerostomia Questionnaire (XQ) has been developed at the University of Michigan.38 The XQ consists of eight questions: four questions related to dryness while eating/talking, and four questions related to dryness at rest. Patients rate each symptom on an 11-point ordinal Likert scale from 0 to 10, with higher scores indicating greater dryness or discomfort because of dryness. Each item scored is added, and the sum is transformed linearly to produce the final summary score ranging between 0 and 100, with higher scores representing greater levels of xerostomia.38

The XQ was found to be reliable, valid, and reproducible in measuring patient-reported xerostomia.39-40 The XQ has been independently validated by investigators at the University of Florida, who found that it distinguished accurately between patient groups according to their parotid gland doses.41
2.0 OBJECTIVES

2.1 Primary Objective
To determine the burden of acute mucositis (defined to be 105 days [15 weeks] or less from the start of treatment) in patients receiving palifermin/placebo during concurrent chemoradiation for HNSCC

2.2 Secondary Objectives (5/23/07)
2.2.1 Incidence and time to onset of mucositis:
2.2.1.1 For grades 3 or 4 oral mucositis, based on the WHO scale.
2.2.2 Patient-reported outcomes:
2.2.2.1 Assessment of symptom burden (MD Anderson Symptom Inventory-Head and Neck (MDASI-HN)
2.2.2.2 Brief Pain Inventory (BPI);
2.2.2.3 University of Michigan Xerostomia Questionnaire (XQ);
2.2.3 Opioid analgesics utilization (total dose in morphine equivalents);
2.2.4 Evaluation of long-term effects of palifermin/placebo on disease outcome, (second primaries other than basal cell), and survival after radiation therapy and chemotherapy.

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED.

3.1 Conditions for Patient Eligibility (5/23/07) (8/7/07)
3.1.1 Pathologically (histologically or cytologically) proven (from primary lesion and/or lymph nodes) diagnosis of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx;
3.1.2 Patients must have at least 2 mucosal sites of the oral cavity/oropharynx mucosa assessable by visual transoral inspection that will receive at least 66 Gy;
3.1.2.1 Patients with tumors of the larynx or hypolarynx are eligible only if it is anticipated that the 2 index sites in the oral cavity/oropharynx mucosa will receive at least 66 Gy;
3.1.3 Patients must be able to be evaluated for the primary endpoint; therefore, patients must be able to eat at least soft solids and not require a feeding tube for nutrition or hydration at study entry.
3.1.4 Selected Stage III (excluding T1N1MO) or IVA-B (AJCC, 6th edition) at study entry, including no distant metastases, based upon the following minimum diagnostic workup:
3.1.4.1 History/physical examination, including documentation of tobacco/alcohol use and current medications (including opioids/dosing), within 8 weeks prior to registration;
3.1.4.2 Chest x-ray (or Chest CT scan) within 6 weeks prior to registration;
3.1.4.3 MRI or CT scan with contrast of tumor site within 6 weeks prior to registration;
3.1.4.4 Assessment of mucositis and xerostomia within 2 weeks prior to registration;
3.1.5 Zubrod Performance Status 0-1;
3.1.6 Age ≥ 18;
3.1.7 Adequate bone marrow function, defined as follows:
3.1.7.1 Absolute neutrophil count (ANC) ≥ 1,800 cells/mm³ based upon CBC/differential obtained within 2 weeks prior to registration on study
3.1.7.2 Platelets ≥ 100,000 cells/mm³ based upon CBC/differential obtained within 2 weeks prior to registration on study
3.1.7.3 Hemoglobin ≥ 8.0 g/dl based upon CBC/differential obtained within 2 weeks prior to registration on study (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)
3.1.8 Adequate hepatic function with bilirubin < 1.5 mg/dl, AST or ALT < 2 x ULN within 2 weeks prior to registration;
3.1.9 Adequate renal function with serum creatinine < 1.5 mg/dl and creatinine clearance (CC) ≥ 50 ml/min within 2 weeks prior to registration determined by 24-hour collection or estimated by Cockcroft-Gault formula:

\[
CCr \text{ male} = \frac{[(140 \text{ – age}) \times (\text{wt in kg})]}{[(\text{Serum Cr mg/dl}) \times (72)]}
\]

\[
CCr \text{ female} = 0.85 \times (\text{CrCl male})
\]
3.1.10 Normal serum calcium or normal corrected serum calcium within 2 weeks prior to registration; formula for corrected calcium if albumin valued is below normal range:

Corrected calcium (mg/dl) = (4 – [patient’s albumin (g/dl)] x 0.8) + patient’s measured calcium (mg/dl);
3.1.11 Serum pregnancy test for women of childbearing potential within 2 weeks prior to registration;
3.1.12 Women of childbearing potential and male participants must practice adequate contraception.
3.1.13 Patient agrees to refrain from using all products listed in Section 9.2, “Non-permitted Supportive Therapy”;
3.1.14 Patient must sign study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility (5/23/07) (8/7/07)
3.2.1 Patients with a history of prior head and neck squamous cancer are ineligible;
3.2.2 Stage IVC (AJCC, 6th edition) [Any T, Any N, M1] or distant metastases at protocol study entry; T1N1M0 patients are excluded.
3.2.3 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years;
3.2.4 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable. See Sections 3.2.1 and 3.2.3.
3.2.5 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
3.2.6 Initial surgical treatment, excluding diagnostic biopsy of the primary site or nodal sampling of neck disease; radical or modified neck dissection is not permitted.
3.2.7 Severe, active co-morbidity, defined as follows:
   3.2.7.1 Symptomatic and/or uncontrolled cardiac disease, New York Heart Association Classification III or IV (see Appendix II);
   3.2.7.2 Transmural myocardial infarction within the last 6 months;
   3.2.7.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
   3.2.7.4 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration.
   3.2.7.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects;
   3.2.7.6 Patients known to be sero-positive for hepatitis B virus (HBV) or hepatitis C virus (HCV);
   3.2.7.7 Patients known to be sero-positive for human immunodeficiency virus (HIV) or patients with Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with HIV or AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.
   3.2.7.8 A history of pancreatitis.
   3.2.8 Collagen vascular disease, such as scleroderma, as this disease is thought to predispose patients to increased risk for radiation-associated toxicities;
   3.2.9 Previous treatment with palifermin or other keratinocyte growth factors, such as velafermin or repifermin;
   3.2.10 Prior allergic reaction or known sensitivity to any of the agents administered during dosing, including E. coli-derived products, such as Nutropin®, Neupogen®, Humulin®, Roferon®; Neumega®, Neulasta®, IntronA®, Betaseron®;
   3.2.11 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

4.0 ADDITIONAL PRETREATMENT EVALUATIONS/MANAGEMENT (5/23/07)
(In addition to the mandatory pre-testing for eligibility in Section 3.0)

4.1 Additional Highly Recommended Pre-treatment Evaluations/Interventions
4.1.1 Functional and Symptom Assessments: MD Anderson Symptom Inventory-Head and Neck (MDASI-HN), Brief Pain Inventory (BPI), and University of Michigan Xerostomia Questionnaire (XQ);
4.1.2 Dental evaluation, treatment, and (if applicable) prophylaxis; see Appendix V.

5.0 REGISTRATION PROCEDURES
5.1 Pre-Registration Requirements
   NOTE: It is mandatory the treating physician determine the radiation therapy technique (3D-CRT vs. IMRT) to be used prior to the site registering the patient.
5.1.1 Pre-Registration Requirements for 3DCRT Treatment Approach
   Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in 3D-CRT Quality Assurance Guidelines may enter patients to this study.
The 3D Questionnaire [one per institution, see Washington University Image-Guided Center (ITC) web site at http://itc.wustl.edu] is to be sent to the ITC for review prior to entering any cases. Upon review and successful completion of “Dry-Run” or “Benchmark” QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution is eligible to enter patients onto this study. Institutions that have previously enrolled patients on 3D CRT trials of this same disease site may enroll patients on this study without further credentialing by the ITC.

5.1.2 Pre-Registration Requirements for IMRT Treatment Approach
In order to utilize IMRT, the institution must have met technology requirements and have provided the baseline physics information described on the Advanced Technology Consortium (ATC) web site, http://atc.wustl.edu. As it pertains to this study, the ATC includes the Image-Guided Therapy Center (ITC) at Washington University; the Radiological Physics Center (RPC) at MD Anderson Cancer Center; and, St. Louis and RTOG RT Quality Assurance.

Institutions that have been certified by the ATC to participate in RTOG head and neck-specific studies (e.g., RTOG 0022 or RTOG 0225) may enroll patients on this study without further credentialing by the ITC.

Institutions that have not been certified by the ATC to participate in head and neck-specific IMRT studies (e.g., RTOG 0022 or RTOG 0225) MUST apply for IMRT certification as described in Sections 5.1.1-5.1.2.

5.1.3 IMRT Certification Process (For institutions not previously certified for RTOG head and neck – specific IMRT studies)
5.1.3.1 First, the institution or investigator anticipating the use of IMRT on this study must complete a new IMRT Facility Questionnaire (see http://atc.wustl.edu). The IMRT Facility Questionnaire requests information regarding the training and experience of the IMRT team; IMRT treatment planning and treatment equipment; and in-house QA procedures.

5.1.3.2 Next, the institution must successfully complete an IMRT “dry-run” or benchmark case with the ITC. This will require that the institution set up an FTP account for digital data submission by contacting the ITC (itc@castor.wustl.edu).

5.1.3.3 Finally, an IMRT phantom study with the Radiological Physics Center (RPC) at MD Anderson Cancer Center must be successfully completed (if the institution has not previously met this credentialing requirement on another RTOG IMRT study). Instructions for requesting and irradiating the phantom are available at the RPC web site, http://rpc.mdanderson.org/rpc/ by selecting “Credentialing” and “RTOG”.

5.1.4 Pre-Registration Requirements for Palifermin/Placebo (5/23/07)
5.1.4.1 U.S. and Canadian sites must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206) prior to registration of the institution’s first case:
- IRB approval letter;
- IRB approved consent form;
- Federalwide Assurance (FWA) number;
- For Canadian sites: Health Canada’s TPD Forms.

5.1.4.2 Note: International sites must receive written approval of submitted LOI forms (http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form_1-2007.pdf) from RTOG Headquarters prior to submitting documents to their Local Ethics Committee for approval.

Approved international sites fax copies of the documentation below to RTOG Headquarters (215-574-0300) prior to registration of the institution’s first case:
- IRB approval letter;
- IRB approved consent form;
- Federalwide Assurance (FWA) number.

5.1.4.3 For shipment of palifermin/placebo:
The Principal Investigator (or authorized designee) at each participating institution may request palifermin/placebo from NCI’s Pharmaceutical Management Branch (PMB). See Section 7.3.8 for details.

5.1.5 Mucositis Training Process (5/23/07) (8/7/07)
In order to enhance consistency in mucositis assessments, investigators are required to complete a computer-based training program prior to enrolling patients to this trial. The training
will include specific diagrams of pre-defined mucosal subsites and photos of mucositis. In addition, investigators must agree to carry out mucositis assessments twice each week during radiation therapy (RT) until ulcerative mucositis resolves or until 8 weeks after completion of RT. Any investigator or designated research staff (nurse; non-nurse research associate) may perform mucositis assessments, as long as they have completed the on-line mucositis assessment training.

5.1.5.1 First, the investigators conducting mucositis assessments at the institution will access the RTOG web site, http://www.rtog.org, using their RTOG user name and password. Next to the protocol, investigators will find "Mucositis Training Instructions", which will provide a link to the training registration site.

5.1.5.2 The training registration site will prompt investigators to enter their institution, name, contact information, and e-mail address. Within 48 hours, investigators will receive a username and password and a link to the training web site.

5.1.5.3 Investigators will access the training web site and complete the training program. A certificate will be issued to the investigators confirming their successful completion of the training.

5.1.5.4 Finally, investigators will fax a copy of the certificate to RTOG Headquarters; FAX 215-574-0300. Note: The fax must include the investigator's name, institution, the institution’s RTOG number, and the institution’s NCI code. A fax without these items will be returned to the investigator and will delay the investigator’s ability to enroll patients.

Note: Investigators can contact ePharmaSolutions (ePS) for assistance with passwords or web site access: 1-800-503-9480 or 1-610-832-8098 or http://help.epharmalearning.com.

5.2 Registration

5.2.1 Online Registration

Patients can be registered only after eligibility criteria are met. Institutions must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The Investigator must have completed Human Subjects Training and been issued a certificate (Training is available via http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp).
- The institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (http://www.rtog.org), going to "Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study’s database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: websupport@phila.acr.org.
In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site’s user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY

Radiation therapy should begin within 2-4 weeks of registration.

A radiation dose of 70 Gy with at least 66 Gy to at least 2 mucosal sites of the oral cavity/oropharynx mucosa must be planned for the patient.

Note: Radiotherapy can be given with 3D conformal (3D-CRT) or with Intensity Modulated RT (IMRT) techniques; however, the chosen modality must be used for the entire course of treatment. See pre-registration requirements for IMRT in Section 5.1.

Patients will be stratified by the radiation technique used. It also should be noted that IMRT generally has little advantage for patients with laryngeal carcinoma with no demonstrable or limited nodal disease, as it is not necessary to irradiate whole parotid glands in these patients.

It is highly recommended that dosimetry information be submitted digitally; see Section 12.2. Sites unable to submit digitally will contact RTOG Headquarters, RTQA Department, 215-574-3219.

6.1 Dose Specifications

6.1.1 Conformal (3D) Radiotherapy

Standard-fraction radiotherapy will be given 2 Gy per day, 5 days per week, for 7 weeks for a total of 70 Gy. Note: It is highly recommended that all patients begin radiation therapy and chemotherapy on a Monday.

The primary tumor and clinically or radiologically involved nodes will receive 70 Gy in 7 weeks and uninvolved nodes will receive at least 50 Gy in 5 weeks. The anterior lower neck field will be treated with 2 Gy per fraction at 3-cm depth to a total dose of at least 50 Gy. A portal reduction off the spinal cord will be made to limit the spinal cord dose to ≤ 45 Gy in all techniques. Therefore, to supplement the dose to the posterior neck and clinically positive nodes, boost techniques may include an additional electron beam of proper energy to the posterior neck, wedge pair or oblique fields.

Radiotherapy will commence with either a 3-field technique or a “caudal tilt technique” (this is also known as “angle down” or “kicked out lateral” technique).

6.1.1.1 The 3-field technique involves opposed lateral portals for the primary tumor and upper nodes and a matching anterior field for the lower neck and supraclavicular fossa. The anterior field should match the lateral fields on the skin, and should have an appropriate method to avoid overlap on the spinal cord at the junction of the fields. The inferior border of the anterior field will be 1 cm below the clavicles.

6.1.1.2 The caudal tilt technique will be used only as an alternative when the inferior border of the lateral fields does not clear the shoulders. Radiotherapy will commence with 2 laterals using table and gantry angles of up to 15 degrees. The off-cord fields after 40-42Gy will commence with 2 laterals using table only angles of up to 15 degrees. The elimination of the gantry rotation improves dosimetry of the matchline for the posterior neck electrons.

6.1.2 IMRT (5/23/07)

IMRT will be given once daily to a total dose of 70 Gy in 35 fractions over 7 weeks, which requires delivery of 5 fractions per week. There will be 3 dose volumes (see Section 6.4 for details). The high-dose volume will receive 70 Gy, the intermediate-dose volume will receive 59.5-63 Gy, and the lower-dose volume or “prophylactic” will receive 56 Gy. See Sections 6.4 and 6.5 regarding target volumes and normal tissue constraints.

6.2 Technical Factors

6.2.1 Megavoltage equipment, linear accelerators, is used to provide appropriate photon energies (4-18 MV) and a wide range of electron energies (6-20 Mev). Telecobalt units can be used for irradiation of the initial large portals.
6.2.2 Treatment distances must be ≥ 80 cm SSD or SAD.

6.2.3 IMRT: Megavoltage equipment capable of delivering intensity modulated beams using a step-and-shoot technique with a multileaf collimator or using dynamically moving leaves. Additionally, a binary multileaf collimator or tomotherapy can be used to modulate the beam. Other techniques, e.g., physical compensators, are acceptable as long as dose specifications and constraints are satisfied.

6.3 Localization, Simulation, and Immobilization

6.3.1 Immobilization

Although a thermoplastic head mask may suffice for conformal radiotherapy, the use of a head and shoulder mask is recommended for better reproducibility. The margins used for expansion of the CTVs to PTVs are discussed in Section 6.4.4.

6.3.2 Planning CT scan

A treatment planning CT scan is mandatory for defining target volumes (see Section 6.4). CT scan thickness should be at most 0.5 cm for conformal radiotherapy or 0.3 cm for IMRT. The treatment planning CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment. All tissues receiving irradiation should be included in the CT scan.

6.4 Treatment Planning/Target Volumes

6.4.1 CT based treatment planning is mandatory for every patient. For 3-D radiotherapy, isodose distributions (composite of all fields) in representative transverse planes through the center of the primary and involved nodal volumes are required. For IMRT, the treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the PTV (CTV with a 5 mm margin) and critical normal structures. An “inverse” planning with computerized optimization should be used.

6.4.2 Gross Tumor Volume (GTV) represents the region judged to contain gross primary tumor or involved node(s) based on clinical and endoscopic examinations, CT scan, and, when applicable, other imaging techniques. Grossly positive lymph nodes are defined as any lymph nodes > 1 cm or nodes with a necrotic center.

6.4.3 (5/23/07) Clinical Target Volume (CTV) is defined as the GTV plus areas considered at risk for containing microscopic disease delineated by the treating physician. CTV₁ represents GTV plus a margin of generally 1 cm and CTV₂ represents GTV with a margin of about 2 cm and nodal regions to receive elective irradiation. When the tumor is infiltrative (endophytic) or when the border is ill defined, it might be desirable to deliver an intermediate dose (e.g., 59.5-63 Gy) to a volume (CTV₁) that is slightly larger than CTV₁. The CTV margins can be narrower when GTV is in the proximity of the spinal cord or critical normal tissues. (The guidelines for CT based delineation of lymph node levels can be found at the RTOG website: http://www.rtog.org/hnatlas/main.html.)

6.4.4 Planning Target Volume (PTV₁ and PTV₂) represents an additional margin around CTV₁ and CTV₂ to compensate for the variability of treatment set up and internal organ motion. A minimum margin of 5 mm around the CTV is required in all directions to define each respective PTV, except for situations in which the CTV is adjacent to spinal cord or other critical normal tissues. In such situations, the margin can be reduced judiciously. A minimum margin of 3 mm can be used in all directions as long as an institution implements a study to define the appropriate magnitude of the uncertain components of the PTV. NOTE: The results of this study must be forwarded to the Image-Guided Therapy Center (ITC) [see Section 12.2.1] for approval before reduced margins can be used. Careful consideration should be made when defining the superior and inferior margins in three dimensions.

6.4.5 The density corrected dose distributions shall be calculated and the dose prescription is to be based on a dose distribution corrected for heterogeneities.

6.5 Critical Structures

6.5.1 Spinal cord: 45 Gy or 1 cc of the PTV (spinal cord with 5 mm margin) not to exceed 50 Gy

6.5.2 Parotid glands: When using IMRT, the objective is to limit the mean dose to at least one gland to ≤ 26 Gy; alternatively at least 20 cc of the combined volume of both parotid glands to < 20 Gy or at least 50% of one gland to < 30 Gy.

6.5.3 Glottic larynx: In patients with oropharyngeal carcinoma without extension to the larynx, placing the isocenter just above the arytenoids and irradiating the lower neck with an anterior matching field with larynx block can minimize the dose to the glottic larynx. Alternatively, the dose to the larynx should be kept < 45 Gy whenever feasible.
6.5.4 **Brachial plexus:** The dose to the brachial plexus must be limited to ≤ 60 Gy in patients with level IV node(s).

6.6 **Documentation Requirements for 3D-CRT**

It is highly recommended that dosimetry information be submitted digitally; see Section 12.2. Sites unable to submit digitally will contact RTOG Headquarters, RTQA Department, 215-574-3219.

6.6.1 Portal image of each field of 3-D radiotherapy or orthogonal images that localize the isocenter placement of IMRT must be obtained on the first day of therapy.

6.6.2 Weekly verification or orthogonal images are required.

6.6.3 Isodose plans for 3-D radiotherapy and IMRT and DVHs of GTV, CTVs, and critical normal structures for IMRT.

6.7 **Compliance Criteria**

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, should ideally not exceed five treatment days at a time and ten treatment days total. Treatment breaks should be allowed only for healing of severe acute adverse event reactions and/or intercurrent illness, and not for social or logistical reasons. Any treatment break(s) exceeding two treatment days for reasons other than adverse event/illness will be considered a protocol deviation.

Plan normalization should provide coverage of 95% of the volume of the PTV of the GTV ($PTV_1$) with the prescribed dose of 69.96 Gy. No more than 1% of the volume of the $PTV_1$ should receive less than 64 Gy. Additionally, no more than 20% of the PTV should receive more than 76 Gy, and no more than 5% of this volume should receive more than 79 Gy. These numbers describe the DVH shown in the figure below with the diamond shaped symbols. Obviously, better DVHs (i.e., with smaller amounts of either underdose or overdose) also are acceptable.

A region of “minor deviation” is also defined in the figure as the DVH represented by the square symbols. Deviations of this magnitude are not desirable, but will be deemed acceptable. That is, a DVH with at least 97% of the volume receiving 64 Gray is acceptable as a minor deviation. Additionally, as a minor deviation for the overdose region, as much as 40% of the $PTV_1$ volume can receive 76 Gray and up to 20% of this volume can receive 79 Gray. DVHs for the $PTV_1$ falling outside the limits for a minor deviation (i.e., increased under or overdose) will be scored as unacceptable “major deviations.”

The DVHs for the other target regions should deliver the prescribed dose, as much as possible, to at least 95% of the volume of that PTV.

<table>
<thead>
<tr>
<th>Overall Evaluation</th>
<th>Radiotherapy Prolongation</th>
<th>Total Variation 3-D RT</th>
<th>Dose Variation IMRT</th>
<th>Total Dose Variation IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Protocol</td>
<td>≤ 5 days</td>
<td>≤ 5% deviation from prescribed dose</td>
<td>See parameters in the figure and table below</td>
<td></td>
</tr>
<tr>
<td>Minor Variation (Acceptable)</td>
<td>6-10 days</td>
<td>&gt; 5% to ≤ 10%</td>
<td>See parameters in the figure and table below</td>
<td></td>
</tr>
<tr>
<td>Major Deviation (Unacceptable)</td>
<td>&gt; 10 days</td>
<td>&gt; 10%</td>
<td>Deviations greater than presented in the figure/table below</td>
<td></td>
</tr>
</tbody>
</table>
6.8 R.T. Quality Assurance Reviews
The radiation therapy data for this study will be archived. The Principal Investigator, David Rosenthal, M.D., and Co-Investigator, Andy Trotti, M.D., will perform an RT Quality Assurance Review only in the event of unusual toxicities.

6.9 Radiation Adverse Events
This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). The CTEP home page also can be accessed from the RTOG web page at http://www.rtog.org/regulatory/regs.html. All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

Reversible mucositis is expected and its timing with dose and severity should be graded (see Section 6.10). For very rare cases of severe grade 4 mucositis, it may be necessary to interrupt radiotherapy for a few days to allow healing (see Section 6.7). Placement of a feeding tube or nutritional supplementation will likely be needed in the majority of patients. Placement of a feeding tube should be recorded, as should use of a feeding tube during and after treatment (e.g., greater than or less than 50% of nutrition by tube). Epilation and various degrees of skin reaction in the treated area also are expected. Other expected acute reactions include: radiation dermatitis, xerostomia, dysgeusia, dysphagia, and odynophagia. Their severity should be recorded, as well as feeding tube placement and use.

Long-term effects may include permanent xerostomia in almost all patients and occasionally, persistent dysphagia and feeding tube dependence. Mandibular osteoradionecrosis will occur in < 5% of the patients but may be reduced through dental evaluation and treatment before irradiation, which is highly recommended. Teeth with problems should be restored or extracted as appropriate. Conservation of restorable teeth should be done before radiotherapy. At least 10 days should be allowed for healing of gingivae post-extraction. Radiation-induced myelopathy is not anticipated provided that the cervical spinal cord dose remains ≤ 45Gy; however, special
attention should be directed to any numbness, paresthesias, or L’Hermitte’s signs, in follow-up exams, particularly in the first 6-12 months of follow up.

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

6.10 Radiation Adverse Event Reporting
See Sections 7.7 and 7.8.

7.0 DRUG THERAPY
Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

7.1 Chemotherapy
Chemotherapy concurrent with radiation therapy (RT) must be planned for the patient. Patients must receive cisplatin, 100mg/m², on days 1, 22, and 43.

A variety of drugs (as single agents or in combination) have been used concurrently with RT, yet no particular chemotherapy regimen has evolved as the single standard of care within the U.S. or globally. Cisplatin is a common chemotherapy drug incorporated into concurrent treatment strategy with radiotherapy and is the only agent tested in multiple prospective phase III trials, found to be feasibly administered in a cooperative group setting, and found to improve overall survival.

7.1.1 Cisplatin
7.1.1.1 Patients will receive cisplatin (100 mg/m²) administered intravenously on days 1, 22, and 43 of the treatment course, i.e., weekends count as days. Use the actual body weight as long as the BSA is ≤ 2.0. If the BSA is > 2.0, recalculate using the ideal weight (use the formulas below), and use the recalculated BSA to determine the dose with no cap.
   Males (kg): 51.65 + (1.85 x (height [inches] – 60))
   Females (kg): 48.67 + (1.85 x (height [inches] – 60))

7.1.1.2 Suggested premedication: 5HT3 inhibitor, such as granisetron, 0.7-1.0 mg i.v. or ondansetron 8-12 mg (maximum 32 mg) i.v. will be given 30 minutes prior to cisplatin chemotherapy, along with dexamethasone per institutional standard. A more aggressive prophylactic antiemetic regimen, such as adding aprepitant, and any "as-needed" antiemetics may be given at the discretion of the treatment physician. Any pre-existing dehydration must be corrected prior to cisplatin administration.

7.1.1.3 Patients must receive vigorous hydration and diuresis. A suggested regimen is pre-hydration with a 1 liter of D5N S over 2-4 hours and mannitol 12.5g i.v. bolus immediately prior to cisplatin. Then cisplatin 100 mg/m2 in 500 ml NS is administered over 1-2 hours with an additional 1 to 1.5 liters of fluid given post-hydration.

Overnight hospitalization for hydration after cisplatin is strongly encouraged if the patient’s insurance company allows it. Additional IV hydration and BUN/creatinine check should be strongly considered later in the week after cisplatin administration, in order to prevent dehydration and severe fluid/electrolyte imbalance.

7.1.2 Dose Modifications for Cisplatin, days 22 and 43
7.1.2.1 Neutropenia may occur. 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. If cisplatin is delayed for 7 days for neutropenic fever, reduce the dose of cisplatin by 25% for the first occurrence, and by 50% for the second occurrence.

7.1.2.2 Thrombocytopenia may occur. 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. If cisplatin is delayed for 7 days for thrombocytopenia with bleeding, reduce the dose of cisplatin by 25% for the first occurrence, and by 50% for the second occurrence.

7.1.2.3 Neurotoxicity: If any signs of grade 3 or greater neurotoxicity occur, discontinue cisplatin.

7.1.2.4 Renal Toxicity: Cisplatin should be administered on the scheduled day of treatment using the following guidelines:
<table>
<thead>
<tr>
<th>Creatinine Clearance*</th>
<th>Cisplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50 ml/min.</td>
<td>100 mg/m²</td>
</tr>
<tr>
<td>40-50 ml/min.</td>
<td>50 mg/m²</td>
</tr>
<tr>
<td>&lt; 40 ml/min.</td>
<td>Discontinue and notify Stuart Wong, MD, Medical Oncology Co-Chair</td>
</tr>
</tbody>
</table>

*If creatinine is > 1.2, creatinine clearance must be done 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 nomogram calculation is less than 50 mL/min, a 24-hour urine collection is mandated.

7.1.2.5 Other Adverse Events:
- Mucositis: Grade 4 will require permanent 25% dose reduction. (See Section 6.5.2)
- 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. If the physician is unsure about the severity of the hearing loss, an audiogram is encouraged.

7.1.2.6 Delay of Therapy
If the third dose of cisplatin is delayed following the completion of radiation therapy (RT), it must be administered no later than 24 hours prior to the first post-RT palifermin/placebo dose. Otherwise, the third dose of cisplatin will be omitted. For questions regarding delay of therapy, contact Stuart Wong, MD, Medical Oncology Co-Chair.

7.2 Cisplatin (Cis-Diamminedichloroplatinum, DDP)
7.2.1 (5/23/07) Formulation: Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each ml containing 1 mg cisplatin and 9 mg NaCl and HCl or NaOH to adjust pH. The lyophilized formulation of cisplatin is not commercially available in the U.S.

7.2.2 Mechanism of Action: The mechanism of action of DDP has not been clearly elucidated. However, preliminary studies have indicated that the most likely mechanism of antitumor action of this drug resides in its ability to inhibit DNA synthesis and to a lesser degree, RNA and protein synthesis. It has also been shown that DDP binds to DNA and produces inter-strand cross-links. Also DDP is not phase-sensitive and its cytotoxicity is similar in all phases of the cell cycle.

7.2.3 Storage and Preparation: The dry, unopened vials should be stored at refrigeration temperature (+4°C to +8°C). Reconstitution results in a solution stable for not more than one hour at room temperature when exposed to normal room illumination, and not more than 8 hours at room temperature when protected from light.

7.2.3 (5/23/07) Administration: Cisplatin is usually administered by slow i.v. infusion over 30 minutes or longer. Cisplatin also has been given intra-arterially, intraperitoneally, and intravesicularly. Following initial entry, cisplatin aqueous solution, provided in a multi-use vial, is stable for 28 days protected from light or for 7 days under fluorescent room light.

7.2.4 Adverse Events: The following toxicities are anticipated.
- Hematologic: Myelosuppression, often with delayed erythrosuppression; rarely, acute leukemia
- Gastrointestinal: Nausea, vomiting, anorexia, loss of taste;
- Dermatologic: Alopecia;
- Renal: Elevation of BUN, creatinine and impairment of endogenous creatinine clearance (as well as renal tubular damage which appears to be transient); hyperuricemia; much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts;
- Hepatic: Hypomagnesemia, hypokalemia, hypocalcemia,
- Neurologic: Restlessness; involuntary movements; loss of coordination; seizures; peripheral neuropathy;
- Allergic: Flushing, bronchoconstriction, tachycardia, hypotension;
- Other: Ototoxicity (with hearing loss which initially is in the high-frequency range, as well as tinnitus); muscle cramps; weakness
Supply: Cisplatin is commercially available.

Protocol Treatment: Palifermin/Placebo (Palifermin, NSC# 740548; IND #100,192)

Arms 1 and 2: Palifermin/Placebo (5/23/07)

Mandatory Dosing Period: Pre-RT to Week 3 of RT

All patients will receive 4 doses of palifermin, 180μg/kg, OR placebo administered as an i.v. bolus injection over 30-60 seconds either centrally or peripherally.

Patients will receive the first dose of palifermin OR placebo on day –3 (Friday) prior to radiation therapy (RT)/chemotherapy and then will receive palifermin OR placebo once weekly, on the next 3 Fridays of RT/chemotherapy, Days 5, 12, and 19, for a total of 4 doses.

During the first 3 weeks of RT/chemotherapy, palifermin or placebo should be given after completion of the last RT dose for the week, typically on Friday. Note: It is highly recommended that all patients begin radiation therapy and chemotherapy on a Monday.

Optional Dosing Period Based on Presence of Ulcerative Oral Mucositis: Last Friday of RT (Week 7) to Week 10-11

At the completion of radiation therapy, if the patient still has ulcerative mucositis based on inspection of the oral mucosa, the patient will receive palifermin OR placebo on the last Friday (or last day) of RT/chemotherapy, and then once weekly post-RT if ulcers are still present, for a total of up to 4 additional doses. If ulcerative mucositis is present at the completion of RT, oral mucositis assessments should continue to be conducted twice per week until ulcerations have resolved.

Note: These final 4 doses only should be given if the patient has ulcerative mucositis upon inspection of the oral mucosa. If the patient has no ulcerative lesions at the last RT treatment, no additional doses of palifermin/placebo will be given. Dosing should be stopped if the patient’s ulcerative mucositis resolves, and no additional doses should be given.

Emergency Code Breaks

The actual treatment assignment will be made available only if an emergency situation arises that in the opinion of the Unblinding Officer meets the following criterion for breaking the code:

- A life-threatening event or
- An extraordinary clinical circumstance for which knowledge of drug assignment will affect clinical decision making

During business hours (8:30 AM to 5 PM ET), call RTOG Headquarters at 215-574-3150 and ask to speak to the Study Statistician. For after hours, weekends, and holidays, call 215-459-3576.

Formulation

Palifermin will be presented as a lyophilized, white powder in 6.25 mg single-dose vials and is to be reconstituted with 1.2 ml of sterile Water for Injection (USP). The reconstituted solution contains 5 mg/mL (± 0.5 mg/mL) palifermin, 4% mannitol, 2% sucrose, 10 mM histidine, 0.010% polysorbate 20, pH of 6.5, and no preservatives. Each vial is designed for single use only and is not to be used to treat more than one subject. Vigorous shaking of the vials may denature the protein in the solution and should be avoided. Vials should be protected from light while being stored. For more information on this agent, refer to the Investigator Brochure or Package Insert, please contact Amgen, Inc. via Michael Hickey at 805-447-0284 and/or mhickey@amgen.com.

Placebo will be presented in identical vials containing all of the ingredients of lyophilized powder except for palifermin. It must also be reconstituted with 1.2 mL sterile water for injection (USP).

Preparation and Reconstitution

Prior to reconstitution of lyophilized palifermin or placebo, allow the investigational product to come to room temperature. Under aseptic conditions, reconstitute the lyophilized product by adding 1.2 mL of sterile Water for Injection (USP) slowly down the side of the vial. Gently swirl the vial until the product is completely dissolved. Vigorous shaking must be avoided to prevent protein denaturation. The protein concentration of each 6.25 mg vial of palifermin or placebo after reconstitution is 5 ± 0.5 mg/mL. The reconstituted solution should have a clear, colorless appearance.
The reconstituted solution contains no preservatives and is intended for single use only. Following reconstitution, it is recommended that the product be used immediately. If not used immediately, the reconstituted solution of investigational product may be stored refrigerated in its carton at 2° to 8°C (36° to 46°F) for up to 24 hours.

In the event that a reconstituted palifermin vial has been stored at a temperature of outside the 2°C to 8°C range, Amgen should be contacted to determine the validity of the drug.

Reconstituted investigational product must not be stored at room temperature. Prior to injection, investigational product may be allowed to reach room temperature for a maximum of 1 hour but should be protected from light. Discard investigational product left at room temperature for more than 1 hour. Do not freeze the reconstituted solution. Note that the product does not have to be protected from light during preparation or administration.

7.3.4 Administration (5/23/07)

The investigational product solution can be administered as an i.v. bolus injection over approximately 30-60 seconds either centrally or peripherally.

NOTE: Palifermin should not be administered within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy (also see Section 7.4). In a clinical trial, administration of palifermin within 24 hours of chemotherapy resulted in increased severity and duration of oral mucositis.

Palifermin has been shown to bind to heparin in vitro. Therefore, if heparin is used to maintain an i.v. line, saline (~ 5 cc) should be used to rinse the line prior to and after investigational product administration.

Drug should be dosed based upon a subject's baseline weight and used throughout the study. There will be no dose adjustments for fluctuations in weight. Please reference the table below for approximate palifermin or placebo injection volumes per subject weight.

For example, a subject weighing 80 kg would receive a total volume of 2.88 mL (80 kg × 180 μg/kg = 14,400 μg; 14,400 μg ÷ 5000 μg = 2.88 mL)

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Weight (kg)</th>
<th>Total Dose (μg)</th>
<th>Total Volume (mL)</th>
<th>Vials Needed Per Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>180 μg/kg</td>
<td>40</td>
<td>7,200</td>
<td>1.44</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>9,000</td>
<td>1.80</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>10,800</td>
<td>2.16</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>12,600</td>
<td>2.523</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>14,400</td>
<td>2.88</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>16,200</td>
<td>3.24</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>18,000</td>
<td>3.60</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>110</td>
<td>19,800</td>
<td>3.96</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>21,600</td>
<td>4.32</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>130</td>
<td>23,400</td>
<td>4.683</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: Calculated injection volumes < x.x5mL may be rounded down to x.xmL; calculated volumes ≥ x.x5mL may be rounded up to x.(x+1)mL.

7.3.5 Palifermin Adverse Events (5/23/07)

Note: See the 0435 CTCAE Grading Tool (on the RTOG web site, next to the protocol) for special issues related to grading of palifermin-related adverse events.

Sub-acute skin and oral reactions have been observed more frequently in cancer patients receiving palifermin than in placebo recipients, and in almost all the volunteers receiving palifermin at doses > 200 μg/kg (Amgen Inc., Data on file). The skin reactions manifested as erythema, flushing, edema and pruritus occurring on all areas of the body. Oral reactions included tingling of lips and mouth, discoloration and/or thickening of tongue and oral mucosa, loss of taste, and mucosal erythema. These reactions typically started 1-2 days after palifermin administration, were generally described as mild to moderate in severity, and mostly
resolved without intervention within a few days. They appeared to be dose related, and are thought to be related to the pharmacological activity of palifermin. Less likely adverse events include difficulty breathing, headache, and swelling around the eyes. Allergic reactions involving flushing, difficulty breathing, irregular heartbeat, and hypotension are rare. No clinical experience of overdose with this product is known at this time.

Swelling of the oral structures or around tracheotomy sites was reported in head and neck cancer patients receiving palifermin. These patients had undergone surgery prior to starting radiation therapy and chemotherapy. The swelling of the oral structures was temporary and occurred after start of radiation therapy. In addition, one of these patients voluntarily discontinued palifermin due to overproduction of saliva. A causal relationship cannot be excluded between palifermin and swelling of the oral structures or overproduction of saliva.

A recent serious adverse event involving palifermin was reported in April 2005 from a study conducted in Europe (study number 20040118), in which a patient developed respiratory insufficiency and severe tongue edema from a head and neck cancer treated with radiation, chemotherapy, and palifermin post-operatively.

Proteinuria was reported in one study in patients with colorectal cancer receiving palifermin. A causal relationship between palifermin and proteinuria has not been established since medical conditions known to be associated with proteinuria were present in these patients before they started the study. Hypertension was reported in cancer patients undergoing transplantation who received palifermin. These events were temporary and did not require treatment discontinuation of drug in any patient and also were reported in patients receiving placebo.

Theoretical considerations
Tumors of epithelial origin carry the palifermin receptor. Whether or not palifermin could cause tumor growth in humans is unknown. The clinical effect of palifermin on disease outcomes of different solid tumor types has not been fully evaluated in clinical trials. In the test tube and in animal studies (in test tube experiments, 7.5 times higher concentrations/doses and in animal studies 12.5 to 33.5 times higher doses than the recommended human doses under investigation), there is evidence that palifermin has stimulated growth of some solid tumors. In humans, the clinical effect of palifermin on disease has not been fully evaluated. A long-term follow-up study in approximately 150 patients with head and neck cancer is ongoing and has not shown any negative effect of palifermin on tumor growth or patient survival after approximately 4 years. Similar results have been seen in follow-up studies in colorectal cancer and in hematologic malignancies. Epithelial cells in other areas of the body (for example, skin, mammary glands, and cornea) can potentially be stimulated by palifermin. There could be unforeseen side effects associated with this growth stimulation.

7.3.6 Storage
The dispensing pack containing palifermin/placebo lyophilized powder should be stored in its carton and refrigerated at 2°C to 8°C. Exposure of the material to temperatures outside these limits, except for warming before reconstitution and administration, is not recommended and may result in a loss of activity. Protect from light. Keep vials in pack until time of use. Material should be reconstituted on the day of injection and stored between 2°C and 8°C until administered. Should a palifermin vial be stored outside the temperature range of 2°C to 8°C, Amgen should be contacted to determine the validity of the drug. Actual storage conditions records during the period of the study must be maintained and include the date, time and initials of the person checking on the “working day” temperatures of the refrigerator used for the storage of trial supplies. Continuous temperature recordings, or regularly maintained temperature alarm systems used in conjunction with temperature recording shall also be included.

7.3.7 Supply
Palifermin and its matching placebo will be manufactured and packaged by Amgen, Inc. and supplied by Amgen, Inc. to NCI for distribution. Amgen, Inc. holds the IND for palifermin (IND #100,192). In addition, this study is planned to be conducted under an investigator IND to be held by RTOG and will require FDA submission and approval of the protocol as part of the IND. Palifermin/placebo will be provided to patients on study free of charge.
Drug Ordering and Accountability (5/23/07) (8/7/07)

All investigators who receive a copy of the protocol should also obtain a copy of the Investigator’s Brochure (IB). IB’s are available directly from Amgen, Inc. (the IND holder for the RTOG-0435 protocol) and may be obtained by emailing (mhickey@amgen.com) or phoning (805-447-0284) Michael Hickey. All requests should include:

- study number (i.e., RTOG-0435)
- RTOG site number
- PI’s name
- email address of PI or study coordinator
- full mailing address for PI or study coordinator

Clinical Supplies: Palifermin (NSC 740548) and matching placebo will be provided free of charge by Amgen, Inc. and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Palifermin and matching placebo will be supplied in glass vials each containing 6.25 mg (Palifermin) or 0 mg (Placebo for Palifermin) of palifermin. The blinded, patient-specific vials will be sealed in a cardboard box with a tamper-evident seal. Each box of palifermin / placebo will be labeled with …

- the protocol number (i.e., “RTOG-0435”)
- the box number (e.g., “Box 1 of 1”)
- the number of vials (e.g., “12 vials”)
- the patient ID number (i.e., the unique patient ID number assigned by RTOG at the time of patient registration)
- the patient initials (i.e., first initial, middle initial, last initial [e.g., “FML”])
- the agent identification (i.e., “Palifermin 100 mg or Placebo”)
- a blank line for the pharmacist to enter the patient’s name
- storage instructions (i.e., “Store in refrigerator [2 – 8 °C]. Do not freeze. Do not shake.”)
- emergency contact instructions
- a Julian date

The Julian date indicates the day the box was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2006 = 06, 2007 = 07) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a box labeled and shipped on January 1, 2006 would have a Julian date of ‘06001’ and a box labeled and shipped on December 31, 2007 would have a Julian date of ‘07365’. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all vials (i.e., both Palifermin and Placebo) shipped on or before that date thus eliminating any chance of breaking the blind.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (301) 496 5725 Monday through Friday between 8:30am and 4:30pm Eastern Time.

Drug Ordering: **No blinded starter supplies will be available for this study.** Blinded, patient-specific clinical supplies will be sent to the registering investigator at the time of randomization. This randomization will be performed by RTOG Headquarters in Philadelphia, PA. The patient ID number assigned by RTOG Headquarters must be recorded by the registering institution for proper study medication dispersion. Once a patient has been registered with RTOG Headquarters, RTOG will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by RTOG Headquarters the day the patient is registered and will be processed by the PMB the next business day and shipped the following business day (see attached table). All shipments will be sent on blue ice by FedEx (generally one to two day delivery). Thus, if a patient is registered on Monday, RTOG would enter a clinical drug request for that patient on Monday and PMB would process the request on Tuesday and ship the drug on Wednesday. Clinical sites could expect to receive their order either Thursday or Friday. Note that PMB will only send blue ice shipments on Monday through
Thursday for delivery on Tuesday through Friday. Thus, if a patient is registered on Wednesday, the order will be processed on Thursday and shipped the following Monday for delivery on Tuesday or Wednesday.

Mandatory Dosing Period (Days -3, 5 [Friday of week 1], 12 [Friday of week 2], and 19 [Friday of week 3]): The initial request will be for a sufficient number of vials of palifermin / placebo to complete 4 doses (i.e., days -3, 5, 12, and 19) based on the patient’s weight in “kg” provided by RTOG at the time of patient registration. No reorders should be required for the “mandatory dosing period”.

Optional Dosing Period (Days 47 [Friday of week 7], 54 [Friday of week 8], 61 [Friday of week 9], and 68 [Friday of week 10]): If the patient still has ulcerative mucositis at the completion of radiation therapy, sites may order additional 4 doses (i.e., days 47, 54, 61, and 68) of palifermin / placebo by completing an NCI Clinical Drug Request form and faxing it to the PMB at 301-480-4612. The NCI Clinical Drug Request form is available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The protocol number (i.e., RTOG-0435), the assigned patient ID number, the patient initials, the number of vials remaining from the previous shipment, and the patient’s weight (in “kg”) should be entered on each order. All drug orders will be shipped directly to the physician registering the patient.

NOTE: At the time a patient permanently discontinues protocol treatment, ALL remaining clinical supplies of palifermin / placebo for that patient should be returned to PMB (see “Drug Returns” below).

Drug Transfers: Vials MAY NOT be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the responsible investigator at a given clinical site changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 301-402-0429) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The patient ID number and the patient initials should be entered in the “Received on NCI Protocol No.” and the “Transferred to NCI Protocol No.” fields in addition to the protocol number (i.e., “RTOG-0435”).

Drug Returns: Only unopened clinical supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The patient ID number and the patient initials should be entered in the “Lot Number” field. A separate line item is required for each patient ID being returned. Opened vials should be destroyed on site in accordance with institutional policy.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. A separate NCI Investigational Agent Accountability Record must be maintained for each patient ID number on this protocol.

Emergency Unblinding: In the event of an emergency or severe adverse reaction necessitating identification of the medication for the welfare of the patient, please contact RTOG Headquarters at 215-574-3150 Monday through Friday between 8:30am and 5:00pm Eastern Time. For unblinding outside of these hours, please call 215-459-3576. RTOG Headquarters or the answering service will require the protocol number (i.e., RTOG-0435”), the patient ID number, and the patient initials to unblind the patient.

**7.4 Dose Modifications: Palifermin/Placebo**

**7.4.1 Management of Palifermin-Specific Adverse Events**

There are no known approaches for managing palifermin-related adverse events, such as reactions of skin, lips, or oral mucosa. Mild to moderate erythema, flushing, edema, and
pruritus may be observed and managed symptomatically with antihistamines or topical emollients. Steroid based topicals are discouraged, since there is no documented experience with these. Grade 1-2 drug reactions typically begin within 1-2 days after palifermin administration, and most reactions resolve within a few days without intervention. Palifermin should be discontinued for ≥ grade 3 reactions or symptoms that are deemed by the treating physician as too uncomfortable or unacceptable to the patient. No dose reductions or escalations are permitted for palifermin/placebo.

If cisplatin is delayed by one week, palifermin/placebo should be given at least 24 hours after the cisplatin (e.g., the last dose of cisplatin should be given by Thursday, a.m. at the latest, with palifermin/placebo given Friday, p.m.).

If radiation therapy is delayed, palifermin/placebo should continue to be given according to Section 7.3.1.

Treatment may be discontinued if medically indicated. Sites should contact Drs. Rosenthal or Trotti with questions regarding discontinuation of palifermin/placebo.

7.5 Criteria for Removal From Protocol Treatment

- Progression of disease;
- Unacceptable adverse events to the patient (at the discretion of the treating physician) — Reasons for removal must be clearly documented on the appropriate case report form/flowsheet (available on the RTOG web site at http://www.rtog.org/members/forms/list.html);
- The patient may withdraw from the study at any time for any reason. Reasons for withdrawal must be clearly documented on the appropriate case report form/flowsheet (available on the RTOG web site at http://www.rtog.org/members/forms/list.html);
- Patients discontinuing treatment should continue to be followed for study endpoints, i.e., for long-term disease outcome for at least 10 years.

7.6 Complementary Therapy Reviews (5/23/07)
The Principal Investigator, David Rosenthal, M.D., the Co-Investigator, Andy Trotti, M.D., and the Medical Oncologist, Stuart Wong, M.D., will perform a Quality Assurance Review of all patients who receive or are to receive palifermin/placebo in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of palifermin/placebo treatment data and mucositis assessment data as specified in Section 12.1. The scoring mechanism is: per protocol; variation, acceptable; deviation unacceptable; not evaluable for complementary therapy review; or, incomplete complementary therapy. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

<table>
<thead>
<tr>
<th>Overall Evaluation</th>
<th>Submission of Palifermin/Placebo Data</th>
<th>Submission of Mucositis Assessment Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per protocol</td>
<td>All needed doses (4-8) delivered</td>
<td>Baseline and twice weekly assessment until resolution of mucositis</td>
</tr>
<tr>
<td>Variation acceptable</td>
<td>Missing only 1 needed dose</td>
<td>Baseline and at least once weekly assessment until resolution of mucositis</td>
</tr>
<tr>
<td>Deviation unacceptable</td>
<td>Missing 2 or more needed doses</td>
<td>Less than once-weekly assessment</td>
</tr>
<tr>
<td>Not evaluable for review</td>
<td>Patient did not receive any doses</td>
<td>Less than 3 assessments</td>
</tr>
<tr>
<td>Incomplete therapy</td>
<td>Patient received less than all needed doses</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Drs. Rosenthal, Trotti, and Wong will perform a Quality Assurance Review after complete data for the first 25 cases enrolled has been received at RTOG Headquarters. The next review will take place after complete data for the next 50 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.
7.7 **Adverse Events**

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). The CTEP home page also can be accessed from the RTOG web page at http://www.rtog.org/regulatory/regs.html. All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (http://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_mainS.startup). Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (http://www.rtog.org/members/toxicity/main.html) for this information.

### 7.7.1 Adverse Events (AEs) — RTOG AE PHONE: 215-717-2762 (available 24 hours/day)

**Definition of an AE:** Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

The following guidelines for reporting adverse events (AEs) apply to all NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported via AdEERS. Use the patient's case number as the patient ID when reporting via AdEERS. AEs reported using AdEERS also **must be reported on the AE case report form (see Section 12.1).**

**NOTE:** If the event is a Serious Adverse Event (SAE) [see next section], further reporting may be required. Reporting AEs only fulfills Data Management reporting requirements.

### 7.7.2 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported to RTOG (SAE PHONE: 215-717-2762, available 24 hours/day) within 24 hours of discovery of the event.

**Definition of an SAE:** Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

Outside of regular business hours (8:30-5:00 EST), leave a message that includes the study/case numbers and the caller's contact information. A Data Manager will return the call the next business day requesting details of the event and also will inform the caller which type of report is required for that study (5 or 10 day AdEERS). The required report must be completed in AdEERS **within 5 or 10 calendar days of the initial phone report, as directed by the Data Manager taking the call.** SAEs reported using AdEERS also **must be reported on the AE case report form (see Section 12.1).**

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported to RTOG via the AE/SAE telephone line within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

**All supporting source documentation, if applicable or if being faxed to NCI, must be properly labeled with the study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the**
pharmaceutical company/companies supporting the RTOG trial. All forms (and supporting source documentation) submitted to RTOG Headquarters must include the RTOG study/case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient’s case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note: Sites must print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.7.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)
AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at http://ctep.cancer.gov/forms/index.html. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.

<table>
<thead>
<tr>
<th>RTOG Headquarters</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML/MDS Report</td>
</tr>
<tr>
<td>1818 Market Street, Suite 1600</td>
</tr>
<tr>
<td>Philadelphia, PA 19103</td>
</tr>
</tbody>
</table>
### 7.8 AdEERS Expedited Reporting Requirements

#### 7.8.1 Phase 2 and 3 Trials Utilizing an Agent under a Non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days\(^1\) of the Last Dose of the Investigational Agent (Palifermin/Placebo) in this Study (Arms 1 & 2)

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5(^2)</th>
<th>Grades 4 &amp; 5(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexpected and Expected</td>
<td>Unexpected Expected</td>
<td>Expected</td>
<td>Unexpected without Hospitalization</td>
<td>Expected without Hospitalization</td>
<td>Unexpected</td>
<td>Expected</td>
</tr>
<tr>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Unrelated Unlikely</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Possible</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>24-Hour; 5 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Probable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a Non-CTEP IND require reporting as follows:
- AdEERS 24-hour notification followed by complete report within 5 calendar days for:
  - Grade 4 and Grade 5 unexpected events
- AdEERS 10 calendar day report:
  - Grade 3 unexpected events with hospitalization or prolongation of hospitalization
  - Grade 5 expected events

\(^2\) Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

\(^3\) Please see exceptions below under section entitled “Additional Instructions or Exceptions.”

**Note:** All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

- Expedited AE reporting timelines defined:
  - **“24 hours; 5 calendar days”** – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - **“10 calendar days”** - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

**Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a Non-CTEP IND:**
Not applicable to this study.

### 7.9 Clinical Trials Agreement

The agent used in this protocol is provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company (hereinafter referred to as “Collaborator”) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator” contained within the terms of award, apply to the use of the Agent in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study.
Collaborator(s)’s data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient’s family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."): 
   a. NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI’s participation in the proposed combination protocol.
   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate. All data made available will comply with HIPAA regulations.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator’s wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to the Division of Cancer Prevention (DCP) for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator’s confidential and proprietary data, in addition to Collaborator(s)’s intellectual property rights, are protected. Copies of abstracts must be provided to DCP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to DCP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   The RTOG Program Director
   Community Oncology and Prevention Trials Research Group
   Division of Cancer Prevention
   National Cancer Institute
   6130 Executive Blvd., Room 2017
   Bethesda, MD 20892-7340

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator(s)’s confidential/ proprietary information.
8.0 SURGERY

8.1 Neck Dissection (5/23/07)

All patients will be assessed at approximately 8 weeks post-treatment with CT scan or MRI by the same technique used at baseline.

A neck dissection is required for patients with persistent nodal disease, any stage, if a palpable abnormality or worrisome radiographic abnormality persists in the neck 8-9 weeks after completion of therapy. A neck dissection is optional for patients with multiple positive lymph nodes or with lymph nodes exceeding 3 cm in diameter at pre-treatment (N2a, N2b, N3) who achieve a complete clinical and radiographic response in the neck. Surgery will be performed within 2 weeks once the decision for neck dissection is made. The status of the primary tumor should be assessed thoroughly at the beginning of the surgical procedure before undertaking nodal dissection. Presence of persistent disease at the primary site, confirmed by frozen section, will be considered a failure of protocol treatment. Further treatment of such a patient will depend on the clinical situation and are at the discretion of the treating physicians.

8.2 For Patients Undergoing a Neck Dissection

Cervical lymphadenectomy will encompass the original levels of lymph node involvement, which should be removed en bloc. Preservation of the accessory nerve, jugular vein, and sternomastoid muscle is encouraged if consistent with complete removal of all residual nodal disease; however, the extent of the neck dissection will be at the discretion of the surgeon. A selective neck dissection should be performed when feasible. At no time will synchronous bilateral radical neck dissections be performed. If bilateral radical neck dissections are necessary the neck procedure must be staged at an interval of 6 weeks between lymphadenectomies.

The neck dissection specimens must be divided and oriented into discrete anatomic levels in the operating room by the supervising surgeon, and submitted for pathologic review in separate containers. Discrete groups of nodes that are matted or spaced too closely to be resolved as separate nodes under the microscope or by CT or MRI (< 0.5 cm intervening distance) will be categorized as "nodal clusters." These clusters will be considered equivalent to solitary nodes to allow for simpler and more accurate categorization of all sampled tissue. An attending pathologist should oversee evaluation of all neck dissection specimens according to Appendix VI.

8.2.1 Institutions must submit a Surgery Form (S1) for all patients, whether or not they undergo planned surgery. In addition, institutions must submit a Surgical Operative Report (S2), and a Surgical Pathology Report (S5) for patients who have surgery to the primary site and/or to regional nodes post-treatment (see Section 12.1).

8.3 Surgical Removal (Salvage) of the Primary Tumor

Directed biopsies at the site of the index lesions will not be performed in the absence of suspicion for relapse. Criteria for biopsy after chemoradiation include a persistent mucosal abnormality or imaging studies that are suspicious for persistent or recurrent disease at 8-9 weeks after completion of therapy. Options for salvage therapy will depend upon the clinical situation and are at the discretion of the treating physicians. Surgical removal (salvage resection) of the primary tumor will be performed, if possible, when biopsy-proven cancer remains more than three months after completion of therapy. The nature of the surgical resection will be dictated by the extent of tumor at the initial evaluation. The operation will be conducted using accepted criteria for primary surgical treatment of the cancer.

Tissues for pathologic evaluation of margins should be taken from the patient (rather than the surgical specimen itself). However, the specimen itself should be marked at sites corresponding to the evaluated margins in order to assess sampling error in obtaining clear margins. If gross tumor remains or when no effort to remove tumor has been made, the patient will be considered to have "gross residual disease." In the absence of residual disease, if the cancer extends to within 5 mm of a surgical margin, the patient would be considered to have "close" margins.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

9.1.1 All supportive therapy for optimal medical care will be given during the study period (e.g., antiemetics, hydration to prevent renal damage, transfusions) at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site’s source documents as concomitant medication.
9.1.2 For oral comfort, normal saline rinses and topical anesthetics such as viscous xylocaine, lidocaine jelly, or UlcerEase® may be used. Data will be collected for all concomitant medication administered up to the conclusion of the week 12 visit (week 15 in subjects who undergo OM assessments until that time) including the following types of concomitant medications: narcotic analgesics, topical anesthetics, therapeutic antimicrobials, anti-emetics, hematopoietic growth factors, mouthwashes, and topical skin aids. No subject should have standard FDA-approved treatment withheld with concomitant medications or therapies that can improve the subject's condition. Concomitant therapy data will not be collected for any subject after week 15 unless that therapy is used for treatment of an adverse event occurring within 28 days of last dose of investigational product.

9.1.3 **Hematopoietic Growth Factors**

Commercially available colony-stimulating factors can be prescribed and used in accordance with the manufacturers' package insert information and the American Society of Clinical Oncology Clinical Practice Guidelines (Ozer et al., 2000).

Exceptions to this, as noted in Section 9.2, are erythropoietin (epo) and granulocyte-macrophage colony-stimulating factor (GM-CSF).

9.2 **Non-permitted Supportive Therapy (5/23/07)**

The following are not permitted during radiation therapy, as none have been proved effective for the treatment of radiation-induced oral mucositis: 'Magic mouthwash', 'Miracle mouthwash' or other mouthwash solutions containing chlorhexidine, Gelclair®, hydrogen peroxide, diphenhydramine (NOTE: Topical anesthetics per Section 9.1.2 are permitted); Pilocarpine hydrochloride (Salagen®); Cevimeline hydrochloride (Evoxac®); Amifostine (Ethylol®); Benzydamine hydrochloride; IL-11 (Neumega®); GM-CSF (e.g., Leukine®); erythropoietin; sucralfate in suspension form (use of sucralfate tablets is not proscribed); steroid rinses; povidone-iodine rinses; glutamine as a prophylactic agent for mucositis; other investigational agents; other biologic response modifiers, with the exception of hematopoietic growth factors for the management of anemia or myelosuppression (see Section 9.1).

10.0 **TISSUE/SPECIMEN SUBMISSION (5/23/07)**

There is no submission of tissue/specimens for banking or translational research.

11.0 **PATIENT ASSESSMENTS**

11.1 **Study Parameters (5/23/07) (8/7/07)**

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Pre-Study Entry</th>
<th>During Radiation Therapy/Chemo</th>
<th>Follow Up</th>
<th>Also see Section 11.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>History/physical, Zubrod</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Mucositis assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>MDASI-HN, BPI</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Opioid analgesic documentation</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Patient reported Xerostomia (XQ)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Chest x-ray or chest CT scan</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI or CT scan with contrast of tumor site</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CBC, diff, platelets</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, AST or ALT</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, creatinine clearance</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum calcium</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum pregnancy test</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Within 8 weeks prior to registration and including documentation of tobacco/alcohol use and current medications (including opioids/dosing);
b. Within 2 weeks prior to start of radiation therapy (baseline); mucositis will be assessed according to the QP form;
c. Within 6 weeks prior to registration;
d. Within 2 weeks prior to registration;
e. Weekly during radiation/chemotherapy;
f. Twice each week during radiation therapy (RT);
g. Once each week during radiation therapy (RT) until mucosal ulceration resolves (via trans-oral visualization) or until 8 weeks post-RT, whichever occurs first; after treatment, the patient will not need to complete the BPI and only completes the MDASI at 1 year.

h. Amounts of opioid analgesics (total dose in morphine equivalents; see Appendix VII) will be documented once each week during radiation therapy (RT) until mucosal ulceration resolves (via trans-oral visualization) or until 8 weeks post-RT, whichever occurs first. Patients will document the daily amount, and sites will monitor this documentation for completeness in each follow-up visit.

i. Three days prior to second and third dose of chemotherapy;

j. Twice each week during RT according to the QP form until mucosal ulceration resolves (via trans-oral visualization) or until 8 weeks post-RT, whichever occurs first;

k. At 15 weeks from the start of treatment; and at 6, 12, 18, and 24 months post-RT;

l. CT/MRI with contrast of the head and neck will be done 8 weeks after completion of RT/chemo for all patients and then at 6 months in year 1, then annually for 5 years. If special circumstances (e.g., patient unable to lie supine) prevent routine imaging, evaluation of the primary site may be done by visual inspection (e.g., visual endoscopy).

11.2 Evaluation During Follow Up (5/23/07) (8/7/07)

11.2.1 Oral mucositis (Form QP) will be assessed twice each week during radiation therapy until mucosal ulceration resolves (evaluated via trans-oral visualization) or until 8 weeks post-radiation, whichever occurs first.

11.2.2 At 8 weeks from the start of treatment, then annually for years 1-5: Evaluation of disease progression, development of second primary, and/or other malignancies by the same technique used at baseline (i.e., MRI/CT scan). Thereafter, clinical examination alone should be done annually for years 6-10.

11.2.3 At 8 weeks, every 3 months for year 1, every 4 months for year 2, every 6 months for years 3-4, then annually for years 5-10:
- Physical examination, including Zubrod and documentation of tobacco/alcohol use; Note: Tobacco/alcohol use will be documented at baseline and up to 6 months only.
- Evaluation of the primary neck/site by direct inspection or palpation, or if clinically indicated, indirect laryngoscopy or fiberoptic nasopharyngolaryngoscopy;
- Evaluation for second primaries according to usual site practice.

11.2.4 Patients will complete the BPI and MDASI-HN once each week from the start of treatment until mucosal ulceration resolves (evaluated via trans-oral visualization) or until 8 weeks post-radiation, whichever occurs first. Patients also will complete the MDASI-HN at one year from start of treatment.

11.2.5 Patients will complete the Xerostomia Questionnaire (XQ) at 15 weeks from the start of treatment, and at 6, 12, 18, and 24 months post-treatment.

11.3 Mucositis Assessment

11.3.1 Mucositis Training
In order to enhance consistency in mucositis assessments, investigators, are required to complete a computer-based training program prior to enrolling patients to this trial. The training will include specific diagrams of pre-defined mucosal subsites and photos of various mucositis grades. Investigators will need to register and complete the computer-based training program before enrolling patients. See Section 5.1.6 for details.

11.3.2 Mucositis assessments will be performed using the 4 step process outlined on the QP form. The WHO grade will be calculated at RTOG Headquarters after collection of specific data components by local investigators. The 4 data components are:
1. The presence of mouth or throat pain (and use of opioids);
2. The mode of nutrition (oral vs. non-oral);
3. The form of nutrition (solids vs. liquids);
4. The presence of ulceration on any of the 9 mucosal sites below:
   - Upper lip and/or lower lip;
   - Right cheek (buccal mucosa);
   - Left cheek (buccal mucosa);
   - Right ventral and lateral tongue;
   - Left ventral and lateral tongue;
   - Right floor of mouth;
   - Left floor of the mouth;
   - Right soft palate/tonsil/posterior wall;
   - Left soft palate/tonsil/posterior wall.
It is imperative that some degree of consistency be maintained in the use of these tools. Although it is not always possible to have the same examiner throughout the entire course of radiation therapy, investigators are encouraged use the same examiner as much as possible. 

**Note:** Any investigator or designated research staff (nurse; non-nurse research associate) may perform mucositis assessments, as long as they have completed the on-line mucositis assessment training.

11.3.3 The presence or absence of mucosal ulceration in the oral or oropharyngeal mucosa will be recorded in each of the sub-sites on the QP form.

11.4 **Measurement of Response**

11.4.1 **Tumor Clearance**

A meaningful response for this study population is a complete response; anything less will be considered a treatment failure. A patient will be considered to have complete response if there is no measurable or palpable tumor either on clinical or radiographic (CT scan or MRI) examination.

The primary tumor and regional nodes will be evaluated and reported separately. Patients that have non-protocol radiation to the primary tumor or regional nodes or chemotherapy prior to achieving complete response will be considered a treatment failure.

11.4.2 **Local or Regional Relapse**

Relapse is defined as reappearance of tumor after complete response. If possible, relapse should be confirmed by biopsy.

11.4.3 **Local or Regional Progression**

Progression is defined as an estimated increase in the size of the tumor (product of the perpendicular diameters of the two largest dimensions) of greater than 25%, taking as reference the smallest value of all previous measurements or appearance of new areas of malignant disease.

11.4.4 **Distant Metastasis**

Clear evidence of distant metastases (lung, bone, brain, etc.); biopsy is recommended where possible. A solitary, spiculated lung mass/nodule is considered a second primary neoplasm unless proven otherwise.

11.4.5 **Second Primary Neoplasm**

Tumor reappearing with the initial and immediate adjoining anatomical region of the primary will be considered local recurrence. Multiple lung nodules/masses are considered distant metastases from the index cancer unless proven otherwise.

11.4.6 **Long-term Follow-up (5/23/07)**

Patients enrolled in the study should be followed until death or for a maximum of 10 years.

11.5 **Protocol-Specific Adverse Event Evaluation**

In an effort to improve the capture and consistency of adverse event (AE) reporting, essential adverse events commonly associated with head and neck treatment are to be assessed at during treatment, and at follow up using CTCAE version 3.0. A CTCAE Grading Tool, designed specifically for RTOG 0435 and containing a subset of CTCAE terms, is available on the RTOG web site next to the protocol, to facilitate grading. In addition, the spiral bound CTCAE booklet distributed by the NCI can be used, as can the 'electronic search tool' on the RTOG web site under the RA Corner (adverse events) [Select the appropriate category (i.e., neurology, etc.), and then find the AE term in alphabetical order]. Additional AE terms and grading criteria can be accessed online at [http://ctep.cancer.gov/reporting/ctc.html](http://ctep.cancer.gov/reporting/ctc.html)

Protocol-specific “essential” (mandatory) AEs should be reported at the end of treatment (the worst grade of each AE term over the course of treatment) and at each follow up.

Essential AEs to be reported for the **acute period** (acute effects = end of treatment and within 90 days of treatment) are: dysphagia, skin reaction in field, skin reaction out of field, edema, and neuropathy.

Essential AEs to be reported for the **late period** (late effects = > 90 days from the end of treatment) are: dysphagia, neuropathy, chronic or new onset of soft tissue, dermis, and bone injury as listed below.
Essential protocol-specific adverse events to be reported, if present, on the Adverse Event (AE) form:

<table>
<thead>
<tr>
<th>Category</th>
<th>AE term</th>
<th>Ref page in CTCAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary/ Upper Respiratory</td>
<td>Edema, larynx (includes need for tracheostomy)</td>
<td>57</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Dysphagia (difficulty swallowing)</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Mucositis/stomatitis (clinical exam) [specify oral cavity, pharynx, or larynx primary site]</td>
<td>24</td>
</tr>
<tr>
<td>Dermatology/Skin</td>
<td>Rash/desquamation [face (out of field), trunk, extremities]</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Rash: dermatitis associated with radiation-Select radiation (radiation dermatitis may be exacerbated by palifermin, but in-field skin changes are graded using the radiation scale)</td>
<td>15</td>
</tr>
<tr>
<td>Neurology</td>
<td>Neuropathy: sensory Neuralgia/peripheral nerve (pain)</td>
<td>50</td>
</tr>
<tr>
<td>Musculoskeletal/ Soft Tissue</td>
<td>Soft tissue necrosis (Chronic Or New Onset MUCOSAL ulceration noted &gt; 3 months after treatment requiring wound care, hyperbaric, or surgical intervention)</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Soft tissue necrosis (Chronic or new onset DERMIS/SOFT TISSUE ulceration noted &gt; 3 months after treatment requiring wound care, hyperbaric, or surgical intervention)</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Chronic or new onset induration/fibrosis (skin and subcutaneous tissue) noted &gt; 3 months after treatment</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>Chronic or new onset osteonecrosis (includes necrosis of mandible, maxilla, skull) noted &gt; 3 months after treatment</td>
<td>45</td>
</tr>
</tbody>
</table>

11.5.1 AEs experienced during treatment and in follow up must be documented on Adverse Event (AE) form. **When reporting AEs, please refrain from using the ‘Other, Specify’ mechanism. This should be the exception, not the rule in the rare event that a suitable CTCAE term cannot be found. If this is absolutely necessary, the investigator must make a note to this affect in the source documentation.** See section 12.1 for submission schedule.

11.5.2 For patients without a feeding tube, a nutritional evaluation based on acute reactions and Zubrod status should be done weekly during treatment. Status of feeding tube and placement/removal of a tracheostomy should be documented on the Follow-up Form (F1).

11.5.3 Whenever possible, patients will be evaluated at two-week intervals after completion of treatment until their acute reactions have resolved.

11.5.4 Treatment for recurrence depends on the site of relapse and is at the discretion of the treating physician.

11.6 Functional and Symptom Assessments

11.6.1 *MD Anderson Symptom Inventory, Head and Neck Module (MDASI-HN)*

The MDASI measures on a numeric rating scale of 0-10 both severity of symptoms and the interference symptoms cause in patients daily activities. The 13 core MDASI symptom items are based on extensive evaluation of symptoms common to cancer and cancer treatment. The Head and Neck module includes 12-14 items specific to head and neck. Patients easily complete it as a self-report tool in approximately 5 minutes, or it can be completed with the help of the research nurse or CRA either in the clinic or over the telephone. Foreign language translations of the MDASI are currently being validated; translations will be available at
The Brief Pain Inventory (BPI)

The BPI asks patients to rate their pain for the last week on 0-10 scales. Patients also are asked to rate how their pain interferes with their quality of life (QOL). Patients also are asked to estimate the pain relief they receive from their pain treatment. The patient can complete the BPI in approximately 5 minutes. The BPI has been validated in 12 languages. Translations can be accessed at http://www.mdanderson.org/departments/prg/ click on “symptom assessment tools”. If a translation is used, the site must transcribe the data to the appropriate RTOG data form and attach the patient’s original.

The Xerostomia Questionnaire (XQ)

The XQ consists of eight questions: four questions related to dryness while eating/talking, and four questions related to dryness at rest. Patients rate each symptom on an 11-point ordinal Likert scale from 0 to 10, with higher scores indicating greater dryness or discomfort because of dryness. Each item scored is added, and the sum is transformed linearly to produce the final summary score ranging between 0 and 100, with higher scores representing greater levels of xerostomia. Patients can complete the XQ in approximately 5 minutes.

The cover sheet that accompanies all functional and symptom assessments must be completed and submitted for every required time point, whether or not the patient completed the assessment. Sites must document why the patient did not complete each functional and symptom assessment.

DATA COLLECTION (5/23/07)

Data should be submitted to:

RTOG Headquarters
1818 Market Street, Suite 1600
Philadelphia, PA 19103

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

Summary of Data Submission (5/23/07) (8/7/07)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry (baseline assessment done prior to start of treatment)</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>MDASI-HN (PQ)</td>
<td>Weekly submission for 15 weeks (during treatment and if oral ulcers continue to be present after treatment)</td>
</tr>
<tr>
<td>BPI (QL)</td>
<td></td>
</tr>
<tr>
<td>Xerostomia Questionnaire (XQ)</td>
<td></td>
</tr>
<tr>
<td>MDASI-HN (PQ)</td>
<td></td>
</tr>
<tr>
<td>BPI (QL)</td>
<td></td>
</tr>
<tr>
<td>Mucositis Assessment/Opioid Documentation Form (QP)</td>
<td>Once weekly for 15 weeks from the start of treatment (twice weekly assessments are documented on each form)</td>
</tr>
</tbody>
</table>

Preliminary Dosimetry Information for 3D-CRT Approach

It is highly recommended that dosimetry information be submitted digitally. Sites unable to submit digitally will contact RTOG Headquarters, RTQA Department, 215-574-3219. For digital submission, See Section 12.2.
### Final Dosimetry Information for 3D-CRT

**Approach** For digital submission, See Section 12.2

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Form (TF)</td>
<td>Within 2 weeks of the completion of RT</td>
</tr>
<tr>
<td>Supplemental Follow-up Form (FS)</td>
<td>Within 1 week of last palifermin/placebo dose</td>
</tr>
<tr>
<td>Xerostomia Questionnaire (XQ)</td>
<td>4 months from start of treatment</td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>6 months from start of treatment, then every 3 months for year 1, every 4 months for year 2, every 6 months for years 3-4, then annually for years 5-10</td>
</tr>
<tr>
<td>MDASI-HN (PQ)</td>
<td>12 months from start of treatment</td>
</tr>
<tr>
<td>Surgical Form (S1)</td>
<td>5 months from start of treatment for all patients, whether or not they have surgery</td>
</tr>
<tr>
<td>Surgical Operative Report (S2)</td>
<td>If patient has surgery</td>
</tr>
<tr>
<td>Surgical Pathology Report (S5)</td>
<td>If patient has surgery</td>
</tr>
</tbody>
</table>

### 12.2 Summary of Dosimetry Data Submission for IMRT (Submit to ITC; see Section 12.2.1)

<table>
<thead>
<tr>
<th>Item</th>
<th>Preliminary Dosimetry Information</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>†Digital Data Submission Form (DDSI)</td>
<td>CT data, critical normal structures, all GTV, CTV, and PTV contours (C1, C3)</td>
<td>Within 1 week of start of RT</td>
</tr>
<tr>
<td>Simulation films and/or digital film images for all initial treatment fields and orthogonal set up pair</td>
<td>First day port films (or digital images) of all initial treatment fields and orthogonal set up pair</td>
<td></td>
</tr>
<tr>
<td>Digital beam geometry for initial and boost beam sets</td>
<td>Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan (DV)</td>
<td></td>
</tr>
<tr>
<td>Doses for initial and boost sets of concurrent treated beams</td>
<td>Hard copy isodose distributions for total dose plan as described in QA guidelines (T6)</td>
<td></td>
</tr>
</tbody>
</table>

### Final Dosimetry Information

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy Form (T1) [copy to HQ and ITC]</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Daily Treatment Record</td>
<td></td>
</tr>
<tr>
<td>Simulation films and/or digital film images (or digital images) of all boost treatment fields and orthogonal set up pair (T8)</td>
<td></td>
</tr>
<tr>
<td>First day port films of all boost treatment fields and orthogonal set up pair (T8)</td>
<td></td>
</tr>
<tr>
<td>Modified digital patient data as required through consultation with Image Guided Therapy QA Center</td>
<td></td>
</tr>
</tbody>
</table>

†Available on the ATC web site, [http://atc.wustl.edu/](http://atc.wustl.edu/)

### 12.2.1 Digital Data Submission to ITC

Digital data submission may be accomplished using magnetic tape or the Internet. For network submission: The FTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:
13.0 STATISTICAL CONSIDERATIONS (5/23/07)

13.1 Study Endpoints

13.1.1 Primary Endpoint
Duration in days of WHO Grades 3 and 4 oral mucositis during the acute period (defined to be 105 days [15 weeks] or less from the start of treatment); duration is calculated from the onset of a Grade 3 or 4 oral mucositis to the day when an oral mucositis of ≤ Grade 2 is reported after the last oral mucositis of Grade 3 or 4.

13.1.2 Secondary Endpoints (Non-exploratory)
- Incidence of acute Grades 3 or 4 oral mucositis based on the WHO scale;
- Time to onset of acute Grades 3 or 4 oral mucositis based on the WHO scale;
- Long-term safety:
  - Overall survival (Event: Death from any cause);
  - Progression-free survival (Event: First occurrence of local, regional, or distant disease progression, occurrence of a second primary other than basal cell, or death from any cause);
  - Time to second primary tumor (Event: Occurrence of a second primary other than basal cell);
- Overall survival, progression free survival (an event is first occurrence of local, regional, or distant disease progression, occurrence of a second primary, or death from any cause), and incidence of second primaries (safety endpoints).

13.1.3 Tertiary Efficacy Endpoints (Exploratory)
- Change in symptom burden measured by the MD Anderson Symptom Inventory- Head and Neck (MDASI-HN);
- Change in pain measured by the Brief Pain Inventory (BPI);
- Change in xerostomia measured by the University of Michigan Xerostomia Questionnaire (XQ);
- Use of nutritional support via NG or PEG feeding tubes;
- Opioid analgesics use (total dose in morphine equivalents);
- Acute short-term safety: Incidence of patients with Grade 3, 4, or 5 adverse events based on the CTCAE, v.3.0 scale.

13.2 Background
This study tests whether palifermin reduces the duration of Grade 3 and 4 mucositis, which frequently occurs with patients receiving chemoradiation for the treatment of their head and neck tumors. Secondary efficacy endpoints are related directly and indirectly to mucositis; directly: incidence and onset of Grade 3 or 4 mucositis and indirectly: the change in the pain and the symptom scores and in the use of feeding tube and opioid analgesics use. The secondary endpoints other than the incidence and the time to onset of Grade 3 or 4 mucositis are considered to be exploratory.

Safety monitoring will take place in two time frames: The timeframe for acute short-term safety monitoring is 105 days [15 weeks] from first administration of palifermin/placebo. The CTCAE, v.3.0 scale will be used to grade and categorize all adverse events during this period. The timeframe for long-term safety monitoring is the period starting after the end of the acute short-term period up to 10 years from first administration of palifermin/placebo. The safety endpoints are overall survival, progression-free survival, and the incidence of second primaries. These
endpoints will be used to determine if palifermin adversely compromises the effectiveness of the chemoradiation.

13.2.1 Stratification
Patients will be stratified before randomization with respect to disease stage (III vs. IVA/B), tumor site (oral cavity or oropharynx vs. hypopharynx or larynx), and use of IMRT (no vs. yes). The treatment allocation scheme described by Zelen\textsuperscript{42} will be used because it balances patient factors other than institution. Within each stratum, patients will be randomized in a 1:1 ratio to palifermin or placebo concurrently with chemoradiotherapy.

13.2.2 Sample Size Derivation
The sample size calculations will address the specific primary hypothesis that the use of palifermin concurrently with chemoradiation for patients with locally advanced head and neck cancer will result in a statistically significant decrease in the mean duration of acute Grades 3 and 4 oral mucositis compared to the mean duration experienced by patients receiving placebo.

Parameters used to determine the required sample size for the primary endpoint of mean duration of acute Grades 3 and 4 oral mucositis are:
- The mean duration and standard deviation of acute Grades 3 and 4 oral mucositis on the placebo are 29 and 23 days, respectively.
- A reduction in the mean duration of acute Grades 3 and 4 oral mucositis of at least 9 days in the palifermin arm.
- Two-sided test at $\alpha = 0.05$;
- Statistical power of 90%;
- One interim analysis for efficacy.

Using a t-test of means with an assumption of equal variance and the same number of patients in each treatment arm, a total of 282 patients is required. The final targeted accrual for this study will be 298 cases. With the sample size of 141 patients per treatment arm, the study will provide 88% statistical power using the Wilcoxon rank sums test to detect a treatment difference in the primary endpoint. All randomized patients will be included in the primary efficacy analysis per randomization.

13.3 Patient Accrual
Based on accrual to RTOG 9901, A Phase III Study to Test the Efficacy and Safety of GM-CSF to Reduce the Severity and Duration of Mucosal Injury and Pain (Mucositis) Associated with Curative Radiation Therapy in Head and Neck Cancer Patients, of over 6 patients per month, the monthly projected accrual for this trial is 8 patients per month. The active accrual period is then 38 months; the total projected period from activation to completion of accrual is 41 months to allow for 3 months of negligible accrual during which institutional IRB approval and CRA training for oral mucositis assessment will take place. The RTOG Data Monitoring Committee (DMC) will evaluate patient accrual semi-annually. If at 24 months after study activation the mean monthly accrual rate between months 18 and 24 (calculated by dividing the actual accrual total for months 19-24 by 6) is less than 30% of the projected total of 48 for 6 months of accrual (15 patients), the study statistician will recommend to the Group Chair and the RTOG DMC that the study be stopped. If the mean monthly accrual rate is more than 30% but less than 50% at 24 months after study activation, the statistical section will be amended to reflect the actual accrual rate.

13.4 Analysis Plan
13.4.1 Statistical Methods
The major (definitive) analysis will take place after a positive significance test in the planned interim analysis or after all patients have been entered in the study and followed for a minimum of 15 weeks from start of treatment if the planned interim analysis is not positive. Critical values used in the sequential interim analysis will preserve an overall, two-sided alpha level of 0.05 for the study, requiring the final primary analysis to use an alpha level of 0.046 if the interim analysis is not statistically significant as specified in Section 13.4.2.

The primary endpoint, the difference in mean duration of acute Grades 3 and 4 oral mucositis measured by the WHO 3.0 clinical mucositis scale between the two arms will be tested using van Elteren’s test, which is an extension of the stratified Wilcoxon rank sums test. It will be obtained from the generalized Cochran-Mantel-Haenszel (CMH) test for mean difference using the standardized midranks (also known the modified ridit scores)\textsuperscript{43} In addition, a second efficacy comparison also will be done as a sensitivity analysis using only those patients who
are found on retrospective review to satisfy the protocol eligibility criteria per randomized treatment assignment.

Oral mucositis (OM) is measured during a twice-weekly clinical assessment until ≤ WHO Grade 1 or up to 15 weeks after the start of treatment. The start and stop dates of acute Grades 3 and 4 oral mucositis will be measured relative to the first day of chemoradiation. The resolution of an acute Grade 3 or 4 oral mucositis is defined as an oral mucositis of ≤ Grade 2 after the last OM of Grade 3 or 4. If an acute Grade 3 or 4 OM is not resolved to ≤ Grade 2, the duration will be imputed with the mean duration among patients who experience at least the same duration. Patients with no acute Grades 3 or 4 OM will be assigned a duration of 0 days. The strata for this and all other analyses will be defined in terms of the 3 variables used to stratify the patients prior to randomization. If there are less than 5 patients in any stratum at the time of the analysis, the patients in that stratum will be combined with the patients from the next smaller stratum with the same value for the IMRT variable. Other studies have shown a reduction with IMRT in the severity and duration of adverse events.

Time-to-event efficacy endpoints will be measured from the first day of randomization to the date of the event (e.g., onset of acute Grades 3 or 4 OM). Time-to-event endpoints between the two arms will be estimated using Kaplan-Meier estimates and tested using the stratified log-rank test statistic. Patients with no events will be censored at the last measurement of the endpoint under analysis.

Incidence of patients with acute Grades 3 and 4 oral mucositis per the WHO scale will be tested between the 2 arms using the CMH test for general association with randomization stratifications as the CMH analysis strata. Patients with no measurement for the above endpoint will be treated as having an acute Grade 3 and 4 oral mucositis. With 141 patients in each arm, there is 83% statistical power using Fisher’s exact test to detect a difference in incidence of 0.70 in the placebo arm and 0.50 in the treatment arm. Using the log-rank test with 141 patients in each arm, there is 84% statistical power to detect a difference between 85% acute Grades 3 and 4 oral mucositis in the placebo arm and 70% acute Grades 3 and 4 oral mucositis in the treatment arm at 7 weeks (i.e., the end of radiation therapy). Rates of prophylactic and non-prophylactic nutritional support via NG or PEG feeding tubes will be compared using Fisher’s exact tests. With 141 patients in each arm, there is 89% statistical power to detect a difference in rates of nutritional support of .38 in the placebo arm and .20 in the treatment arm. The opioid analgesics use will be collected during the acute mucositis evaluation period. Opioid use will be transformed to morphine equivalents. The total morphine equivalent doses will be compared between the 2 arms using the van Elteren’s test. With 141 patients per arm and an effect size of 0.35 or higher, where the effect size is
\[ \delta = \frac{|\mu_1 - \mu_2|}{\sigma}, \text{where } \sigma \text{ is the common standard deviation}, \] there is 83% statistical power to detect this effect.

For the safety endpoints, the analysis will be performed on all randomized patients who have received one dose of palifermin/placebo but by treatment actually received not treatment randomly assigned. In addition, a second comparison also will be done as a sensitivity analysis using all the patients randomized. With respect to the acute safety period, the incidence rates of Grade 3-5 adverse events according to the CTCAE, v.3.0 will be computed and reported as follows:

1. Adverse event attributed by the investigator to palifermin/placebo as definite, likely, possibly, or unknown;
2. Adverse event attributed by the investigator to the entire protocol treatment (chemoradiation and investigational drug [palifermin/placebo] as definite, likely, possibly, or unknown;
3. Adverse event attributed to the entire protocol treatment (chemoradiation and investigational drug [palifermin/placebo] regardless of attribution.

The incidence of adverse events (per the 3 categories above) also will be summarized for the following subgroups: age (< 65 and ≥ 65); gender (male and female); and race (NCI categories). All races that include less than 5% of the patients randomized will be pooled into
one race group for summary purposes. Incidence of patients with any Grade 3, 4, or 5 adverse events per the CTCAE, v3.0 will be tested between the two arms using the stratified CMH test for general association with randomization stratifications as the CMH analysis strata.

Long-term safety will be evaluated in terms of overall survival (OS), progression-free survival (PFS), and incidence of second primary. OS, PFS, and incidence of second primary will be estimated by the Kaplan-Meier method and tested using the stratified log-rank test. The event time is defined as the time elapsed between the date of first palifermin/placebo administration and the date of the given event. Long-term safety data will be analyzed for patients who received at least one dose of palifermin/placebo and reported on an annual basis after the results of the primary efficacy analyses have been submitted to a peer reviewed journal for publication. Exploratory analyses of safety endpoints will use the Cox proportional hazard regression model adjusting for stratification factors (disease stage [III vs. IVA-B]; tumor site [oral cavity or oropharynx vs. hypopharynx or larynx]; and use of IMRT [no vs. yes]), neck dissection (yes or no), and other covariates known to be prognostic.

Long-term safety data will be analyzed on an annual basis for patients who received at least one dose of palifermin/placebo.

### 13.4.2 Significance Testing for Early Termination and Reporting

One interim treatment comparison will be performed after accruing 141 randomized patients and getting follow-up data on these patients for 15 weeks after treatment start. A modified Haybittle-Peto boundary of $p < 0.005$ will be used to test the null hypothesis of treatment efficacy. The results of this planned interim analysis will be reported to the RTOG DMC with the treatment blinded. The study statistician will recommend early reporting of the results and/or stopping the trial if the treatment effect, with respect to mean duration of acute Grades 3 and 4 oral mucositis, shows strong evidence of efficacy by crossing the boundary of $p = 0.005$. The DMC will then make a recommendation about the trial to the RTOG Group Chair.

### 13.4.3 Significance Testing of the Long-Term Safety for Early Reporting

Interim testing of survival between the two arms will be performed to identify any large effect that warrants early reporting before 10 year follow-up data are collected on all patients. The first significance testing of survival will be done as part of the final efficacy analysis. Subsequent testing of survival will be performed every 2 years until all protocol patients have potentially been followed for 10 years. If a p-value from any of these interim tests is less than 0.005, additional analysis of the PFS and time to second primary tumor will be generated for RTOG DMC review. After reviewing these results, the DMC will then make a recommendation to the RTOG Group Chair relative to early reporting of the long-term safety data. Regardless of the decision, the data collection will continue for all patients until death or a maximum of 10 years. If the significance boundary is not crossed during the collection of long-term follow-up data, a final report will be generated after the collection of 10 year follow-up data on all subjects.

### 13.4.4 Interim Analyses of Accrual and Adverse Event Data

Interim reports will be prepared every 6 months until the initial manuscript reporting the treatment efficacy results has been submitted for publication. The major components of this report are:

- The patient accrual rate with a projected completion date for the accrual phase;
- Accrual by institution;
- The distribution of pretreatment characteristics by blinded assigned treatment arms;
- The frequency and severity of the adverse events combined over assigned treatments

The study statistician will report any problems identified to the study chairs, RTOG CCOP committee, the RTOG DMC, and if appropriate, to the RTOG Executive Committee. The RTOG DMC will review these reports and make recommendations as deemed appropriate. Following the completion of the efficacy analysis, interim reports for long-term safety will be prepared every 12 months until every patient could have potentially been followed for 10 years. The RTOG DMC will review these reports and make recommendations as deemed appropriate. Once all the patients have been potentially followed for 10 years, there will be no further interim reports generated.

In addition, this study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.
13.4.5 Analysis for Reporting Efficacy Results
The final analysis will take place after a positive significance test in the planned interim analysis or after all patients have been entered in the study and followed for a minimum of 15 weeks from start of treatment, if the planned interim analysis is not positive.

The usual components of this analysis include:
- Tabulation of all cases entered, and any excluded from analysis with reasons for exclusion;
- Patient accrual rate;
- Institutional accrual;
- Distribution of important baseline pre-treatment characteristics;
- Frequency and severity of adverse events for acute safety;
- Observed results with respect to the study endpoints (See Section 13.1).

The difference in durations of Grades 3 and 4 mucositis between the palifermin arm and the placebo arm will be compared using van Elteren’s test, at the significance level of 0.046, given that the one interim analysis is carried out and does not achieve statistical significance at p < 0.005.

In addition, a second efficacy comparison also will be done as a sensitivity analysis using only those patients who are found on retrospective review to satisfy the protocol eligibility criteria per randomized treatment assignment.

13.4.6 Analysis for Reporting Long-Term Safety Results
The final analysis will take place after a positive significance test in a planned interim analysis or after all patients have been potentially followed for 10 years. This analysis will include:
- Distribution of important baseline pre-treatment characteristics;
- Observed results with respect to the long-term safety endpoints (See Section 13.1.2);
- The difference in survival between the palifermin arm and the placebo arm will be compared using the log rank statistic at the significance level of 0.040, given that the other interim analyses were performed and did not achieve statistical significance at p < 0.005.

13.4.7 Patient Reported Outcomes
13.4.7.1 Brief Pain Index (BPI)
The primary patient-reported endpoint for the BPI will be differences between arms in the mean BPI score using all assessments from baseline (i.e., pre-study) to 15 weeks from start of chemoradiation for each patient. Only patients alive at 15 weeks with baseline BPI scores will be included in this analysis. Longitudinal data analysis will be performed to describe the change trend of the scores over time across the 2 treatments using an appropriate model, such as the hierarchical formulation of the linear mixed model. The model will include the stratification factors (disease stage, tumor site, and use of IMRT). An Area Under the Curve (AUC) analysis will also be done using all assessments from baseline (i.e., pre-study) to 15 weeks from start of chemoradiation for each patient. Missing assessments will be imputed using the worst BPI score for the patient as the most conservative imputation approach. A 2-sided van Elteren’s test with \( \alpha = 0.05 \) will be used to test the null hypothesis that the mean AUCs are the same versus the alternative that they are different. With 141 patients per arm and an effect size of 0.35 or higher, where the effect size is \( \delta = \frac{\mu_1 - \mu_2}{\sigma} \), where \( \sigma \) is the common standard deviation, there is 83% statistical power to detect this effect. BPI scores will also be tested using the maximum score for each patient in the same time period. A 2-sided van Elteren’s test with \( \alpha = 0.05 \) will be used to test the hypothesis that the distribution of maximum BPI scores is the same in both arms.

13.4.7.2 The MD Anderson Symptom Inventory for Head and Neck Cancer (MDASI-HN)
The goals for the MDASI-HN instrument are to determine if the levels of symptoms return to baseline levels and to compare the change in MDASI-HN scores over time across the 2 treatment arms. The MDASI-HN has 13 core items, 9 head and neck items, and 6 interference items. There are four different subscale scores of potential interest: core items, head and neck items, core plus head and neck items, and interferences items. The primary patient-reported endpoint for the MDASI-HN will be the 9 head and neck items subscale score. Longitudinal data analysis will be performed to describe the change trend of the scores over time across the 2 treatments using an appropriate model, such as the hierarchical formulation of the linear mixed model. The model will include the stratification factors (disease stage, tumor site, and use of IMRT). All assessments from baseline (i.e.,
pre-study) to 15 weeks from start of chemoradiation for each patient. Only patients alive at 15 weeks with baseline MDASI-HN head and neck item subscale scores will be included in this analysis. Missing assessments will be imputed using the worst MDASI-HN score for the patient as the most conservative imputation approach. An AUC analysis will also be done using all assessments from baseline (i.e., pre-study) to 15 weeks from start of chemoradiation for each patient. A 2-sided van Elteren’s test with \( \alpha = 0.05 \) will be used to test the null hypothesis that the mean AUCs are the same versus the alternative that they are different. With 141 patients per arm and an effect size of 0.35 or higher, where the effect size is \( \delta = \frac{\mu_1 - \mu_2}{\sigma} \), there is 83% statistical power to detect this effect. If other subscales (i.e., core items, head and neck items, or the interference items) also are tested, the Hochberg procedure\(^{45}\) will be used to adjust for the multiple testing. Total MDASI-HN scores also will be tested using the maximum total score for each patient in the same time period. A 2-sided van Elteren’s test with \( \alpha = 0.05 \) will be used to test the hypothesis that the distribution of maximum total MDASI-HN scores is the same in both arms.

To test if levels of symptoms return to baseline levels, the difference in each patient’s baseline and final MDASI-HN head and neck items scores will be calculated. The mean difference for each treatment arm will be calculated. Let \( \mu_{\text{KGF}} \) be the mean difference for the KGF arm and \( \mu_{\text{PLC}} \) be the mean difference for the placebo arm. These mean difference will be tested separately for each treatment arm using a 2-sided t-test with \( \alpha = 0.025 \). The null hypothesis for the KGF arm is that \( \mu_{\text{KGF}} = 0 \) versus the alternative hypothesis that \( \mu_{\text{KGF}} \) is different from 0. The null hypothesis for the placebo arm is that \( \mu_{\text{PLC}} = 0 \) versus the alternative hypothesis that \( \mu_{\text{PLC}} \) is different from 0. If this null hypothesis is rejected in at least one treatment arm, then another test of the null hypothesis that \( \mu_{\text{KGF}} - \mu_{\text{PLC}} = 0 \) versus the alternative that \( \mu_{\text{KGF}} - \mu_{\text{PLC}} \neq 0 \) is different from 0 will be conducted. This last test will characterize any difference in mean change from baseline to final MDASI-HN core plus head and neck items scores between the 2 treatment arms. The final MDASI-HN core plus head and neck items scores will be at 15 weeks from start of chemoradiation or when mucositis resolves to \( \leq \) grade 1. Missing data will be imputed using the maximum patient score as the most conservative method.

13.4.7.3 Xerostomia Questionnaire (XQ)

Xerostomia will be evaluated via the University of Michigan Xerostomia Questionnaire (XQ) at baseline (pre-treatment), at 15 weeks from start of treatment, and at 6, 12, 18, and 24 months post-treatment. The change in the XQ scores from baseline (i.e., pre-treatment) to 15 weeks from start of chemoradiation for each patient will be compared between arms as well as the change from baseline (i.e., pre-treatment) to 12 months to assess xerostomia during the acute and the long-term safety periods. Only patients alive at 15 weeks and at 12 months who are taking their nutrition orally, not by feeding tube, with baseline XQ scores will be included in these two these analyses. Missing assessments will be imputed using the worst XQ score for the patient as the most conservative imputation approach. A 2-sided van Elteren’s test with \( \alpha = 0.05 \) will be used to test the null hypothesis that the mean change are the same versus the alternative that they are different. Longitudinal data analysis will be performed to describe the change trend of the XQ scores over time across the 2 treatments using an appropriate model, such as the hierarchical formulation of the linear mixed model.\(^{40}\) The model will include the stratification factors (disease stage, tumor site, and use of IMRT).

13.5 Gender and Minorities

**Projected Distribution of Gender and Minorities**

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<thead>
<tr>
<th>Ethnic Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
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<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
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<td>180</td>
<td>276</td>
</tr>
<tr>
<td>Ethnic Category: Total of all subjects</td>
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<td>194</td>
<td>298</td>
</tr>
</tbody>
</table>

Gender

---

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<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
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<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Black or African American</td>
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<td>15</td>
<td>24</td>
</tr>
<tr>
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<td>1</td>
<td>1</td>
</tr>
<tr>
<td>White</td>
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<td>174</td>
<td>266</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
<td>104</td>
<td>194</td>
<td>298</td>
</tr>
</tbody>
</table>
REFERENCES (5/23/07)


REFERENCES (Continued)


REFERENCES (Continued)


APPENDIX I

RTOG 0435

Informed Consent Template for Cancer Treatment Trials (English Language)

A Randomized, Phase III, Double-Blind, Placebo-Controlled Study To Evaluate The Efficacy And Safety Of Palifermin (NSC # 740548; IND #100,192) For The Reduction Of Oral Mucositis In Patients With Locally Advanced Head And Neck Cancer Receiving Radiation Therapy With Concurrent Chemotherapy (Followed by Surgery For Selected Patients)

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

You are being asked to take part in this study because you have head and neck cancer for which you are receiving radiation therapy and chemotherapy.

Why is this study being done?

Painful sores in the mouth are a common side effect of radiation therapy and chemotherapy. There is no current treatment to prevent these sores. The purpose of this study is to compare the effects, good and/or bad, of a drug, palifermin, with placebo to find out if palifermin prevents these sores.

Palifermin is a drug that speeds up the growth of epithelial cells, cells that line the inside and outside surfaces of the body, such as the mouth, throat, or skin. Palifermin has been approved by the FDA for patients that are receiving radiation therapy and chemotherapy for cancer of the blood or lymph nodes. It has not been approved for patients with head and neck cancer. Palifermin is considered an investigational drug in this study.

The placebo looks like palifermin but is not an active medicine. In this study, you will get either palifermin or the placebo. You will not get both.

How many people will take part in the study?

About 298 people will take part in this study.

What will happen if I take part in this research study? (5/23/07)

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

- A physical exam
- Evaluation of the lining of your mouth and throat
- An evaluation of your weight and the calories and fluids you are receiving each day
- A chest X-ray or CT (Computed Tomography) scan of your chest; a CT scan is a study using x-rays to look at one part of your body
- CT scan or MRI (Magnetic Resonance Imaging) of your tumor; an MRI is imaging using a strong magnetic field to look at one part of your body
- Blood tests
- For women able to have children, a pregnancy test
During the study, you will need these tests and procedures once a week during radiation therapy and chemotherapy to see how the study is affecting your body:

- Physical exam
- Blood tests

In addition, you will need these tests and procedures twice a week during radiation therapy and chemotherapy to see how the study is affecting your body:

- Evaluation of the lining of your mouth and throat
- The study doctor or research nurse will ask you how much pain medicine you are taking each day.

**3 days before the second and third dose of chemotherapy**

- Blood tests

All patients in this study will receive 7 weeks of radiation therapy and chemotherapy (cisplatin) while they receive palifermin or placebo. Radiation therapy will be given 5 days a week, Monday through Friday. Each radiation treatment will take about 5-10 minutes. You will receive cisplatin through your vein on days 1, 22, and 43 before RT. Receiving the cisplatin takes about 30 minutes.

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

If you participate in this study, you will receive up to 8 doses of palifermin or placebo through your vein. Receiving a dose takes about 5 minutes. You will receive palifermin or placebo the Friday before your radiation therapy and chemotherapy begin, then on the next 3 Fridays, days 5, 12, and 19. If you still have sores in your mouth at the end of radiation treatment, you also will receive palifermin or placebo on the last Friday of radiation therapy and chemotherapy, then after completing therapy, once a week for 3 weeks or until the sores in your mouth have gone away, up to an additional 3 doses.

When you are finished taking palifermin or placebo:

- For about 8 weeks after radiation treatment and cisplatin has ended, the study doctor will examine the lining of your mouth and throat twice a week.
- At 8 weeks and then once a year for years 1-5, you will have a CT scan or MRI of the head and neck to see if your cancer has responded to chemotherapy and radiation therapy, or is stable, or is progressing. Patients with remaining large tumors after chemotherapy/radiation will have surgery to remove the cancer, if it is found that surgery can be done to remove the remaining cancer. The study doctor and surgeon will discuss the need for this re-evaluation and surgery with these patients.
- For 4 months from the start of treatment, you will be asked to write down how much pain medicine you take each day. You will bring this information with you to each follow-up visit with the study doctor.

In follow-up visits, you will need these tests and procedures. You will be seen in follow-up visits at 8 weeks, every 3 months for year 1, every 4 months for year 2, every 6 months for years 3-4, then once a year for years 5-10.

- A physical exam
- Evaluation of the lining of your mouth and throat
- An evaluation of your weight and of the calories and fluids you are receiving each day
Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.

All Patients
Radiation Therapy, once daily, M-F for 7 weeks with cisplatin on days 1, 22, and 43
7 weeks

Randomize
(You will be in one Group or the other. Neither you nor your doctor can choose the group you will be in, and neither you nor your doctor will know in which group you are placed.)

Up to 8 doses of Palifermin
Up to 8 doses of placebo

On the Friday before radiation therapy and cisplatin, then on the next 3 Fridays (days 5, 12, and 19)

If you still have sores in your mouth on the last day of radiation therapy, then you will receive another dose of palifermin or placebo.

You will continue to receive up to 3 more doses of palifermin or placebo once a week for 3 weeks until the sores in your mouth have gone away, (for a total of up to 4 doses after radiation).

Re-Evaluation for all patients
8 weeks after Radiation therapy and chemotherapy
CT scan or MRI

Surgery
For patients with remaining large tumors after radiation therapy and chemotherapy
How long will I be in the study?

You will receive treatment for about 10 weeks. You will receive 4 doses of palifermin or placebo during the 7 weeks of radiation therapy and cisplatin. After completing radiation therapy and cisplatin, if you still have sores in your mouth, you will receive up to 4 more doses of palifermin and placebo, once a week for 4 weeks or until the sores in your mouth have gone away.

After radiation therapy and cisplatin are finished, you will be seen in follow-up visits twice a week for about 8 weeks, if you still have sores in your mouth. In addition, at 6-8 weeks after radiation therapy and cisplatin is finished, you will be re-evaluated to see if your cancer has responded to radiation therapy and chemotherapy.

After you are finished taking palifermin or placebo, the study doctor will ask you to visit the office for follow-up exams. You will be seen in follow-up visits every 3 months for year 1, every 4 months for year 2, every 6 months for years 3-4, then once a year for years 5-10.

Can I stop being in the study?

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

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

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

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

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don’t know all the side effects that may happen. Side effects may be mild or very serious.

Your health care team may give you medicines to help lessen side effects. Some medicines for painful sores in the mouth besides palifermin are allowed in this study. Some medicines, such as mouthwash solutions or Gelclair®, are not allowed. If you participate in this study, the study doctor will talk to you about these other medicines.

Many side effects go away soon after you stop radiation therapy, cisplatin, and palifermin/placebo. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

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

Risks Related to Radiation Therapy When Given in Combination With Cisplatin

Very Likely
- Sores in the mouth and throat that are likely to interfere with swallowing
- Dryness of the mouth or altered taste that may be permanent
- Temporary hair loss (of the face/chin/neck)
- Tanning, redness, or blistering or peeling of skin in treatment area
- Loss of teeth, or cavities in teeth, if strict dental care is not followed
- Hardness and tightness of the skin and muscles of the head and neck
- Loss of appetite
- Weight loss
Less Likely, But Serious

- Permanent hair loss (of the face/chin/neck)
- Decrease in function of thyroid gland which may require you to take thyroid replacement medicine to prevent you from feeling tired or sleepy
- Difficulty with swallowing and eating for which you might need a long term or permanent feeding tube
- The possibility of inhaling food and/or liquids into the lungs, which could also result in pneumonia
- Serious ear infections and/or hearing loss
- Damage to the spinal cord leading to permanent weakness and/or symptoms like a "stroke"

Rare

- Severe damage to the jawbone and/or voice box which could require major surgery to correct or even to remove the jaw bone and/or voice box

Risks and Side Effects Related to Cisplatin

Cisplatin is a standard (not experimental) treatment for head and neck cancer. The side effects listed below under “Likely” are expected to occur. The study doctor or your hospital may want to admit you to the hospital overnight to treat these side effects.

Likely

- Tiredness and/or general weakness
- Nausea and/or vomiting
- Decrease in white blood cell count, which may increase the risk of infection, decreased healing, and/or bleeding
- Decrease in red blood cell count, which may result in anemia, tiredness, and/or shortness of breath
- Decrease in platelets, the cells in the blood that help blood clot normally
- Loss of appetite and/or weight loss
- Ringing in the ears and/or hearing loss

Less Likely

- Decrease in the kidneys’ ability to handle the body’s waste, which may be permanent
- Changes in electrolytes, which may result in tiredness, cramps, and/or numbness and tingling
- Involuntary movements, restlessness, muscle cramps, and/or loss of coordination
- Numbness and tingling in the fingers, hands, toes, and feet

Rare

- Hair loss
- Loss of taste
- Seizures
- Loss of muscle or nerve function, which may result in weakness
- Allergic reactions, which can involve flushing, difficulty breathing, irregular heartbeat, low blood pressure, and can even be life threatening
- Another cancer called acute leukemia

Risks and Side Effects Related to Palifermin (5/23/07)

Palifermin is a drug that speeds up the growth of epithelial cells, cells that line the inside and outside surfaces of the body, such as the mouth, throat, or skin. Whether or not palifermin could cause growth of your cancer is not yet known. In laboratory and animal studies, there is evidence that palifermin did speed up the growth of some cancers, but the dose of palifermin used in these studies was higher than the recommended dose for humans. A study of palifermin given to patients with head and neck cancer is ongoing and after four years, this study has not shown that palifermin causes growth of tumors or decreases patients’ survival.

In this study, the study doctor will be carefully checking the effects of your treatment (radiation therapy and chemotherapy) and the effects of palifermin on you and on your cancer. In addition, many parts of the body have epithelial cells, such as the milk-producing glands or parts of the eye. Since palifermin could speed up growth of these cells, there could be unexpected side effects.
**Likely**
- Skin reactions, which can occur on all areas of the body and can include rash, reddening of the skin, flushing, itching, increased sensitivity of the skin, and swelling due to fluid in the tissue
- Discoloration, swelling or thickening of the tongue and lining of the mouth
- Loss of taste, which is temporary
- Tingling of the lips and mouth
- Reddening of the lining of the mouth
- Temporary increase in blood levels of certain salivary gland enzymes that is unlikely to cause serious symptoms or problems

**Less Likely**
- Headache
- Swelling around the eyes

**Less Likely, but Serious**
- Difficulty breathing

**Rare but serious**
- Allergic reactions, which can involve flushing, difficulty breathing, irregular heartbeat, low blood pressure, and can be life threatening; patients who have had allergic reactions to *E. coli*-derived products, such as Nutropin®, Neupogen®, Humulin®, Roferon®, Neumega®, Neulasta®, Intron-A®, and/or Betaseron® should not participate in this study.

**Other possible serious side effects**
- Swelling of the back of the throat, tongue, windpipe, or around a surgical opening into the neck to allow the passage of air were reported in some patients with head and neck cancer receiving palifermin. This swelling might have led to breathing difficulties in one patient. These patients had undergone surgery to remove their cancer before starting radiation therapy and chemotherapy. The swelling was temporary and started after the patients began radiation therapy. Also, one of these patients decided to stop palifermin as the patient was making too much saliva. These side effects may have been related to palifermin.
- Protein in the urine was reported in some patients with colorectal cancer receiving palifermin. It is not yet known if this was related to the palifermin or to the patients’ medical conditions.
- High blood pressure was reported in cancer patients undergoing a transplant and receiving palifermin. This was temporary and also was reported in the patients who received placebo.
- Development of antibodies (natural materials produced by your body to fight unfamiliar matter) was reported in 2% of patients who received palifermin and 2% of patients who received placebo. These antibodies could decrease the effect of palifermin in the body, but it did not in these patients, and the antibodies did not make these patients unhealthy.

**Risks Associated with Neck Surgery**

Patients with remaining large tumors after RT/chemotherapy will have surgery to remove the cancer, if it is found that surgery can be done to remove the remaining cancer. The study doctor and surgeon will discuss the need for surgery with you. You will need to review and sign a separate permission form from your doctor/hospital for this surgery.

The serious risks of surgery are infection, bleeding, poor healing of the skin and/or muscles in the neck, clots in the legs and/or lung, pneumonia, heart attack stroke, and/or death.

These risks may be more likely or severe for people in this study than for someone having neck surgery without having had chemotherapy and/or radiation therapy before surgery.

**Reproductive risks**: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women who are able to have children will have a pregnancy test before beginning treatment. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask your study doctor.
Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope that palifermin will be useful against painful mouth sores, there is no proof of this yet. We do know that the information from this study will help doctors learn more about palifermin as a treatment for this side effect of cancer treatment. This information could help future cancer patients.

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

Your other choices may include:

- Getting treatment or care for your painful mouth sores without being in a study
- Taking part in another study
- Getting no treatment

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

Will my medical information be kept private?

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

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

- The Radiation Therapy Oncology Group
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Amgen, Inc., the manufacturer of palifermin and placebo

What are the costs of taking part in this study?

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

Amgen, Inc. is supplying palifermin and placebo at no cost to you. However, you or your health plan may need to pay for costs of the supplies to administer the drug and for the personnel who give you the palifermin or placebo.

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

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

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

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

It is important that you tell your study doctor, __________________ [investigator's name(s)], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at __________________ [telephone number].
You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

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

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

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

A Data Safety Monitoring Board will be meeting regularly to monitor safety and other data related to this study. The Board members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

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

**Who can answer my questions about the study?**

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

For questions about your rights while taking part in this study, call the ___________________________ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at __________________ [telephone number].

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [*Only applies to sites using the CIRB.]*

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in any of these additional studies.

You can say “yes” or “no” to each of the following studies. Please mark your choice for each study.

**Quality of Life Study**

We want to know your view of how your life has been affected by cancer and its treatment. This “Quality of Life” study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities.

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer and the side effects of cancer treatment.

You will be asked to complete 3 questionnaires. You will be asked to complete the MD Anderson Symptom Inventory and the Brief Pain Inventory, at the following times: At your first visit, once a week during radiation therapy and until the sores in your mouth are healed or for 8 weeks after radiation therapy, whichever comes first. You also will be asked to complete the MD Anderson Symptom Inventory at 12 months from the start of treatment. You will be asked to complete the third questionnaire, The Xerostomia (dry mouth) Questionnaire at
about 15 weeks from the start of treatment and at 6, 12, 18, and 24 months after treatment. It takes about 5 minutes to fill out each questionnaire.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this study, the only thing you will be asked to do is fill out the three questionnaires. You may change your mind about completing the questionnaires at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the Quality of Life Study. I agree to fill out the three Quality of Life Questionnaires.

YES     NO

Where can I get more information?

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

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

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

- For NCI’s clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI’s general information about cancer, go to http://cancer.gov/cancerinfo/

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

Signature

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

Participant ______________________________

Date _____________________________________
APPENDIX II

KARNOFSKY PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints; no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some sign or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most personal needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalization is indicated, although death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospitalization necessary; active support treatment is necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>

ZUBROD PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100).</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

NEW YORK HEART ASSOCIATION CLASS DEFINITIONS

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Cardiac Symptoms</th>
<th>Limitations</th>
<th>Need for Additional Rest*</th>
<th>Physical Ability to Work**</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Full Time</td>
</tr>
<tr>
<td>II</td>
<td>Only moderate</td>
<td>Slight</td>
<td>Usually only slight or occasional</td>
<td>Usually full time</td>
</tr>
<tr>
<td>III</td>
<td>Defined, with less than ordinary activity</td>
<td>Marked</td>
<td>Usually moderate</td>
<td>Usually part time</td>
</tr>
<tr>
<td>IV</td>
<td>May be present even at rest, &amp; any activity increases discomfort</td>
<td>Extreme</td>
<td>Marked</td>
<td>Unable to work</td>
</tr>
</tbody>
</table>

*To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.
**At accustomed occupation or usual tasks.
APPENDIX III

AJCC STAGING SYSTEM, 6th Edition
HEAD & NECK

STAGING-PRIMARY TUMOR (T)

TX  Primary tumor cannot be assessed
T0  No evidence of primary tumor
Tis Carcinoma in situ

PHARYNX

Nasopharynx

T1  Tumor confined to the nasopharynx
T2  Tumor extends to soft tissues of oropharynx and or nasal fossa
   T2a without parapharyngeal extension
   T2b with parapharyngeal extension
T3  Tumor invades bony structures and/or paranasal sinuses
T4  Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space.

Oropharynx

T1  Tumor 2 cm or less in greatest dimension
T2  Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3  Tumor more than 4 cm in greatest dimension
T4a Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible.
T4b Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery.

Hypopharynx

T1  Tumor limited to one subsite of hypopharynx and 2 cm or less in greatest dimension.
T2  Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx.
T3  Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx.
T4a Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus or central compartment soft tissue.
T4b Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures.

LARYNX

Supraglottis

T1  Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2  Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx.
T3  Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex).
T4a Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus).
T4b Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.
APPENDIX III (Continued)

Glottis

T1  Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
   T1a  Tumor limited to one vocal cord
   T1b  Tumor involves both vocal cords
T2  Tumor extends to supraglottis and/or subglottis, or with impaired vocal cord mobility
T3  Tumor limited to the larynx with vocal cord fixation, and/or invades paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex).
   T4a  Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus).
   T4b  Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

Subglottis

T1  Tumor limited to the subglottis
T2  Tumor extends to vocal cord(s) with normal or impaired mobility
T3  Tumor limited to larynx with vocal cord fixation
   T4a  Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus).
   T4b  Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

REGIONAL LYMPH NODES (N) Excluding Nasopharynx

NX  Regional lymph nodes cannot be assessed
N0  No regional lymph node metastasis
N1  Metastasis in a single ipsilateral node, 3 cm or less in greatest dimension.
N2  Metastasis in a single ipsilateral node, more than 3 cm, but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none greater than 6 cm in greatest dimension, or bilateral or contralateral nodes, none more than 6 cm in greatest dimension.
   N2a  Metastasis in a single ipsilateral node more than 3 cm, but not more than 6 cm in greatest dimension.
   N2b  Metastasis in multiple ipsilateral nodes, none more than 6 cm in greatest dimension.
   N2c  Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.
N3  Metastases in a lymph node, more than 6 cm in greatest dimension.

DISTANT METASTASIS (M)

MX  Distant metastasis cannot be assessed
M0  No distant metastasis
M1  Distant metastasis
<table>
<thead>
<tr>
<th>STAGE GROUPING Excluding Nasopharynx</th>
<th>STAGE GROUPING Nasopharynx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0 Tis, N0, M0</td>
<td>Stage 0 Tis, N0, M0</td>
</tr>
<tr>
<td>Stage I T1, N0, M0</td>
<td>Stage I T1, N0, M0</td>
</tr>
<tr>
<td>Stage II T2, N0, M0</td>
<td>Stage IIA T2a, N0, M0</td>
</tr>
<tr>
<td>Stage III T3, N0, M0</td>
<td>Stage IIB T1-T2a, N1, M0</td>
</tr>
<tr>
<td></td>
<td>T2b, N0-1, M0</td>
</tr>
<tr>
<td>T1-3, N1, M0</td>
<td>T3, N0-2, M0</td>
</tr>
<tr>
<td>Stage IVA T4a, N0-2, M0</td>
<td>Stage IVA T4, N0-2, M0</td>
</tr>
<tr>
<td>Any T, N2, M0</td>
<td>Stage IVB Any T, N3, M0</td>
</tr>
<tr>
<td>Stage IVB T4b, Any N, M0</td>
<td>Stage IVC Any T, Any N, M1</td>
</tr>
<tr>
<td>Any T, N3, M0</td>
<td></td>
</tr>
<tr>
<td>Stage IVC Any T, Any N, M1</td>
<td></td>
</tr>
</tbody>
</table>
## APPENDIX IV

**WHO Toxicity Criteria: Oral Mucositis**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Soreness, erythema</td>
</tr>
<tr>
<td>2</td>
<td>Erythema, ulcers, ability to eat solid food</td>
</tr>
<tr>
<td>3</td>
<td>Ulcers, requires liquid diet</td>
</tr>
<tr>
<td>4</td>
<td>Alimentation not possible</td>
</tr>
</tbody>
</table>

The following is given as guidance in the oral mucositis assessments:

**Grade 1** may include buccal mucosal scalloping with or without erythema. No ulcers. Patient can swallow solid diet.

**Grade 2** must include ulcers with or without erythema. Patient can swallow solid diet.

**Grade 3** must include ulcers with or without (extensive) erythema. Patient is able to swallow liquid but not solid diet.

**Grade 4** to mean mucositis to the extent that alimentation is not possible. If total parental nutrition was started for reasons other than mucositis, a determination of the subject’s ability to swallow must be made using the above criteria.
APPENDIX V

MANAGEMENT OF DENTAL PROBLEMS IN IRRADIATED PATIENTS

Dental Care for Irradiated Patients
Goals for a dental care program include:
- To reduce incidence of bone necrosis.
- To reduce incidence of irradiation caries.
- To allow proper fitting of dentures following treatment.

Pre-irradiation Care and Procedures
The patients may be grouped into four groups in accordance with the problems they present prior to irradiation.

Group 1
Includes edentulous patients. They may require surgical removal of any symptomatic cysts, infected retained root tips, or alveolar hyperplasia. These patients require hygiene instruction and precautionary instruction about trauma with premature use of a prosthesis.

Group 2
Includes those with poor dental hygiene, including those patients whose teeth are beyond repair by ordinary dental procedure, those with generalized oral sepsis, those with generalized periodontal disease, and those with chronic periapical abscesses or granulomas.

Procedures performed on this group include removal of all remaining teeth prior to irradiation with primary closure and surgical preparation of the alveolar ridges to laterally support a prosthesis. There should be antibiotic coverage during the healing stage and adequate time prior to the start of radiation therapy. These patients need complete hygiene instruction and precautionary instruction about premature use of a prosthesis.

Group 3
Includes those in whom dental condition is fair, including those patients whose teeth are restored, ordinary dental procedures, periodontal pockets are less than 3 mm deep, carious lesions are not in proximity to the pulp, and no more than 20 restorable carious lesions are present. X-ray examinations show at least 1/2 of the bone still present around root surfaces. These patients require removal of any teeth that are non-salvageable in accordance with the above and restorations of the remaining teeth as required. The patients are instructed for dental prophylaxis and the patients utilize custom-made fluoride carriers.

Group 4
Includes those in whom dental hygiene is good. This includes patients who do not have severe malocclusion in whom few carious lesions are present. Carious lesions are not in close proximity to the pulp and are correctable by conventional methods. These patients require periodontal evaluation and dental prophylaxis training, restorations as needed, no extractions prior to radiation therapy, and fitting for custom carriers.

Extraction of Teeth
If extraction of teeth is necessary prior to radiation therapy, the bone must be contoured so that closure at the extraction site is possible. All loose spicules and sharp projections must be removed. The approximation of the gingival tissue must be such that the closure is neither too loose nor too tight. At least 10 days are required for adequate healing prior to initiation of therapy.

Causative Factors
The major causative factors appear to be the reduction of the amount of saliva and secondarily, reduced pH in the mouth. This occurs following high dose radiation to the major salivary glands using parallel opposed fields. The decay process usually occurs in the first year following radiation therapy. It tends to occur more quickly in teeth which have a large amount of root cementum exposed to those teeth with large amounts of plaque formation present. Doses of radiation in excess of 20 Gy to salivary tissue place the teeth at risk.

Preventive Program
The rationale behind the use of fluoride treatments is to make the tooth surfaces less susceptible to the decay process. This is accomplished by a combination of increasing fluoride concentration on the tooth surface and by the effect of fluoride on the plaque and flora that are present in the oral cavity. Adequate results are obtained by:
1) cleansing the teeth thoroughly, followed by a good home care dental prophylaxis program, 2) construction of
fluoride carriers, custom-made mouth guards, which provide local application of fluoride solution to the gingiva and tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth guard is "Sta-Guard" plastic used in conjunction with vacutrole unit produced by Jelrus Technical Products, Corp., both of which are available through local dental supply. This material is molded to the cast impression and allowed to harden. A fluoride solution prepared at the M.D. Anderson Hospital is now available from the Emerson Laboratories, Inc., Dallas, Texas 75221. It has been used to coat the plastic carrier for use in the mouth. The patients are instructed to cleanse their teeth prior to placement of the carrier. It is then worn in place for 5 minutes each day. The patients are instructed to rinse their mouths thoroughly following the use of the carrier. This will be continued for an indefinite period of time. Close follow-up is necessary.

Results
In the 5-1/2 year program at the M.D. Anderson Hospital beginning in 1966, a study of 304 patients shows that the incidence of necrosis of the jaw was reduced to approximately 21% compared to 37% prior to initiation of the study. Groups 3 and 4 patients randomized with and without fluoride treatment showed reduction in radiation carries from 67% to 34% among Group 3 patients, and from 65% to 22% among Group 4 patients.

Failure to Control Decay
Management of failure to control radiation decay includes silver fillings with continued use of fluoride treatments. If the decay process is sufficiently advanced that a filling will no longer stay in place, these teeth are merely smoothed so that there will be no sharp, irritating edges. The mere existence of such a decayed tooth is not necessarily reason for extraction, for it must be remembered that extraction could lead to complications such as bone necrosis.

Pulp exposure resulting from the decay process can usually be handled by use of antibiotics and/or root-canal therapy.

Hypersensitivity of Teeth
Occasionally, a patient will exhibit extreme sensitivity of the teeth secondary to diminished amounts of saliva. This has been shown to be reduced in incidence with the fluoride treatments. Should this problem become manifest, increasing the fluoride treatment to 10 to 15 minutes 3 times a day is recommended.

Infections
Infections occurring in patients under or after radiation therapy are best managed conservatively with good oral hygiene, irrigation and flushing procedures, and systemic antibiotics.

Bone Necrosis
The patients receiving radiation therapy to a high dose to the head and neck region have increased susceptibility to bone necrosis for several reasons including: impairment of normal metabolism, increased susceptibility to infection and severely limited repair process. Bone necrosis occurs most often after post-irradiation surgery or other traumas. Conservative management should be tried first, though in more aggressive lesions a more radical approach may ultimately be necessary.
APPENDIX VI

Cervical Lymph Node Dissection: Documentation and Processing of the Specimen

Operative report
The surgeon will document the preoperative clinical examination and radiographic findings in reference to the presence or absence of primary and nodal disease. The operative report will describe the lymph node levels dissected and removed for pathologic examination. The non-lymphatic structures removed at the time of neck dissection also should be included in the operative report.

Processing the neck dissection specimen
Upon completion of the neck dissection, the surgeon will divide the specimen into nodal levels and submit each level in a separate container. Accompanying documentation for each specimen container will include the patient case number, the side or sides of the neck dissected, and lymph node level.
APPENDIX VII (5/23/07)

Opioid Analgesic Documentation

Instructions: The patient will be seen twice each week during radiation therapy (RT) and for 8 weeks after RT or until mucositis resolves to \( \leq \) grade 1. At one of these twice-weekly visits, the site will record the opioids and doses the patient used in the previous 24 hours (see worksheet below).

Eight weeks after RT or when mucositis has resolved to \( \leq \) grade 1, patients will report the daily amount of opioids and sites will monitor this documentation for completeness in each follow-up visit.

The patient is to bring medication containers to each visit.

WORKSHEET

Regular Opioid (defined as the longest-acting opioid used)
- **Type** (e.g., MS contin, Lortab®, Duragesic®, etc.)
  - Specify type of regularly used opioid: __________
- **Route** (p.o., transdermal, transmucosal, SC, IV [includes PCA])
  - Specify route of regularly used opioid: __________

ITEM #1: Total 24 hour regular opioid dose: __________

Break-through Opioid
- **Type** (e.g., morphine, Actiq®, Dilaudid, etc.)
  - Specify type of breakthrough opioid used: __________
- **Route**: (p.o., transmucosal, SC, IV [includes PCA])
  - Specify route of breakthrough used opioid: __________

ITEM #2: Total 24 hour break-through opioid dose: __________

ITEM #3: Total number of break-through doses/24 hours: __________

Sites will submit the results of the worksheet on the Mucositis Assessment/Opioid Documentation Form (QP); see Section 12.1.
### APPENDIX VIII (8/7/07)

**RTOG 0435 Drug Shipment Schedule**

<table>
<thead>
<tr>
<th>Patient Randomized with RTOG</th>
<th>Initial e-Order Transmitted by RTOG</th>
<th>Initial e-Order Received and Approved by PMB</th>
<th>Initial Order Shipped By PMB</th>
<th>Initial Order Received at Site *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td>Monday</td>
<td>Tuesday</td>
<td>Wednesday</td>
<td>Thursday</td>
</tr>
<tr>
<td>Tuesday</td>
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<td>Thursday</td>
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<td>Monday</td>
<td>Tuesday</td>
</tr>
<tr>
<td>Friday</td>
<td>Friday</td>
<td>Monday</td>
<td>Tuesday</td>
<td>Wednesday</td>
</tr>
</tbody>
</table>

*Arrival time approximate/shipments sent by Federal Express*