

RADIATION THERAPY ONCOLOGY GROUP

RTOG 99-13

A PHASE III COMPARISON OF BIAFINE® TO DECLARED INSTITUTIONAL PREFERENCE FOR RADIATION INDUCED SKIN TOXICITY IN PATIENTS UNDERGOING RADIATION THERAPY FOR ADVANCED SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK

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SCHEMA

| | | | |
|----------|-----------------------------|----------|---|
| S | | R | |
| | <u>RT Dose</u> | | <u>Arm 1:</u> Declared Institutional Preference |
| T | 1. 50-60 Gy | A | Skin care may include no treatment, or the use of any creams standardly used by the institution. It may not include the use |
| | 2. > 60 Gy | | of Biafine®. |
| R | | N | |
| | <u>Palpable</u> | | |
| A | <u>Nodal Status</u> | D | <u>Arm 2:</u> Prophylactic Biafine® Cream |
| | 1. Negative | | Biafine® is applied 3 times daily at the initiation of radiotherapy. |
| T | 2. Positive | O | See Section 7.2.2. |
| I | | M | <u>Arm 3:</u> Interventional Biafine® Cream |
| | <u>Treatment</u> | | Biafine® is applied, as in Arm 2, only after the skin becomes |
| F | 1. Radiation & Chemotherapy | I | symptomatic. See Section 7.2.3. |
| | 2. Radiation Alone | | |
| Y | | Z | |
| | <u>Fractionation</u> | | |
| | 1. Concomitant Boost | E | |
| | 2. Standard | | |

Eligibility (See Section 3.0 for details)

- Patients with biopsy proven clinical stage III or IV, squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx for either radical radiation alone or post-operative treatment following primary surgical resection
- Radiation doses equal to or greater than 50 Gy will be given
- Zubrod Performance equal 0 and 1
- No rash, ulceration or open wound in treatment field
- No tumor involvement of the skin
- No known skin allergy or sensitivity to Biafine®
- No previous radiation therapy to the head and neck
- No inflammatory or connective tissue disorders of the skin
- No mental incompetence, including psychological or addictive disorders which would preclude completion of questionnaires
- Amifostine use is not permitted
- Patients on other RTOG studies are excluded
- Signed study-specific consent form prior to randomization

Required Sample Size: 498

Institution # _____

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ELIGIBILITY CHECK (10/9/00)

(page 1 of 2)

Case # _____

- _____(Y) 1. Biopsy-proven clinical stage III or IV squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx?
- _____(Y) 2. Is patient referred for post-op radiation therapy or radical RT alone?
- _____(Y) 3. RT doses \geq 50 Gy to the primary field?
- _____(Y) 4. Zubrod Score of 0-1?
- _____(N) 5. Does the patient have a rash, ulceration, or open wound in the treatment field?
- _____(N) 6. Is there tumor involvement of the skin?
- _____(N) 7. Does the patient have a skin allergy or sensitivity to Biafine®?
- _____(N) 8. Any prior radiotherapy to the head and neck?
- _____(N) 9. Does the patient have any inflammatory or connective tissue disorders of the skin?
- _____(Y) 10. Does the patient have any mental incompetence, including psychological or addictive disorders which would preclude completion of questionnaires?
- _____(N) 11. Do you plan to administer amifostine during RT?
- _____(N) 12. Is the patient on any other RTOG study?

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case?
- _____(Y) 2. Has the Eligibility Checklist (*above*) been completed?
- _____(Y) 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 Name
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race

Institution # _____

(continued on next page)

Case # _____

- _____ 10. Social Security Number
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code
- _____ 14. Patient's Insurance Status
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Treatment Start Date
- _____ 17. Planned RT Dose (*50-60 Gy vs. > 60 Gy*)
- _____ 18. Palpable Nodal Status (*Negative vs. Positive*)
- _____ 19. Planned Treatment (*RT and Chemo vs. RT Alone*)
- _____ 20. Fractionation (*Concomitant Boost vs. Standard*)
- _____ 21. Treatment Assignment

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 It is estimated that there will be 70,200 cases of head and neck cancer diagnosed in the USA in 1999 and 634,000 worldwide.¹ Radiation is a common treatment modality for patients with advanced stage disease.² Radiation doses range from 50 to 60 Gy post operatively up to 66 to 70 Gy when used as the sole curative treatment modality.

Patients sustain skin reactions, which range from mild to brisk erythema through to desquamation. The Radiation Therapy Oncology Group (RTOG) 90-03 was a four arm study evaluating differing fractionation regimens for patients with stages III and IV head and neck cancer. The standard arm treated similar stage patients to a total dose of 70 Gy in 2 Gy daily fractions. Acute toxicity reporting has revealed Common Toxicity Criteria (CTC) skin toxicities as outlined in the table below.

| Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|----------------|----------------|----------------|----------------|
| 35% | 48% | 7.4% | 0% |

At present there is no standard intervention for the prevention or treatment of radiation-induced skin toxicities. In the hopes of reducing skin toxicity, a variety of creams have been tested, both as prophylactic and as interventional agents. Neither natural gel³, Topical Vitamin C solution⁴, Aloe Vera Gel⁵, Bepanthen Cream (*dexpanthenol cream*)⁶, Chamomile Cream and Almond Ointment⁷ nor Topical Cortisone Cream⁸, have demonstrated positive results.

Studies conducted at the Regional Centre for Combating Cancer in Marseille⁹ have found the agent Biafine® to be effective at preventing and treating radiation-induced skin reactions. Initial reports of its effectiveness were published in 1973 and there is now over 25 years of experience with this agent for patients undergoing radiation therapy.

Biafine®'s mechanism of action includes the early recruitment of macrophages and the stimulation of granulation tissue¹⁰. A recent RTOG study, 97-13, compared the prophylactic use of Biafine® against institutional preference in the management of skin reactions from adjuvant breast irradiation. The initial results of this study have suggested no significant difference between the institutional preference creams and Biafine®. There was an increased benefit for those patients who used Biafine® and continued to smoke while receiving radiation therapy. Patients with larger breasts who were treated with larger field sizes also benefited from the use of Biafine®. Final results are pending. The study was designed to detect a 57% reduction in maximum toxicity observed during treatment (*grades 2 through 4*), with a standard alpha of 0.05 and a beta of 0.10. A total of 185 patients were randomized.

The potential benefit of Biafine® may be clinically more significant in the head and neck patient population because of the greater proportion of grade 2 and 3 toxicities experienced.

This study is designed to compare Biafine® with usual institutional practices and to compare the use of Biafine® as an interventional agent to the use of Biafine® as a prophylactic agent in reducing skin toxicity.

This study will also attempt to assess the quality of life (QOL) of patients while they are receiving radiation therapy. Skin toxicity may affect a patient's compliance with treatment and overall quality of life. Unfortunately there has been little specific research in this area. A published study from Switzerland¹¹ evaluated the effect of a hyaluronic acid (*Ialugen cream*) on skin reactions in head and neck, breast and pelvic cancers in a double blind, placebo-controlled randomized study. It concluded that the prophylactic use of the cream reduced the incidence of high-grade dermatitis leading to improved compliance and QOL.

It has been recognized that the unique aspects of head and neck cancer and its treatments are not adequately addressed with general health measures.^{12, 13,14} The Head and Neck Radiotherapy Questionnaire (HNRQ) was developed to measure radiation related acute morbidity and quality of life from the perspective of patients with head and neck cancer that are treated with radiation therapy¹⁵. It consists of 22 questions which are interviewer administered. Each question uses a 7 point Likert scale for responses. The questions relate to six domains: oral cavity (*mouth*), throat, skin, digestive function, energy and psychosocial. In a study conducted to validate the instrument an expected decline in quality of life was noted through the

course of radiation treatments which corresponded to increased skin toxicity. The importance of the inclusion of a skin domain to this study cannot be minimized, especially when results show the skin domain as one of the two domains with the highest percentage change from baseline.

The inclusion of chemotherapy in this study is due to the increasingly frequent use of chemotherapeutic agents in the treatment of late stage head and neck cancers. It is of interest to note, that the HNRQ also discriminated between treatment groups treated with and without chemotherapy.¹⁵

Assuming that a more general tool may be useful to assess overall QOL, the Spitzer Quality of Life Index (*SQLI*) will be used. The *SQLI* is a five item categorical questionnaire summed in a Likert format, with previous reliability and validity testing.^{16,17} The *SQLI* will be used as a patient self-assessment tool.

Skin assessments are essential to this study. In order to assess the effectiveness of Biafine® versus other supportive care and the most efficacious use of Biafine®, this trial will utilize both clinician assessments and patient self- assessments. Evidence exists suggesting that clinicians and patients may differ in their assessments of the severity of toxicities.¹⁸ Physician's skin assessments will be scored utilizing the revised Common Toxicity Criteria (*CTC*) version 2.0.

2.0 OBJECTIVES

2.1 General

2.1.1 To reduce radiation-induced acute skin toxicities in patients treated for head and neck cancers.

2.2 Primary

2.2.1 To determine whether Biafine®, used as a prophylactic agent is effective in reducing the proportion of head and neck cancer patients that experience grade 2 or higher radiation-induced acute skin toxicity observed during therapy as measured by the *CTC* version 2.0 and the *ONS Toxicity Scoring* when compared to standard best supportive care.

2.3 Secondary

2.3.1 To determine if prophylactic or interventional use of Biafine® is more effective based upon a reduction in maximum skin toxicity observed during treatment.

2.3.2 To compare patient's quality of life between interventions using the *SQLI* and *HNRQ Instruments* with specific focus on end of radiation and four weeks post-radiation measurements.

2.3.3 To assess toxicities of Biafine®.

3.0 PATIENT SELECTION

3.1 Eligibility

3.1.1 Patients with biopsy-proven clinical stage III and IV squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx referred for either radical radiation alone or for post-operative treatment following primary surgical resection.

3.1.2 Patients to receive minimum of 50 Gy to primary field.

3.1.3 Zubrod performance status 0 and 1.

3.1.4 No rash, ulceration or open wound in treatment field.

3.1.5 No tumor involvement of the skin.

3.1.6 No known skin allergy or sensitivity to Biafine®.

3.1.7 Patients may be receiving concurrent chemotherapy.

3.1.8 Study-specific signed informed consent prior to randomization.

3.2 Ineligibility

3.2.1 Inflammatory or connective tissue disorders of the skin.

3.2.2 Mental incompetence, including psychological or addictive disorders which would preclude completion of questionnaires.

3.2.3 Amifostine use while on this study (*pilocarpine is permitted*).

3.2.4 Patients on other RTOG studies.

3.2.5 Previous radiation therapy to the head and neck.

4.0 PRETREATMENT EVALUATION

4.1 Completion of baseline *SQLI* and *HNRQ Instruments*.

4.2 Documentation of weight and height.

4.3 Documentation of radiation field size, dose and treatment energy.

- 4.4 Documentation of bolus area and thickness.
- 4.5 Skin pigmentation will be recorded using the NCI's Office of Management and Budget (*OMB*) Directive 15 which defines racial and ethnic categories. See Appendix VII.

5.0 REGISTRATION PROCEDURES

- 5.1 Prior to registration of its first patient, each institution will submit a copy of Patient Instructions for Standard Institutional Skin Care (*Appendix V*) to RTOG Headquarters. The Product Shipping Form (*Appendix VIII*) must also be included. Both must be submitted (*together*) to FAX 215-574-0300.
- 5.2 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. 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.

6.0 RADIATION THERAPY

6.1 Physical Factors

6.1.1 Equipment

- 6.1.1.1 Linear Accelerator with 4-6MV photon energy or Cobalt⁶⁰ units will be used. Electron beam therapy may be used for the posterior aspect of the treatment fields to limit the dose to the spinal cord. Selection of the appropriate electron energy will depend on the thickness of the neck and or the depth of the disease. Photon and electron fields will be matched on the skin. Brachytherapy is not permitted in this study. Treatment distance of minimum 80 SSD/SAD is allowed. Decisions regarding the use and thickness of bolus over clinically involved nodes will be left to the discretion of the treating physician. This will be recorded per Section 4.4.
- 6.1.1.2 Immobilization devices such as plastic masks should be "cut out" where clinically possible while still preserving setup stability, to reduce skin doses.

6.2 Localization

6.2.1 Simulation

- 6.2.1.1 Simulation of the initial fields and any planned boost fields is required. Appropriate immobilization devices should be used, as per usual clinical practice. Solder wire can be used to indicate areas of nodal involvement unless CT planned. Copies of simulation films of each field and portal films will be sent to RTOG at the end of treatment only if requested. The completed treatment chart and calculations will be sent to RTOG after treatment completion only if requested by RTOG HQ.
- 6.2.1.2 Verification films will be taken on day one, and at a minimum when any adjustments are made to fields or shielding. These films will be sent to RTOG only if requested.
- 6.2.1.3 See Section 12.0 for dosimetry submission specifications.

6.3 Dose Fractionation

Standard fractionation will be once daily. Accelerated fractionation with concomitant boost as delivered in RTOG 90-03 is also acceptable.

6.3.1 Standard Fractionation

- Initial Fields
The dose to the prescription point will be 50-54 Gy delivered at 1.8-2 Gy per fraction.
- Boost Fields
The boost fields will deliver 1.8-2 Gy per fraction. Boosts of up to 20 Gy will be allowed as part of this protocol.

6.3.2 Concomitant Boost

- Initial Fields
The dose to the prescription point will be 32.4 Gy delivered at 1.8 Gy per fraction for 18 fractions, 5 days a week over 3 ½ weeks.
The initial fields continue at 1.8 Gy per fraction for 12 fractions for another 21.6 Gy to a total dose of 54 Gy.
- Boost
The initial fields are given concurrently with the boost fields for the last 2 ½ weeks, 6 hours apart.
Boost: 1.5 Gy per fraction per day given at least 6 hours after the large field treatment for 12 fractions over the last 2 ½ weeks of treatment. Total dose: 72 Gy in 42 fractions over 6 weeks.

6.3.3 Electron Fields

Electron supplements and electron boost fields when required will be delivered at 1.5-2 Gy per fraction. Total dose must not exceed dose outlined for fields in Sections 6.3.1 and 6.3.2.

6.4 Target Volume Irradiated Portals

6.4.1 Initial Treatment Fields

A minimum of 1.5 cm, or preferably a 2 cm margin, should be placed around all clinical evidence of disease or the preoperative extent of disease for postoperative patients. The treatment portals should also attempt to include areas at significant risk of occult nodal involvement.

6.4.2 Boost Fields

The boost field, necessary for all but low risk postoperative patients, should cover original disease with a 1.5 to 2 cm margin.

6.5 Dose Calculation

6.5.1 Initial Fields

The doses shall be prescribed and calculated according to the ICRU recommendations for external beam treatment using photons and electrons. Most fields will require full compensation to correct for tissue contours, or at a minimum, wedges to minimize inhomogeneity. The maximal permissible inhomogeneity is 10%. If a matching third anterior field is used to treat the lower neck and supraclavicular areas, prescribing at d_{max} or up to a 3 cm depth is preferred. The specification of the target dose is in terms of a dose to a point at or near the center of the target volume. The following portal arrangements are specified for photon beams.

6.5.1.1 For two opposed coaxial equally weighted beams: on the central ray at mid separation of beams.

6.5.1.2 For arrangement of 2 or more intersecting beams: at the intersection of the central ray of the beams.

6.5.1.3 Other or complex treatment arrangements: at the center of the target(s) area.

6.5.1.4 The electron beam energy should be chosen such that the target volume is covered by the distal 90% if the depth dose curve. This dose should be prescribed to d_{max} .

6.5.2 Boost fields

Boost fields will utilize prior compensators when available, or new wedge plans must be generated achieving similar homogeneity.

6.6 Radiation Treatment Duration

Treatment duration is expected to range from 35 calendar days for post operative radiation to a maximum of 60 days for a full therapeutic course of radiation.

6.7 Toxicity Scoring

Skin assessments are essential to this study. In order to assess the effectiveness of Biafine® versus other supportive care and the most efficacious use of Biafine®, this trial will utilize both clinician assessments and patient self- assessments. Evidence exists suggesting that clinicians and patients may differ in their assessments of the severity of toxicities.¹⁸ Physician's skin assessments will be scored utilizing the revised Common Toxicity Criteria (CTC) version 2.0 and the ONS Toxicity Scoring.

7.0 DRUG THERAPY

7.1 Product Information: Biafine®

7.1.1 Biafine® has been used in France for over 25 years. It has been indicated for the treatment of all types of wounds, from minor abrasions and sunburns to major thermal wounds, radiation dermatitis, pressure ulcers and diabetic leg ulcers. Biafine® is a pleasant fragrant non-toxic cream. It is a non-prescription product.

7.1.2 Pharmacokinetics

Biafine® enhances the first stage of the healing process by recruiting a significant number of macrophages. It stimulates the production of granulation tissue, and has an indirect action on epithelialization.

7.1.3 Supply

Supplied by Médix Pharmaceuticals Americas; available in 1.5 oz (42.0g) and 0.66 oz (18.6g) lined tubes, 12 and 24 tube cases.

7.1.4 Ingredients

Biafine® consists of purified water, liquid paraffin, glycol monostearate, stearic acid, propylene glycol, paraffin wax, squalene, avocado oil, trolamine sodium alginate, cetyl palmitate, methylparaben, sorbic acid, propyl paraben, and fragrance.

7.2 Application

7.2.1 Arm 1
Participating Institutions will declare their institutional preference (*other than Biafine®*) before entering patients on the study. This may include no active treatment.

7.2.2 Arm 2
Patients will apply the Biafine® cream to the treatment area starting the first day of radiation treatment. The cream will be applied three times a day with a minimum of four hours between applications. The cream must not be applied within four hours prior to treatment. The treated area must be regularly cleansed with warm water and a mild soap and patted dry gently with a cotton towel to prevent any buildup of cream. It will be used through the course of radiation and for two weeks after the last fraction of radiation.

7.2.3 Arm 3
Patients will begin to apply Biafine® once the skin becomes erythematous and symptomatic (*slightly itchy, tender and or dry - grade 1 reaction*). Biafine® will be applied to the treatment area as detailed in Arm 2 throughout the remainder of the treatments and for two weeks following the last fraction. The treated area must be cleansed regularly with water and a mild soap and patted dry with a cotton towel to prevent any buildup of cream.

7.3 Treatment Modifications

7.3.1 If not part of usual institutional practice, Hydrocortisone cream may be added to the treatment if greater than grade 2 toxicity is experienced. See Appendix IX.

7.3.2 Protocol treatment is to be discontinued **immediately** if an allergic response occurs, or a confluent desquamation of greater than or equal to 1.5 cm, or if grade ≥ 3 skin toxicity, or bleeding occurs.

7.4 Distribution

7.4.1 The Biafine® Shipping Form (*Appendix VII*) must be completed and returned to RTOG Headquarters prior to randomizing any patient on study. Allow adequate processing time (*7-10 days*) before calling to randomize your first patient.

7.4.2 MédiX Pharmaceuticals will supply Biafine® to the person designated on the Biafine® Shipping Form. Other products used for Arm 1 will be the responsibility of the individual institution or patient. Biafine® is to be distributed only to patients randomized to this study. The product log in Appendix VI will be used to record both the receipt of shipments from MédiX Pharmaceuticals and the dispensing of product to the patient.

7.4.3 Additional product during the accrual phase of this study may be ordered directly from MédiX Pharmaceuticals. See Section 7.4.4.

7.4.4 At the completion of this study all unused product will be returned to:

MédiX Pharmaceuticals, Americas, Inc.
12505 Starkey Road
Largo, FL 33773
(727) 507-9844
FAX (727) 507-9855

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Pilocarpine use is permitted.

9.2 The use of amifostine is not permitted as its action on the skin has not been evaluated.

10.0 PATHOLOGY

Not applicable to this study.

11.0 PATIENT ASSESSMENT:

11.1 Study Parameters

| Assessment | Pre Entry | Weekly | Post Treatment |
|--|-----------|--------|-------------------|
| Skin assessment (<i>CTC & ONS</i>) | X | X | Weeks 1, 2, 3 & 4 |
| Spitzer Quality of Life (<i>SQLI</i>) | X | X | Weeks 1, 2, 3 & 4 |

| | | | |
|-------------------------------------|---|---|-------------------|
| Patient self assess (<i>HNRQ</i>) | X | X | Weeks 1, 2, 3 & 4 |
| Weight | X | X | Weeks 1, 2, 3 & 4 |

11.2 Patient Assessments

- 11.2.1** All questionnaires and instructions will be reviewed with the patient prior to randomization.
- 11.2.2** Skin assessments will be done prior to treatment, weekly during radiation therapy, and weekly for four weeks post radiation therapy by the designated health care professional using the revised Common Toxicity Criteria (*CTC*) for Skin and the ONS Toxicity Scoring Criteria. See Appendix IX and Appendix X.
- 11.2.3** Patients will complete the HNRQ and the SQLI forms prior to treatment, weekly during treatment, and weekly for four weeks post radiation. The end of treatment and 4-week post treatment evaluation are the primary endpoints.
- 11.2.4** Centers should attempt to perform all weekly assessments on a single scheduled day of the week.

12.0 DATA COLLECTION

(*RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153*)

12.1 Summary of Data Submission

| <u>Item</u> | <u>Due</u> |
|---|---|
| Demographic Form (A5) | Within 2 weeks of study entry |
| Initial Evaluation Form (I1) | |
| Pretreatment Professional Skin Assessment (F2)* | |
| Pretreatment Quality of Life (PQ)* | |
| Pre-tx H&N Radiotherapy Questionnaire (QL)* | |
| Radiotherapy Form (T1) | At end of RT |
| Product Log (PL) | At the end of Biafine® Treatment |
| H&N Radiotherapy Questionnaires (QF) | Weekly during RT (<i>submit at end of RT</i>); for weeks 1, 2, 3, and 4 post treatment (<i>submit at week 4</i>). |
| Post treatment Quality of Life Forms (PF) | |
| Skin Assessment Form (F3) | |
| Initial Follow-up Form (F1) | At 4 weeks post RT |

*Skin Assessment (*CTC & ONS*); Spitzer Quality of Life (*SQLI*); Patient Self Assessment (*HNRQ*)

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

- 13.1.1** Compare incidence of skin toxicities between Biafine® and Best Supportive Care (*BSC*).
- 13.1.2** Compare the response of skin toxicities among the three arms.
- 13.1.3** Compare the quality of life among the three arms.
- 13.1.4** Tabulate frequency of toxicities to Biafine®.

13.2 Sample Size

13.2.1 *Incidence of Skin Toxicities*

The incidence of grade 2 or worse radiation-induced skin toxicity during therapy is expected to be 56% in the BSC arm. The incidence of skin toxicity on the interventional Biafine® arm is expected equal to or higher than 56%. The study is designed to detect a 33% reduction in grade 2 or higher skin toxicity due to prophylactic use of Biafine®. Using a two-sided significance level (*0.05*) and power of 90% then 151 patients per arm will be required.¹⁹ Assuming a 10% ineligibility/inevaluability rate **then a total of 166 patients per arm will be required.**

13.2.2 *Response of Skin Toxicities*

A response will be considered a return to grade 0. It is expected that 25% of the patients on the BSC arm will have grade 0 skin toxicity at 4 weeks post radiation therapy. If the best Biafine® arm increases the response to 50% then 124 patients per arm will be required to maintain the statistical parameters presented in Section 13.2.1.

13.2.3 *Quality of Life*

There will be two quality of life instruments used in this study: the Head and Neck Radiotherapy Questionnaire (*HNRQ*) and the Spitzer Quality of Life Index (*SQLI*). According to Browman et al. a 20% change in HNRQ scores is a clinically important change. In RTOG 97-13, skin toxicity in breast cancer patients, a grade 2 or worse skin toxicity was correlated with worse quality of life by the SQLI.²⁰ A 0.5 point difference in SQLI scores was clinically meaningful. Assuming a common standard deviation of 18 in HNRQ across arms, measuring HNRQ at the end of radiation therapy and four weeks post, then 76 patients per arm at each of these time points will be required to detect a clinically meaningful difference in HNRQ. A common standard deviation of 0.54 is assumed for SQLI. Ninety patients per arm with SQLI scores at the end of RT and four weeks post will be required to detect a clinically meaningful difference. These sample size estimates will preserve the statistical parameters presented in Section 13.2.1

13.3 Patient Accrual

Patient accrual is expected to be robust. Accrual is expected to be 30 patients per month and should be completed in 17 months. If the accrual is less than 10 patients per month, this study will be re-evaluated for feasibility.

13.4 Randomization Scheme

The treatment allocation will be done using a randomized permuted block within strata. The arms will be stratified by nodal status, chemotherapy, radiation dose and fractionation. There will be check on institutional balance by treatment arm.

13.5 Analysis Plans

13.5.1 Interim Analyses of Accrual and Toxicity Data

Interim reports with statistical analyses will be prepared every six months until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about:

- i) the patient accrual rate with projected completion date for the accrual phase
- ii) the distribution of patients with respect to pretreatment characteristics
- iii) the frequency and severity of the toxicities for treatment arms combined
- iv) compliance with the submission of the HNRQ and SQLI.

13.5.2 Interim Analyses of Study Endpoints

It is expected that accrual will be too rapid to perform any outcome analyses during the accrual phase.

13.5.3 Analysis and Reporting of Initial Treatment Results

The major analysis will be undertaken when all patients have completed the four-week follow-up. The usual components of this analysis are:

- i) tabulation of all cases entered and any excluded from the analysis with the reasons for such exclusions;
- ii) reporting of institutional accrual;
- iii) distribution of pretreatment characteristics by treatment arm;
- iv) observed results with respect to the study endpoints:
 1. Skin toxicities will be assessed weekly by the Common Toxicity Criteria (*CTC*). The worst toxicity observed over the study will be compared across arms using a Kruskal-Wallis Test.
 2. The CTC will be used to assess toxicity weekly during the treatment and four-week post radiation follow-up period. Response to intervention will be considered as the percentage of patients achieving a grade 0 by week 4 post RT. The three arms will be compared by the Chi-square test.
 3. Quality of Life (*QOL*) will be measured weekly. Change scores from baseline measurement will be computed. The end of RT and four-week post RT QOL scores will be the primary endpoints. Treatment comparisons across will be made using the analysis of variance.
 4. Weekly skin toxicity and QOL assessments will be correlated to determine the impact of toxicity on QOL.
 5. The pattern and duration of toxicity and QOL will be examined using an area under the curve analysis. These averages will be compared using a Z-test.
 6. Since smoking status (*current vs. non smoker*) at the time of study entry provided a possible interaction with intervention effectiveness in RTOG 97-13 (*a prior breast skin toxicity study*), then the treatment comparisons will be made with smoking status.

13.6 Estimated Minority and Gender Accrual

In conformance with the National Institute of Health (*NIH*) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we make the following observations. There has been no information published to date that indicates that women have distinct skin reactions from men when treated with head and neck irradiation. A subset analysis will be performed to determine if such an

interaction exists. The skin toxicity scale to be used in this study does not differentiate between skin pigmentation. If the projected accrual rates are observed there will be an opportunity to determine if different levels of skin pigmentation interact with observed skin toxicity.

| | American Indian or Alaskan Native | Asian | Black | Hispanic or Latino | White | Other or Unknown | Total |
|--------|--|--------------|--------------|---------------------------|--------------|-------------------------|--------------|
| Female | 1 | 1 | 30 | 10 | 158 | 0 | 200 |
| Male | 1 | 1 | 45 | 15 | 236 | 0 | 298 |
| Total | 2 | 2 | 75 | 25 | 394 | 0 | 498 |

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APPENDIX I

RTOG 99-13

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

A PHASE III COMPARISON OF BIAFINE® TO DECLARED INSTITUTIONAL PREFERENCE FOR RADIATION INDUCED SKIN TOXICITY IN PATIENTS UNDERGOING RADIATION THERAPY FOR ADVANCED SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. You are being asked to take part in this study because you have advanced cancer of the head and neck region.

Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, *Taking Part in Clinical Trials: What Cancer Patients Need To Know*, is available from your doctor.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to compare the effects (good and bad) of the skin care cream, Biafine®, with the treatment(s) institutions normally use to prevent skin reactions caused by radiation therapy of the head and neck region. The study will also compare the effectiveness of Biafine® when it is used at the beginning of radiation treatment through the course of radiation treatment, and for two weeks after radiation treatment to when use is started only once the skin becomes red, tender, dry or slightly itchy. Use is continued for the remainder of treatment and for two weeks after treatment. The study will also try to determine the quality of life of patients in the different groups.

This research is being done because we do not know which of these treatments is better.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 500 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

You will be “randomized” into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. A computer decides which group you are put into. Neither you nor the researcher will choose what group you will be in. You will have an equal chance of being placed in one of the three groups. Patients will be randomized to one of the following groups:

Group 1: Standard Skin Care:

Radiation therapy treatments will be given once a day, five days per week for up to 7 weeks. You will use the skin care that is usually given by the doctors at your radiation treatment center. This may include skin cream or no treatment at all depending on how much effect the radiation has on your skin. Everyone at your institution assigned to this treatment will use the same kind of skin cream. It **will not** include the use of Biafine®.

Group 2: Prophylactic (preventive) Biafine® Cream and Radiation Therapy:

Radiation therapy treatments will be given once a day, five days per week for up to 7 weeks. You will apply Biafine® cream 3 times a day to the skin in the area where the radiation is being given, every day (*7 days a week*) starting the first day until the last day of radiation and for two weeks after the end of radiation. The treated area must be cleaned with warm water and a mild soap and patted dry gently with a cotton towel to keep the cream from building up on the skin. You will gently rub the Biafine® cream into the skin no less than 4 hours before your treatment and no less than 4 hours between applications.

Group 3: Interventional (healing) Biafine® Cream:

Once a day, five days per week for up to 7 weeks. Radiation therapy treatments will be given at your institution. You will apply Biafine® cream 3 times a day (*7 days a week*) only if the skin starts to turn red, tender, dry or slightly itchy. You will use Biafine® every day exactly as described in Treatment 2 from then on until the last day of radiation and for two weeks after the end of radiation.

- Procedures that are part of regular cancer care and may be done even if you do not join the study.

Radiation Therapy: daily treatment five days a week for up to 42 treatments (8+ weeks).

Risks Associated with Radiation Therapy:

Very Likely

Sore throat

Temporary hair loss

Tanning or redness of skin in treatment area

Loss of teeth if strict dental care is not followed.

Dryness of the mouth or altered taste

Less Likely, But Serious

Permanent hair loss in the treatment area

Decrease in function of thyroid gland

Temporary pain or scarring around the nerves in the shoulder which can cause numbness and/or weakness

Procedure

Skin Assessments

Schedule

Pretreatment, weekly during radiation, and weekly for four weeks after radiation. These will be performed by an investigator at your institution.

- Standard procedures being done because you are in this study.

Quality of Life Questionnaire

Pretreatment, weekly during radiation, and weekly for four weeks after radiation. This will be completed by you.

Quality of Life Self Assessment

Pretreatment, weekly during radiation, and weekly for four weeks after radiation. You will complete this while you are at your treatment facility.

HOW LONG WILL I BE IN THE STUDY?

You will be in the study for about 11 weeks.

The researcher may decide to take you off this study if it is in your medical best interest, Biafine® supply is insufficient, your condition worsens, or new information becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of funding or participation.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs may be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the treatment is stopped, but in some cases side effects can be serious or long lasting or permanent.

Risks Associated with Biafine®

Very Likely

None

Less Likely

Allergic skin reactions causing itching and/or rash

SPECIAL NOTE:

If Biafine® is used incorrectly (applied less than four hours before the daily radiation treatment), it can cause or worsen a skin reaction. It is important that the area being treated be washed gently with a mild soap and patted dry with a cotton towel once a day to prevent a buildup of Biafine® on the skin. A buildup of Biafine® will increase the chances of or worsen a skin reaction.

Risks Associated with (Declared Institution Preference)

Institutions must complete this section for their Declared Institutional Preference prior to submitting this protocol and the sample study-specific consent form to their IRBs.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients undergoing radiation therapy for advanced head and neck cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) the standard care provided by your institution to reduce radiation-induced skin reactions; and (2) waiting to see if a skin reaction develops.

Another option may be to get the Biafine® treatment described in this study at your center or another center even if you do not take part in the study.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

If you are assigned to Groups 2 or 3, Médix Pharmaceuticals Americas, Inc. will supply the Biafine® cream free of charge. Unless your physician provides you with another product, the cost of anything besides Biafine® will be your responsibility. Taking part in this study may lead to other added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

If, during the study, Médix Pharmaceuticals ceases to supply the drug, you may have to pay for the amount of drug needed to complete the study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

For information about your disease and research-related injury, you may contact:

_____ Name

_____ Telephone Number

For information about this study, you may contact:

Name

Telephone Number

For information about your rights as a research subject, you may contact:

(OPRR suggests that this person not be the investigator or anyone else directly involved with the research)

Name

Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Visit the NCI's Web sites for comprehensive clinical trials comprehensive clinical trials information <http://cancertrials.nci.nih.gov> or for accurate cancer information including PDQ <http://cancernet.nci.nih.gov>.

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (*full study plan*).

Patient Signature (*or legal Representative*)

Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

- 0 Fully active, able to carry on all predisease activities without restriction
(*Karnofsky 90-100*).
- 1 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*).
- 2 Ambulatory and capable of all self-care but unable to carry out any work
activities. Up and about more than 50% of waking hours (*Karnofsky 50-60*).
- 3 Capable of only limited self-care, confined to bed or chair 50% or more of waking
hours (*Karnofsky 30-40*).
- 4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or
chair (*Karnofsky 10-20*).

APPENDIX III

AJCC STAGING HEAD & NECK, 5th Edition

STAGING-PRIMARY TUMOR (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T_{is} Carcinoma *in situ*

ORAL CAVITY

- Buccal mucosa
- Lower alveolar ridge
- Upper alveolar ridge
- Retromolar gingiva (*Retromolar trigone*)
- Floor of mouth
- Hard palate
- Anterior two-thirds of the oral tongue

- 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
- T4 Tumor invades adjacent structures (*e.g. through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin. Superficial erosion of bone/tooth socket by gingival primary is not sufficient to classify as T4*).

PHARYNX

Nasopharynx

- Postero-superior walls
- Lateral walls
- Inferior (*anterior*) wall, consists of the superior surface of the soft palate

- 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, or orbit.

APPENDIX III

AJCC STAGING **HEAD & NECK, 5th Edition (cont'd)**

Oropharynx

Faucial arch including soft palate, uvula and anterior tonsillar pillar
Glossotonsillar sulci and pharyngeal tonsils
Base of tongue
Pharyngeal wall including lateral and posterior walls and posterior tonsillar pillar

- 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
- T4 Tumor invades adjacent structures (*e.g. pterygoid muscle[s], mandible, hard palate, deep muscle of tongue, larynx*)

Hypopharynx

Pyramidal fossae
Postcricoid region
Lateral and posterior hypopharyngeal walls

- 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.
- T4 Tumor invades adjacent structures (*e.g. thyroid/cricoid cartilage, carotid artery, soft tissues of neck, prevertebral fascia/muscles, thyroid and/or esophagus*).

LARYNX

Supraglottis

Suprahyoid epiglottis
Infrahyoid epiglottis
Aryepiglottic folds (*laryngeal aspect*)
Ventricular bands (*false cords*)
Arytenoids

- 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.
- T4 Tumor extends through the thyroid cartilage, and/or extends into soft tissues of the neck, thyroid and/or esophagus.

APPENDIX III

AJCC STAGING
HEAD & NECK, 5th Edition (cont'd)

Glottis

True vocal cords including anterior and posterior commissures

- T1 Tumor limited to the vocal cord(s) (*may involve anterior or posterior commissures*) with normal mobility
 - T1a Tumor limited to one vocal cord
 - T1b Tumor involves both vocal cords
- T2 Tumor extends to supraglottis and/or subglottis and/or with impaired vocal cord mobility
- T3 Tumor limited to the larynx with vocal cord fixation
- T4 Tumor invades through thyroid cartilage and/or extends to other tissues beyond the larynx (*e.g., trachea, soft tissues of neck including thyroid, pharynx*)

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
- T4 Tumor invades through cricoid or thyroid cartilage and/or extends to other tissues beyond the larynx (*e.g. trachea, or soft tissues of the neck including thyroid, esophagus*)

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 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 none more than 6 cm in greatest dimension.

REGIONAL LYMPH NODES (N) Nasopharynx Only

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa
- N2 Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa
- N3 Metastasis in a lymph node(s)
 - N3a greater than 6 cm in dimension
 - N3b in the supraclavicular fossa

APPENDIX III

AJCC STAGING

HEAD & NECK, 5th Edition (cont'd)

DISTANT METASTASIS (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

STAGE GROUPING Excluding Nasopharynx STAGE GROUPING Nasopharynx

| | | | |
|-----------|-------------------------------|-----------|---------------------------------|
| Stage 0 | Tis, N0, M0 | Stage 0 | Tis, N0, M0 |
| Stage I | T1, N0, M0 | Stage I | T1, N0, M0 |
| Stage II | T2, N0, M0 | Stage IIA | T2a, N0, M0 |
| Stage III | T3, N0, M0 T1-3, N1, M0 | Stage IIB | T1-T2a, N1, M0 T2b, N0-1, M0 |
| Stage IVA | T4, N0-1, M0 Any T, N2, M0 | Stage III | T1-T2b, N2, M0 T3, N0-2, M0 |
| Stage IVB | Any T, N3, M0 | Stage IVA | T4, N0-2, M0 |
| Stage IVC | Any T, Any N, M1 | Stage IVB | Any T, N3, M0 |
| | | Stage IVC | Any T, Any N, M1 |

APPENDIX IV

PATIENT INSTRUCTIONS FOR SKIN CARE STUDY

BIAFINE® APPLICATION

BIAFINE®

Radiodermatitis emulsion, for topical application only

A. Product Description

Biafine® is a water-based wound dressing which helps in the healing process of skin wounds. When applied properly to a wound, Biafine® provides an optimum moist environment for the healing process, assists in the cleansing of the wound, and helps prevent infection.

B. Indication for Use:

Biafine® is indicated for use in:

- Minor scrapes
- Superficial wounds
- Full thickness wounds, pressure sores, and skin ulcers including lower leg ulcers
- 1st and 2nd degree burns, including sunburns
- Radiation therapy-induced skin reactions
- Skin donor and graft sites

C. Ingredients:

Biafine® consists of purified water, liquid paraffin, glycol monostearate, stearic acid, propylene glycol, paraffin wax, squalene, avocado oil, trolamine sodium alginate, cetyl palmitate, methylparaben, sorbic acid, propyl paraben, fragrance.

D. Contraindications:

A known allergy to one of the ingredients in Biafine®.

E. Warnings:

In radiation therapy-induced skin reactions and/or in conjunction with ongoing radiation therapy do not apply Biafine® to the radiation treatment area less than 4 hours prior to a radiation treatment. Biafine® should be applied immediately following radiation sessions. It is important that the area being treated be washed before treatment everyday to prevent a build up of Biafine®. A buildup of Biafine® will increase the chances of or worsen a skin reaction (*See Instructions for Use*).

F. Instructions for Use for Radiation Therapy Patients:

Apply a generous amount of Biafine® to the treatment area, gently rubbing in the Biafine® until it is completely absorbed. A white waxy residue may remain. Apply Biafine® three times each day (*seven days a week*) but not within four hours before radiation therapy. There should be a minimum of four hours between applications.

APPENDIX IV (continued)

PATIENT INSTRUCTIONS FOR SKIN CARE STUDY

BIAFINE® APPLICATION

G. Precautions and Observations:

1. For the treatment of any skin wound, consult a physician.
2. Biafine® is non-toxic, however, it is for external use only and should not be ingested or taken internally.
3. Biafine® does not contain a sun screen and should not be used prior to or during extensive exposure to the sun.
4. Do not use Biafine® in a bleeding wound until the bleeding has stopped.
5. The use of Biafine® on skin rashes due to allergies has not been studied sufficiently and is therefore not recommended.
6. Following the application of Biafine®, a temporary tingling sensation may occur (*for 10 - 15 minutes*) which is due to the stimulation of circulation at the wound site.
7. If signs of infection are present, appropriate antibiotic treatment should be started. Use of Biafine® can be continued during the antibiotic therapy
8. Keep this and all medications out of the reach of children.

H. How Supplied:

Biafine® Radiodermatitis Emulsion for local application is available in 1.5 oz. (*42.0g*) and 0.66 oz (*18.6g*) lined tubes.

I. Manufactured For:

Médix Pharmaceuticals, Americas, Inc.
12505 Starkey Road
Largo, FL 33773

J. Manufactured By:

Laboratoire Medix, S.A.
18, rue Saint-Mathieu 78550
Houdan, France

APPENDIX V

(Submit to RTOG with the Biafine® Shipping Form in Appendix VIII)

PATIENT INSTRUCTIONS FOR STANDARD INSTITUTIONAL SKIN CARE

RTOG 99-13

A PHASE III COMPARISON OF BIAFINE® TO DECLARED INSTITUTIONAL PREFERENCE FOR RADIATION INDUCED SKIN TOXICITY IN PATIENTS UNDERGOING RADIATION THERAPY FOR ADVANCED SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK

Product Name: _____ *(institution to fill in)* **RTOG Institution Number** _____

Product Ingredients: *(institution to fill in)*

Contraindications: *(institution to fill in)*

Instructions for Use: *(institution to fill in)*

To the Patient:

Your doctor will provide you with instructions prior to study participation.

APPENDIX VI

PRODUCT LOG

RTOG 99-13

A PHASE III COMPARISON OF BIAFINE® TO DECLARED INSTITUTIONAL PREFERENCE FOR RADIATION INDUCED SKIN TOXICITY IN PATIENTS UNDERGOING RADIATION THERAPY FOR ADVANCED SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK

Product: _____

Unit Size: _____

| Date | <u>Case#</u> | Patient's Initials | Quantity Dispensed or Received | Balance Forward | Lot # | Expiration Date | Recorder's Initials |
|-------------|---------------------|---------------------------|---------------------------------------|------------------------|--------------|------------------------|----------------------------|
| 1. | | | | | | | |
| 2. | | | | | | | |
| 3. | | | | | | | |
| 4. | | | | | | | |
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| 19. | | | | | | | |
| 20. | | | | | | | |

APPENDIX VII

Skin Pigmentation – OMB Directive 15

NCI's Office of Management and Budget (OMB) Directive 15 defines racial and ethnic categories as listed below:

American Indian or Alaskan Native: A person having origins in any of the original peoples of North America, and who maintains cultural identification through tribal affiliation or community recognition.

Asian: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian Subcontinent. This area includes, for example, China, India, Japan, and Korea.

Black or African American: A person having origins in any of the black racial groups of Africa.

Hispanic or Latino: A person of Mexican, Puerto Rican, Cuban, Central or South American or other Spanish culture or origin, regardless of race.

Native Hawaiian or Other Pacific Islander: A person having origins in any of the original peoples of Hawaii or the Pacific Islands including Hawaii, the Philippine Islands, and Samoa.

White: A person having origins in any of the original peoples of Europe, Northern Africa, or the Middle East.

Other: Includes any not covered by the above.

Unknown: Includes "prefers not to answer"

NIH has chosen to use these definitions for all reporting, including all competing and non-competing grant applications and progress reports, because they allow comparisons to many National data bases, especially National Health data bases.

APPENDIX VIII
BIAFINE® SHIPPING FORM
RTOG 99-13

Biafine® will be mailed only to institutions who have identified a single individual for receipt of shipment. This form must be completed and returned to RTOG Headquarters prior to registering any patient on study. The Patient Instructions for Standard Institutional Skin Care (*see Appendix V*) must be attached to this form. Allow adequate processing time (*7-10 days*) before calling to register your first patient.

SHIP TO:

Name: _____

Address: _____

Telephone: _____

Fax#: _____

RTOG Institution#: _____

Institution Name: _____

IRB Approval Date: _____

Investigator (*PI*) Signature _____ Date: _____

Investigator Name (*Print*) _____

Investigator NCI # _____

Institutional Preference

Institutional declared preference for Arm One will be:

(*circle one*)

1. a) Standard treatment involves no active agents.
- b) Standard treatment involves the following agent: _____

(*circle one*)

2. a) Agent is started at beginning of radiation treatment
- b) Agent is used when the patient becomes symptomatic
- c) Not applicable, no other agent will be used

Send Completed Form to:

RTOG Headquarters

1101 Market Street

Philadelphia, PA 19107

ATTN: ELAINE PAKURIS

FAX# 215-574-0300

RTOG Headquarters Approval _____

Date: _____

| Adverse Event | Grade | | | | |
|--|--------|--|--|--|--|
| | 0 | 1 | 2 | 3 | 4 |
| Fever (in the absence of neutropenia, where neutropenia is defined as AGC <1.0 x 10 ⁹ /L) Also consider Allergic reaction/hypersensitivity. Note: The temperature measurements listed above are oral or tympanic. | none | 38.0 - 39.0°C (100.4 - 102.2°F) | 39.1 - 40.0°C (102.3 - 104.0°F) | >40.0°C (>104.0°F) for <24hrs | >40.0°C (>104.0°F) for >24hrs |
| Hot flashes/flushes are graded in the ENDOCRINE category. | | | | | |
| Rigors, chills | none | mild, requiring symptomatic treatment (e.g., blanket) or non-narcotic medication | severe and/or prolonged, requiring narcotic medication | not responsive to narcotic medication | - |
| Sweating (diaphoresis) | normal | mild and occasional | frequent or drenching | - | - |
| Weight gain Also consider Ascites, Edema, Pleural effusion (non-malignant). | <5% | 5 - <10% | 10 - <20% | ≥20% | - |
| Weight gain associated with Veno-Occlusive Disease (VOD) for BMT studies, if specified in the protocol. Also consider Ascites, Edema, Pleural effusion (non-malignant). | <2% | ≥2 - <5% | ≥5 - <10% | ≥10% or as ascites | ≥10% or fluid retention resulting in pulmonary failure |
| Weight loss Also consider Vomiting, Dehydration, Diarrhea. | <5% | 5 - <10% | 10 - <20% | ≥20% | - |
| Constitutional Symptoms - Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| DERMATOLOGY/SKIN | | | | | |
| Alopecia | normal | mild hair loss | pronounced hair loss | - | - |
| Bruising (in absence of grade 3 or 4 thrombocytopenia) Note: Bruising resulting from grade 3 or 4 thrombocytopenia is graded as Petechiae/purpura and Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia in the HEMORRHAGE category, <u>not</u> in the DERMATOLOGY/SKIN category. | none | localized or in dependent area | generalized | - | - |
| Dry skin | normal | controlled with emollients | not controlled with emollients | - | - |
| Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) | absent | - | scattered, but not generalized eruption | severe or requiring IV fluids (e.g., generalized rash or painful stomatitis) | life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support) |
| Flushing | absent | present | - | - | - |
| Hand-foot skin reaction | none | skin changes or dermatitis without pain (e.g., erythema, peeling) | skin changes with pain, not interfering with function | skin changes with pain, interfering with function | - |
| Injection site reaction | none | pain or itching or erythema | pain or swelling, with inflammation or phlebitis | ulceration or necrosis that is severe or prolonged, or requiring surgery | - |

| Adverse Event | Grade | | | | |
|---|--------|---|--|---|--|
| | 0 | 1 | 2 | 3 | 4 |
| Nail changes | normal | discoloration or ridging (koilonychia) or pitting | partial or complete loss of nail(s) or pain in nailbeds | - | - |
| Petechiae is graded in the HEMORRHAGE category. | | | | | |
| Photosensitivity | none | painless erythema | painful erythema | erythema with desquamation | - |
| Pigmentation changes (e.g., vitiligo) | none | localized pigmentation changes | generalized pigmentation changes | - | - |
| Pruritus | none | mild or localized, relieved spontaneously or by local measures | intense or widespread, relieved spontaneously or by systemic measures | intense or widespread and poorly controlled despite treatment | - |
| Purpura is graded in the HEMORRHAGE category. | | | | | |
| Radiation dermatitis | none | faint erythema or dry desquamation | moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema | confluent moist desquamation ≥ 1.5 cm diameter and not confined to skin folds; pitting edema | skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion |
| Note: Pain associated with radiation dermatitis is graded separately in the PAIN category as Pain due to radiation. | | | | | |
| Radiation recall reaction (reaction following chemotherapy in the absence of additional radiation therapy that occurs in a previous radiation port) | none | faint erythema or dry desquamation | moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema | confluent moist desquamation ≥ 1.5 cm diameter and not confined to skin folds; pitting edema | skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion |
| Rash/desquamation | none | macular or papular eruption or erythema without associated symptoms | macular or papular eruption or erythema with pruritus or other associated symptoms covering $<50\%$ of body surface or localized desquamation or other lesions covering $<50\%$ of body surface area | symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering $\geq 50\%$ of body surface area | generalized exfoliative dermatitis or ulcerative dermatitis |
| Also consider Allergic reaction/hypersensitivity. | | | | | |
| Note: Stevens-Johnson syndrome is graded separately as Erythema multiforme in the DERMATOLOGY/SKIN category. | | | | | |
| Rash/dermatitis associated with high-dose chemotherapy or BMT studies. | none | faint erythema or dry desquamation | moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema | confluent moist desquamation ≥ 1.5 cm diameter and not confined to skin folds; pitting edema | skin necrosis or ulceration of full thickness dermis; may include spontaneous bleeding not induced by minor trauma or abrasion |
| Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol. | None | macular or papular eruption or erythema covering $<25\%$ of body surface area without associated symptoms | macular or papular eruption or erythema with pruritus or other associated symptoms covering $\geq 25 - <50\%$ of body surface or localized desquamation or other lesions covering $\geq 25 - <50\%$ of body surface area | symptomatic generalized erythroderma or symptomatic macular, papular or vesicular eruption, with bullous formation, or desquamation covering $\geq 50\%$ of body surface area | generalized exfoliative dermatitis or ulcerative dermatitis or bullous formation |
| Also consider Allergic reaction/hypersensitivity. | | | | | |
| Note: Stevens-Johnson syndrome is graded separately as Erythema multiforme in the DERMATOLOGY/SKIN category. | | | | | |

| Adverse Event | Grade | | | | |
|---|--------|--|--|--|---|
| | 0 | 1 | 2 | 3 | 4 |
| Urticaria (hives, welts, wheals) | none | requiring no medication | requiring PO or topical treatment or IV medication or steroids for <24 hours | requiring IV medication or steroids for ≥24 hours | - |
| Wound-infectious | none | cellulitis | superficial infection | infection requiring IV antibiotics | necrotizing fasciitis |
| Wound-non-infectious | none | incisional separation | incisional hernia | fascial disruption without evisceration | fascial disruption with evisceration |
| Dermatology/Skin - Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| ENDOCRINE | | | | | |
| Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae) Also consider Hyperglycemia, Hypokalemia. | absent | - | present | - | - |
| Feminization of male | absent | - | - | present | - |
| Gynecomastia | none | mild | pronounced or painful | pronounced or painful and requiring surgery | - |
| Hot flashes/flushes | none | mild or no more than 1 per day | moderate and greater than 1 per day | - | - |
| Hypothyroidism | absent | asymptomatic, TSH elevated, no therapy given | symptomatic or thyroid replacement treatment given | patient hospitalized for manifestations of hypothyroidism | myxedema coma |
| Masculinization of female | absent | - | - | present | - |
| SIADH (syndrome of inappropriate antidiuretic hormone) | absent | - | - | present | - |
| Endocrine - Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| GASTROINTESTINAL | | | | | |
| Amylase is graded in the METABOLIC/LABORATORY category. | | | | | |
| Anorexia | none | loss of appetite | oral intake significantly decreased | requiring IV fluids | requiring feeding tube or parenteral nutrition |
| Ascites (non-malignant) | none | asymptomatic | symptomatic, requiring diuretics | symptomatic, requiring therapeutic paracentesis | life-threatening physiologic consequences |
| Colitis | none | - | abdominal pain with mucus and/or blood in stool | abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation | perforation or requiring surgery or toxic megacolon |
| Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Melena/GI bleeding, Rectal bleeding/hematochezia, Hypotension. | | | | | |
| Constipation | none | requiring stool softener or dietary modification | requiring laxatives | obstipation requiring manual evacuation or enema | obstruction or toxic megacolon |

APPENDIX X

RTOG ACUTE RADIATION MORBIDITY CRITERIA

ONS SKIN ASSESSMENT SCORING CRITERIA

COMFORT ALTERATION

Fatigue:

- 0- None, able to carry on daily routine
- 1- Able to carry on daily routine with rest periods and earlier bedtime
- 2- Must curtail daily activities even with rest periods and earlier bedtime
- 3- Unable to maintain daily activities: able to perform only short episodes of activity
- 4- Confined to bed

Pain:

- 0- None
- 1- Minimal pain requiring no medication
- 2- Minimal pain controlled with over-the counter medication
- 3- Pain controlled with prescription medication and /or oral narcotics
- 4- Pain controlled with IV narcotics
- 5- Pain uncontrolled with IV narcotics

Pain Rating:

Patients subjective rating of degree of pain ranging from 0 (*no pain*) up to 10 (*severe pain*)

MUCOUS MEMBRANE ALTERATION

Esophagitis/Pharyngitis:

- 0- None
- 1- Dry sensation in throat and/or mild discomfort
- 2- Moderate pain requiring medication and soft diet
- 3- Severe pain requiring oral narcotics: unable to swallow soft foods
- 4- Severe pain requiring IV narcotics: chokes when tries to swallow water

SKIN INTEGRITY

Drainage:

- 0- None
- 1- Small to moderate amount of clear serous fluid: no odor noted
- 2- Moderate to large amount of serous fluid: no odor present
- 3- Moderate to large amount of serosanguineous fluid.
- 4- Moderate to large amount of seropurulent fluid: foul odor present

Integrity:

- 0- No changes noted
- 1- Faint or dull erythema: follicular reaction: itching
- 2- Bright erythema: tender to touch
- 3- Dry desquamation with or without erythema
- 4- Small to moderate amount of wet desquamation
- 5- Confluent moist desquamation: edema
- 6- Ulceration, hemorrhage or necrosis

VENTILATION ALTERATION

Cough:

- 0- None
- 1- Occasional non-productive (*dry*) cough
- 2- Persistent non-productive (*dry*) cough
- 3- Persistent dry or productive cough requiring over the counter antitussive agents
- 4- Persistent cough requiring narcotic antitussive agents
- 5- Severe dry or productive cough unresponsive to narcotic antitussive agents
- 6- Severe respiratory insufficiency requiring continuous oxygen therapy

Shortness of Breath:

- 0- None
- 1- Mild dyspnea with exertion
- 2- Dyspnea with minimal effort but not at rest
- 3- Dyspnea at rest: intermittent oxygen and/or steroid required
- 4- Severe respiratory insufficiency requiring continuous oxygen therapy