CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20221/S012

MEDICAL REVIEW(S)

MEDICAL OFFICER'S REVIEW OF AN NDA SUPPLEMENT

NDA # 20-221
Sponsor: U.S. Bioscience, Inc.

Submission Date: December 24, 1998
Review completed: May 21, 1999 (Draft 1)

GENERAL DRUG INFORMATION

Drug name Ethyol
Generic name: Amifostine
Pharmacological Category: chemoprotective agent

Proposed Indication

"To reduce the incidence and severity of radiation-induced xerostomia."

Ethyol is currently approved for the reduction of cumulative renal toxicity associated with repeated administration of cisplatin in patients advanced ovarian cancer or non-small cell lung cancer.

Mechanism of Action

Amifostine is dephosphorelated to a free thiol by membrane bound alkaline phosphatase.[1] It provides an alternate target to DNA and RNA, detoxifying agents like platinum before it can damage

[1] Capizzi RL. Amifostine: The preclinical basis for broad-spectrum selective cytoprotection of normal tissues from cytotoxic therapies. Semin Oncol 1996; 23:2-17.

SCOPE OF NDA SUBMISSION

Table 1. Scope of NDA Submission

Adequate and Well-Controlled Study		
Study (Investigator)	Title	N (Ethyol)
WR-0038	Phase III Trial of Radiation Therapy ± Amifostine in Patients with Head and Neck Cancer	315 (157)
Supporting Studies		
Investigator Protocol (Antonadou)	Randomized Trial of the Prophylactic Use of Amifostine in the Prevention of Chemoradiation Induced Mucositis and Xerostomia in Head and Neck Cancer	45 (22)
Investigator Protocol (Bohuslaviski)	Randomized Double-Blind, Placebo-Controlled Trial of High-Dose Radioiodine (HD-RIT) ± Ethyol in Patients with Thyroid Cancer	50 (29)
WR-9001 (Liu)	Randomized Trial of Fractionated Radiation Therapy ± Amifostine in Patients with Rectal Cancer	104 (49)

REVIEW DESIGNATION: PRIORITY

"Priority review will be granted if the product, if approved , would be a significant improvement compared to marketed products in the treatment, diagnosis or prevention of disease." *(FDA Guidance for Industry on Standards for the Prompt Review of Efficacy Supplements)*

A priority review designation was granted for this application since the proposed indication for ethyol is for prevention of radiation induced xerostomia that may significantly impact patients' quality of life.

CONSULTS

1. Division of Scientific Investigations

The sites chosen for audit were #0012 (Sacramento, CA: 16 patients) and # 0008 (Durham, NC: 11 patients) where most U.S. patients were enrolled. These patients comprise 9% of the total population.

Table 2. Study Sites: WR-0038

COUNTRY	# Study Sites (N=40)	Accrual (%) N=315	Site Code/ #Patients Enrolled	Investigator Name	Location
Germany	14	153 (49)	0018/34 0038/30 0013/26	Wanenmacher Henke Sauer	Heidelberg Freiburg Erlangen
France	5	43 (14)	0042/20	Monnier	Cedex
Other European	3	9 (3)			
U.S.A.	14	72 (23)	**0012/16** **0008/11** 0051/9	**Jones** **Brizel** Machtay	**Sacramento,CA** **Durham, NC** Philadelphia, PA
Canada	4	38 (12)	002/16 003/12	Gelinas Fortin	Montreal Quebec

Reviewer's comment 1 . Result of DSI Inspection

The inspection report for Site 0012 and 0008 (dated May 10 and 12, 1999 respectively) showed that there were no discrepancies between the reported data and the source documents.

3. Division of Dermatologic and Dental Drug Products

Comments regarding the methods used for analyses of the efficacy endpoints (xerostomia, mucositis, salivary collections and PBQ) on the pivotal trial was requested and incorporated in the body of the review.

CLINICAL BACKGROUND

Reviewer comment: *These notations "Reviewer comment" represent the FDA reviewer commentary and evaluation of the study. These comments are found throughout this NDA review (in italicized text) to point out differences in the interpretation of study results, discrepancies in the data, or to emphasize certain aspects of the study that maybe relevant to the marketing approval and/or the approved labeling.*

Earlier Clinical Trials Using Amifostine in Head and Neck Cancer

1. Buntzel, et al., Selective Cytoprotection with Amifostine in Concurrent Radiochemotherapy for Head and Neck Cancer. Annals of Oncology 1998; (9) 505-509

   Thirty-nine patients with Stage III or IV squamous cell carcinoma of the head and neck received radiochemotherapy following surgery. Radiation was given daily in fractions of 2 Gy for a total dose of 60 Gy in conjunction with carboplatin , 70 mg/m^2 on days 1 to 5 and 21 through 26. Eligible patients were randomized to receive RCT ± amifostine (500 mg) on the days when carboplatin was administered. Patients receiving amifostine +RCT (n=25) had significantly reduced mucositis and xerostomia vs. patients who received RCT alone (n=11).

   Reviewer comments*: The study was small, and treatment assignment was determined by randomization in only 28 of 39 patients. There were many efficacy endpoints, and the statistical results were not corrected for multiple analysis. The small size of the study cited (39 patients) precludes a conclusion that Amifostine does not have a negative impact on antitumor efficacy. A much larger randomized trial would be required to demonstrate that Amifostine has no clinically significant protective effect on the tumor.*

2. Wagner, et al., Amifostine: a Radioprotector in Locally Advanced Head and Neck Tumors. Oncology Reports 1998; (5) 1255-1257

   Reviewer comments: *The design of the study is not adequately described in the article. The details of selection of a historical control group were not given. Since this is not a randomized trial, one cannot assume that "significant" differences between the study groups are due to treatment with Amifostine; the differences may be due to prognostic differences in the populations selected.*

Regulatory History of Ethyol for Radiation Therapy of the Head and Neck

Table 3. Regulatory History of Ethyol for Radiation Therapy of the Head and Neck	
1993	Initial discussions with the FDA regarding plans to develop ethyol as a radioprotectant
September 1995	Phase 3 Protocol (WR-0038) submitted to the FDA
February 1997	Teleconference with the FDA to review the study endpoints Revisions to the statistical plan were proposed
May 1998	Orphan drug designation for radiation –induced xerostomia
October 1998	Interim analysis results of WR-0038 and planned NDA submission discussed with the FDA
Dec 7, 1998	Teleconference with the FDA to discuss the format and content of the sNDA
Dec 24, 1998	SNDA submitted

CLINICAL PROTOCOL (WR-0038)

Reviewer's comment: *The June 1995 version of the protocol is the basis for the following summary. Important amendments starting on December 1995 are annotated as text in italics and highlighted.*

Study Title

Phase III Trial of Radiation Therapy ± Amifostine in Patients with Head and Neck Cancer

Investigators, Location of Trial:

U.S. CHAIRPERSONS:
David Brizel, M.D.
Department of Radiation Oncology
Duke University Medical Center
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France

Publications:

1. Brizel D, Sauer R, Wannenmacher M, Henke M, Eschwege F, Wasserman T. Randomized Phase III Trial of Radiation +/- amifostine in patients with head and neck cancer. Proc Am Soc Clin Oncol 1998; 17: (abs 1478)

2. Sauer R, Wannenmacher M, Brizel D, Jones C, Henke M, Strnad V, et al. Randomized Phase III trial of radiation (RT) +/- Ethyol (amifostine) in patients with head and neck cancer. Int J Radiat Oncol Biol Phys 1997; 39:234 (abs 1038)

3. Sauer R, Wannenmacher M, Brizel D, Jones C, Henke M, Strnad V, Wasserman T, Eschwege F. Randomized Phase III trial of radiation ± Ethyol ® (amifostine) in patients with head and neck cancer. European Society of Therapeutic Radiology and Oncology 1998; 17th Annual Meeting, 20-24 September 1998

4. Sauer R, Wannenmacher M, Brizel D, Jones C, Henke M, Strnad V, Wasserman T. Randomized Phase III Trial of Radiation ± Ethyol® (amifostine) in Patients with Head and Neck Cancer. Int J Radiat Oncol Biol Phys 1998.

5. Sauer R, Henke M, Wannenmacher M, Brizel D, Eschwege F , Wasserman T. Randomized Phase III Trial of Radiation ± Ethyol® (amifostine) in Patients with Head and Neck Cancer. American Radium Society Annual Meeting 1998.

Study Enrollment Period: September 14, 1995 to August 1997

Completion of Treatment: October 31, 1997

Cut-off date for Interim Analysis: November 25, 1998

Study Design - Methodology:

This study will be an open, prospective, multi-center, randomized, parallel groups Phase III trial comparing amifostine plus standard radiation therapy with radiation therapy alone for treatment of patients with head and neck cancer.

Objectives:

Primary Efficacy Endpoints

- Reduction of severity of xerostomia in patients with carcinoma of the head and neck receiving standard fraction irradiation, with no reduction in antitumor efficacy.

The following changes resulted from discussions with the Agency in an attempt to define the intensity of mucositis and xerostomia that are clinically meaningful.

1. *May 1996: (Specification of Multiple Primary Endpoints) Reduction of the incidence of Grade 2 or higher oral radiation reactions defined as acute mucositis, acute xerostomia and/or late xerostomia*

2. *November 1996: (Timing of Late Xerostomia)*

   Acute Toxicities: Grade 2 or higher acute xerostomia and/or mucositis
   Late Toxicities: Grade 2 or higher xerostomia occurring 9-12 months following radiation

3. *March 1997: (Definition of Significant Mucositis)*
   Acute Toxicities: ...xerostomia and/or Grade 3 mucositis

***Dental Consultant Comment**: Avoiding both acute and chronic side effects are equally desirable. Acute xerostomia is very unpleasant for the patient and result in missed treatments. Chronic xerostomia is just that-chronic.*

***Reviewer's comment:** Adjustment for multiple primary endpoints was done in the statistical analysis.*

- Locoregional tumor control rate at one year

(November 1996: Addition of disease-free survival and overall survival at the two year follow-up visit as secondary endpoints.)

(April 1997: Incidence of locoregional tumor control at 24 months as well as time to locoregional recurrence)

Secondary Efficacy Endpoints

- Reduction in the severity of xerostomia as determined by measurement of whole and parotid salivary production

  April 1997: ...measurement of whole and parotid saliva production and scintigraphy in selected institutions

- Reduction in the duration of xerostomia and mucositis.

- Reduction in the global effects of oral discomfort and dryness based on the total scores of the patient questionnaire

Toxicities

- The toxicities associated with amifostine plus standard fraction irradiation versus standard fraction irradiation will be assessed

Study Schema

Figure 1. Study Schema, WR-0038

S T R A T I F Y	**Treatment Center** **Site of Disease** (Oropharynx vs Nasopharynx vs Oral Cavity vs Larynx) **Nodal Status** (N_0 vs N_+) **Karnofsky Performance Status** (Appendix 1) (100, 90, 80 vs 70, 60) **Percent of Parotid gland for Radiation** (100% vs. 75-99%) **Type of Radiation** Post-operative (180 cGy) vs. Post-operative (200 cGy) vs. Radiation alone (180 cGy) vs. Radiation alone (200 cGy) Post-operative Low Risk Patients (50 -60 Gy)* (Primaries with negative tumor margins (R_0), node negative (N_0), node positive (N_1) without extra capsular extension) vs Post-operative High Risk Patients (60-66 Gy)* (Positive tumor margins (R_1,R_2), N_2, N_3, any extracapsular extension in the neck) vs Definitive Patients (66-70 Gy)* * According to local practice
R A N D O M I Z E	**Arm I: A+RT** Amifostine — 200 mg/m^2 i.v. over 3 minutes daily prior to radiation Radiation Therapy — 1.8-2.0 Gy/Day for 30-35 fractions beginning 15-30 min. after amifostine (see Appendix 1 for details) **Arm II:RT** Radiation Therapy — 1.8 - 2.0 Gy/Day for 30-35 fractions

Inclusion Criteria

- Patients undergoing definitive or adjuvant radiation therapy for histologically confirmed squamous cell carcinoma of the head and neck region where at least 75% of each parotid gland is included in the treatment field and would receive a total dose to each gland of 45 Gy or more.
- Patients entering protocol following surgery no later than 12 weeks post operatively.
- 18 years of age
- Expected survival of $\geq$ 12 months
- Karnofsky performance scale of $\geq$ 60
- No evidence of distant metastatic disease
- Granulocyte count (segs & bands) $\geq 2000/mm^3$ and platelet count $\geq 100,000/mm^3$
- Serum creatinine < 1.5 mg/dl
- Total bilirubin <2.0 mg%, SGOT 3 times the upper limit of normal
- Not entered on any other investigational therapeutic trials
- Written informed consent

Exclusion Criteria

- Less than 75% of each parotid gland in the treatment field
- Primary lesion of the parotid gland
- Karnofsky performance scale <60
- Patients who will be receiving hyperfractionated or accelerated radiotherapy
- History of prior malignancies within the past five years
- Prior chemotherapy for this malignancy or concurrent use of chemotherapy while enrolled in this study.
- Patients may have received prior radiation therapy, but not for head or neck cancer.
- Use of prophylactic pilocarpine
- Investigational drugs $\leq$ 4 weeks prior to study entry.
- General medical or psychological conditions which would not permit the patient to complete the study or sign the informed consent.
- Pregnancy. Women of child bearing potential should use an effective method of birth control throughout their participation in this study.

Patient Monitoring

Summarized as follows (see Tabulation in Appendix 2) :

Pretreatment Evaluation

- Informed consent
- Patient history and Physical Examination
- Dental Exam
- Notation of concomitant medications
- Baseline patient benefit questionnaire
- CT scan or MRI of the head and neck
- Chest X-ray
- Tumor assessment including measurement of clinically palpable disease. The method used to assess the tumor must remain the same throughout the study
- Saliva sampling: Unstimulated whole saliva and stimulated whole saliva. In some institutions, unstimulated and stimulated parotid saliva collection will be done
- CBC with differential and platelets
- Chemistries (glucose, calcium, albumin, total bilirubin, alkaline phosphatase, magnesium, SGOT, SGPT, LDH and serum creatinine)
- CT scan of the liver and bone scan if alkaline phosphatase is elevated 3 times the upper limit of normal; CT scan of the liver if SGOT is elevated 3 times the upper limit of normal

Assessments While Receiving Protocol Therapy

The following tests are performed <u>weekly</u> prior to receiving radiation ± amifostine therapy:

- Patient benefit questionnaire
- Notation of all concomitant medications
- Assessment of Radiation Reactions especially scoring of mucositis and dry mouth
- Physical exam
- Measurements of clinically palpable disease if measurable disease is present at the end of week 3 of therapy

Assessments at Completion of Protocol Therapy

- Physical exam
- Assessment of Radiation Reactions especially scoring of mucositis and dry mouth
- Serum chemistries
- CBC with differential and platelets
- Measurements of clinically palpable disease, if measurable disease is present
- Completion of patient benefit questionnaire
- Notation of all concomitant medications

Concomitant Medications

All patients were allowed to receive full supportive care including antiemetics, antibiotics, transfusions of blood and blood products, etc. as appropriate. In the event of excessive mucosal reaction and nutritional deterioration, nutritional support was provided by means of i.v. fluids, hyperalimentation, nasogastric tube feedings, or percutaneous enterogastrostomy (PEG).

Radiation Therapy

Summarized as follows: (see Appendix 1 for complete description)

- Equipment: Linear accelerator with supplemental nodal boosting
- Schedule of Treatment: 1.8 to 2.0 Gy 5 days/week for 6-7 weeks; A total dose of 50-60 Gy for post-operative low-risk patients, 55-65 Gy for post-operative high risk patients, and 66-70 Gy for definitive radiation
- Localization Requirements: Simulation of all fields with delineation of parotid glands and nodal disease
- Irradiation Portals: Combination of lateral opposing fields for the primary tumor site; Nonlateral fields can be used for boost volumes after 45 Gy to 75% of each parotid gland through lateral fields; Field reductions recommended to avoid overexposure of the spinal cord and increase primary tumor and nodal exposure
- Time and Dose Modifications: Treatment breaks allowed for healing of severe reactions but not to exceed five days
- Nutritional Support: IV fluids, hyperalimentation, NG tube or PEG feeding allowed
- Radiation Therapy Review Team: Two reviews of radiation therapy were conducted. This review was coordinated by the In the USA and Canada, the reviews were conducted by Drs. David Brizel and Todd Wasserman. In Europe, the reviews were conducted by he Department of Radiotherapy, Institut Gustave-Roussy in Villejuif, France, with concurrence from Dr. Todd Wasserman and Dr. David Brizel.

Reviewer's comment 2. Central Review of Radiation Therapy

The assignment of a central review team reduces investigator bias and assures adherence to the prescribed radiotherapy.

Literature citation 1. Determination of Radiation Dosage

In general, radiation dosage is determined by the tumor site, size of the lesion, irradiated volume, number of fractions of treatment, fractions size, total time, various techniques of radiation delivery, patient tolerance and tumor control. The definition of an "optimum" tumor control dose may be different for reach individual radiation

oncologist and is guided by his/her individual experience, tolerance for risk and the availability of support to manage complications such as osteoradionecrosis, soft tissue necrosis, radiation pneumonitis, etc.

Literature citation 2. Shrinking Field and Mixed Beam Therapy

Peripheral subclinical microscopic disease may be controlled with relatively smaller total doses of radiation (i.e. 50 Gy in 5 weeks). After this dose level is reached, the residual macroscopic mass can be irradiated with reduced fields at higher dose levels without undue damage to adjacent normal tissues (i.e. the dose carried on to 65-70 Gy to avoid damage to structures, e.g. parotid glands).[3]

Reviewer's comment 3. Choice of Radiation Dose for WR-0038

The radiation doses prescribed were usual and not unreasonably high in this study. This is an important point in designing trials for cytoprotective agents like ethyol where efficacy of the drug should to be demonstrated using standard doses of therapy. In addition, multifield treatments were administered, boost doses and treatment rests were employed as necessary in order to avoid radiation related complications.

Reasons for Treatment Termination

- Disease progression
- Physician withdraws the patient from the study because of significant toxicity to the patient; this will be reported to U.S. Bioscience/USB Pharma Ltd (as appropriate) and recorded on the adverse experience page of the case report form.
- Patient requests discontinuation of protocol therapy.
- Physician withdraws patient from the study because of patient's lack of compliance with scheduled visits.
- Patient has a concurrent illness precluding continued administration of study medication or follow-up.
- Administrative withdrawal e.g. patient relocates.
- All reasons for withdrawal will be documented on the discontinuation page of the case report form. All patients in whom protocol therapy has been discontinued will be followed until resolution of toxicities.

Efficacy Assessment

Patients are considered evaluable for efficacy after receiving 45 Gy of radiation *(May 1996: changed to 40 Gy)*

Reviewer's comment: *According to the literature, late onset and permanent xerostomia are usually experienced after doses of 40 to 45 Gy.*

Assessment of Radiation Effect

1. RTOG Acute and Late Radiation Morbidity Scoring Criteria

Table 4. RTOG Acute Radiation Morbidity Scoring Criteria for Mucositis and Xerostomia

Grade	Mucous Membrane	Salivary Gland
0	No change over baseline	No change over baseline
1	Injection, may experience mild pain not requiring analgesic	Mild mouth dryness/ slightly thickened saliva, may have slightly altered taste such as metallic taste/these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids in meals
2	Patch mucositis which may produce an inflammatory serosanguinous discharge/may experience moderate pain requiring analgesia	Moderate to complete dryness, thick, sticky saliva/ markedly altered taste
3	Confluent fibrinous mucositis/may include severe pain requiring narcotic	
4	Ulceration, hemorrhage or necrosis	Acute salivary gland necrosis

The primary efficacy endpoints are the incidence of grade 2 or higher acute xerostomia and grade 3 or higher acute mucositis (shaded). Acute effects are those toxicities which occur ≤90 days from the start of protocol therapy and late effects are those toxicities which occur >90 days from the start of protocol therapy. Patients are evaluated at the 9-12 month time interval for incidence of late effect xerostomia.

2. Patient questionnaire

The Patient Benefit Questionnaire (PBQ) was designed by radiation oncologists and dentists to rate patient symptoms. This was validated by the Scientific Advisory Committee on the Medical Outcomes Trust using the following eight instruments: (1) Conceptual and Measurement Model, (2) Reliability, (3) Validity, (4) Responsiveness, (5) Interpretability, (6) Burden (7) Alternative Forms, and (8) Cultural and Language Adaptations. The PBQ was administered at baseline, weekly while receiving therapy, and at follow up visits: month 1, 3, 5, 7, 9, and 11. (See Appendix 3 for the sample questionnaire)

For each questionnaire filled out, the total score will be calculated and used for analysis. A missing item will be replaced with the adjusted mean of the non-missing items in the same questionnaire. The total scores and the change from baseline on the total score at each weekly visit will be analyzed for treatment group differences. A repeated measures analysis will be performed.

3. Assessment of salivary gland function

The measurement of whole saliva production is being performed at all institutions. The measurement of parotid salivary production and scintigraphy is being performed at selected institutions. These measurements will be analyzed using the two-sample t-test (or the Wilcoxon Rank Sum test).

Criteria for Tumor Assessment

Loco-regional control is assessed in all patients using CT scan or MRI measurements performed at baseline and final follow-up visit *(March 1997: added 23 month and when clinically indicated)*. Local regional tumor control at 12 months will be used as the primary endpoint for evaluation of the antitumor efficacy of radiotherapy. A patient will be assigned as a success under the category of tumor control if for that patient there is no evidence of local or regional recurrence. Development of other primary tumors are not evidence of local or regional recurrence.

Clinical tumor assessment, by inspection and by palpation (use photography when applicable), are made before therapy, at the end of week 3, and subsequently at each follow-up. Failure of clearance (persistence) is documented. Time of apparent beginning regrowth are noted. Clinically suspected persistence or recurrence are biopsied when feasible.

Twelve month and 24 month tumor control rates will be analyzed using Pearson Chi-Square test and a ratio of tumor control rates. Subgroup analyses will be performed separately. Lower limits of one-sided 95% confidence interval will be used to assess statistical equivalency between treatment groups. The one-sided confidence interval reflects the concept that no penalty should be applied to the experimental group for better-than-expected tumor control. Disease-free survival and overall survival will be assessed at the two year follow-up visit.

An interim evaluation of antitumor efficacy is scheduled after 160 patients have been assessed for local regional tumor control rate at the follow-up visit in the 9-12 month interval. Lower limit of one-sided 95% confidence interval (LCL) will be calculated to compare with a critical value of 0.7. An LCL greater than 0.7 is considered as statistical evidence of equivalency in antitumor efficacy between treatment groups. A final analysis is planned after all 250 patients are assessable in the 9-12 month follow-up interval.

(December 95: The interim analysis was changed from 160 patients (75/arm) to 200 patients (100/arm), and included a stopping rule for xerostomia at the 9 to 12 month assessment and a modified stopping rule for local or regional tumor control.)

(March 1997: Changed the number of evaluable patients from 180 to 300 patients (150 /arm) and added an interim and subgroup analyses)

(April 1997: Changed the number of evaluable patients from 300 to 250 patients (125 /arm) and added an interim and subgroup analyses)

(April 21, 1999) Added an interim analysis for late effect xerostomia to be performed when 160 evaluable patients have been assessed for local regional tumor control at 12 months.

Safety Assessment

Incidence and duration of side effects associated with amifostine administration will be tabulated. Incidence, severity, and duration of other toxicities associated with this radiation schedule will be assessed according to the RTOG acute and late effects radiation morbidity criteria. *(May 1995: Allowed for amifostine dose reduction based on hypotension)*

Statistical Analysis

An estimated 300 evaluable patients (150 per arm) will be enrolled in the study. All patients who have received at least one dose of protocol therapy will be evaluable for safety. All patients who have received at least 45 cGy will be evaluable for efficacy.

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ON ORIGINAL

Table 5. Statistical Analyses of Study Endpoints

Reviewer's comment: *There were several meetings held between the sponsor and the FDA regarding the statistical analysis of this trial. The following table summarizes the changes:*

Efficacy Endpoints	Test Planned in Protocol	Test Used in Study Report
Primary Endpoints		
Incidence of ≥Gr. 2 Acute Xerostomia	Pearson x^2 Test[a]	Fisher's Exact Test[c]
Incidence of ≥Gr. 2 Chronic Xerostomia	Pearson x^2 Test[a]	Fisher's Exact Test[c]
Incidence of ≥Gr. 3 Acute Mucositis	Pearson x^2 Test[a]	Fisher's Exact Test[c]
Secondary Endpoints		
Severity distribution and incidences by cumulative RT doses	Mantel-Haenzel x^2 Test	Mantel-Haenzel x^2 Test
Duration of Toxicity	Two Sample T-test	Logrank Test
Time to Onset of Acute Toxicities	Kaplan-Meier Test	Logrank Test
Time to Recovery of Xerostomia to Grade 1 or Better	Kaplan-Meier Test	Not Done
Radiation Dose Intensity	Pearson x^2 Test	Not Done
One Year Locoregional Control[b]	Pearson x^2 Test and Ratio of Tumor Control Rates	Pearson x^2 Test
Saliva Measurements	Two Sample t-test	Fisher's Exact Test[c]
Patient Benefit Questionnaire	Mean Score Analysis Change from Baseline Repeated Measures Analysis	Longitudinal Analysis for the mixed effect model of Laird and Ware[d](in addition)
Survival and DFS[b]		Kaplan-Meier Estimates and Cox proportional hazards regression model

[a] p-values were adjusted for multiple endpoints using the permutation approach by Westfall and Young.

[b] During our meetings with the sponsor, the FDA reviewers recommended logrank analysis for these endpoints, Cox regression model to be considered secondary; however, sponsor's analysis did not reflect this

[c] Because of the relatively small sample size, use of the Fisher's Exact Test was recommended by the FDA

[d] Longitudinal analysis of the PBQ recommended by the FDA in addition to their planned analyses

Data Quality Assurance

According to the applicant's report, routine monitoring of investigational sites were conducted. They included a review of the regulatory documents, test article accountability records, and CRFs to verify adherence to GCP and the study protocol. The monitor assessed the completeness, consistency, and accuracy of the data entered on the CRFs relative to source documentation. Completed CRFs (top page of two-part form) were collected during the monitoring visits and submitted to the sponsor, and the back page of the two part form was retained at the investigational site. Independent quality assurance field audits were also undertaken at selected institutions.

CRFs were reviewed and sent to the Data Coordination Department for coding and data entry. One data entry operator entered the data, and another, independent operator key verified the data using a commercially available software package that identified any discrepancies between the two data entry operators. Data in the database were verified against data recorded on patient CRFs by generation and review of screening tables. After resolution of any data errors which were identified at screening, additional diagnostic programs were run before designation of a clean data file.

STUDY RESULTS

Patient Demographics

Patient pretreatment characteristics were balanced.

Table 6. Sponsor's Summary of Baseline Demographic Characteristics (Intent-to-Treat Patients)

Parameter	A + RT (N=150)		RT (N=153)		p-value
Age (yr)					0.6238[a]
Median	55.6		56.7		
Range	(36.4 - 79.1)		(28.3 - 78.3)		
<50	41	(27%)	42	(27%)	0.5608[d]
50-59	64	(43%)	57	(37%)	
>60	45	(30%)	54	(35%)	
Gender					0.4729[b]
Male	123	(82%)	120	(78%)	
Female	27	(18%)	33	(22%)	
Race					0.3995[b]
Caucasian	138	(92%)	133	(87%)	
Black	4	(3%)	7	(5%)	
Other	8	(5%)	13	(8%)	
KPS					0.6998[b]
100-80	108	(72%)	109	(71%)	
81-60	39	(26%)	44	(29%)	
Missing	3	(2%)	0	—	
Weight Loss in Past 6 Months					0.3930[c]
None	76	(51%)	77	(50%)	
>10%	19	(13%)	18	(12%)	
Unknown	6	(4%)	2	(1%)	
Tobacco Use					1.0000[b]
Yes	135	(90%)	138	(90%)	
No	15	(10%)	15	(10%)	
Alcohol Use					1.0000[b]
Yes	134	(89%)	134	(88%)	
No	16	(11%)	17	(11%)	
Not stated	0	—	2	(1%)	

[a] P-value based on Wilcoxon rank sum test
[b] P-value based on Fisher exact test
[c] P-value based on Pearson Chi-square test
[d] P-value based on Mantel-Haenszel Chi-square test.

(From NDA 20-221, vol 9, p.11)

Table 7.Baseline Tumor Characteristics (cont'd) (Intent-to-Treat Patients)

Parameter	A + RT (N=150)		RT (N=153)		p-value
Primary Site of Disease					0.6133[a]
Oropharynx[c]	77	(51%)	66	(43%)	
Oral Cavity	28	(19%)	33	(22%)	
Larynx[d]	22	(15%)	24	(16%)	
Hypopharynx[e]	13	(9%)	15	(10%)	
Nasopharynx	5	(3%)	6	(4%)	
Pharynx	1	(1%)	0	–	
Unknown	4	(3%)	9	(6%)	
Clinical Staging (T Stage)					0.1591[b]
T0	2	(1%)	1	(1%)	
T1[h]	25	(17%)	21	(14%)	
T2	51	(34%)	53	(35%)	
T3	29	(19%)	27	(18%)	
T4	38	(25%)	34	(22%)	
TX	5	(3%)	17	(11%)	
Nodal Status					0.7448[b]
N0	42	(28%)	46	(30%)	
N1	37	(25%)	32	(21%)	
N2	68	(45%)	66	(43%)	
N3	2	(1%)	8	(5%)	
NX	1	(1%)	1	(1%)	
Left Parotid Volume in Radiation Field (%)					0.9629[b]
100%	80	(53%)	82	(54%)	
75%-99%	69	(46%)	70	(46%)	
<75%	1	(1%)	1	(1%)	
Right Parotid Volume in Radiation Field (%)					
100%	80	(53%)	82	(54%)	0.9629[b]
75%-99%	69	(46%)	70	(46%)	
<75%	1	(1%)	1	(1%)	
Type of Radiation					
Post-Operative					
High-risk[f]	70	(47%)	65	(42%)	
Low-risk[g]	30	(20%)	36	(24%)	0.7339[b]
Definitive and Inoperable	50	(33%)	52	(34%)	

[a] P-value based on Pearson Chi-square test
[b] P-value based on Mantel-Haenszel Chi-square test
[c] Oropharynx includes oro-hypopharynx
[d] Larynx site includes epiglottis and epilarynx
[e] Hypopharynx includes piriform sinus
[f] High-risk criteria: RT (60-66 Gy), positive tumor margins (R1,R2), node positive (N2, N3) with any extracapsular extension in the neck
[g] Low-risk criteria: RT (50-60 Gy), primaries with negative tumor margins (R0), node negative (N0) or node positive (N1) without extracapsular extension in the neck
[h] T1 stage includes one patient with T *in situ*

(from NDA 20-221 vol. 9, p. 12)

Literature citation 3. Pretreatment Risk Factors

Carcinomas arising from the various sites of the head and neck possess different tumor characteristics with its own natural history, biological behavior, and mode of tumor growth and spread. The therapeutic management and results may differ greatly. The choice of treatment modalities depends on many factors such as (1) cell type and degree of differentiation; (2) site and extent of the primary lesion; (3) metastatic nodal status; (4) gross characteristics of the tumor (i.e. exophytic, superficial vs. endophytic, infiltrative); (5) presence or absence and extent of muscle involvement; (7) the physical condition, social status, and occupation of the patient; (8) the experience and skill of both the surgeon and the radiation oncologist; and (9) cooperation and wishes of the patient.[2]

Reviewer's comment 4. *Protocol Deviations Identified by the Radiation Oncology Quality Assurance Team*

Twenty-eight patients (11 patients on the amifostine + RT arm and 17 patients on the RT alone arm) were identified by the RTQA as having variations in their planned radiation treatment. Based on this review, 12 patients (six patients in the amifostine + RT arm and six patients in the RT alone arm) of the 28 patients actually had less than 75% of parotid glands in the radiation field. The following table summarizes the findings of the RTQA.

Table 8. FDA Summary of Protocol Deviations Identified by the Radiation Oncology Quality Assurance Team

Findings (Intent to Treat Analysis)	A+ RT (n=150)	RT (n=153)
Less than 75% of the Parotid Glands in the Radiation Treatment Fields	6	6
Significant Amount of Normal Tissue Treated: Possible Treatment Overlap at Cord, Excess Brain, Brachial Plexus, Pituitary and Lungs in Fields	2	4
Inadequate Second Boost Primary Tumor or Supraclavicular Nodes	1	4
No Treatment of Supraclavicular Nodes	1	2
Prolonged Treatment Duration	1	0
Inadequate Margins Primary Tumor and Nodal Drainage	0	1

[2] Basic Concepts of Radiation Therapy for Head and Neck Cancer: Radiation Doses, Fractions and Complications.

Reviewer's comment 5. FDA Reviewer's Comparison of Total Radiation Doses Administered

An exploratory analysis of the distribution of total radiation doses according to treatment arm. According to the literature, permanent late xerostomia is common beyond doses of 60 to 70 Gy. This analysis only evaluates total dose, recognizing that the degree of damage to salivary glands may be affected by other factors such as the use of several ports, shrinking fields, etc.

Significantly more patients in the RT alone arm received more than 65 Gy. There were numerically more patients who received between 45 and 650 Gy in the A+RT arm but the difference was not statistically significant. The overall difference on the distribution between treatment arms was marginally significant. (p=0.056)

Table 9. FDA Summary of the Distribution of Total Radiation Dose Received

Total Dose (Gy)	A+RT (n=150)	RT (n=153)	p-value (95% C.I.)
0-4500	4 (3%)	1 (0.6%)	
4501-6500	81 (54%)	67 (44%)	0.07
>6501	65 (43%)	85 (56%)	0.02

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Reviewer's comment 6. Diagnoses of Patients who received >65 Gy vs. All Patients

The distribution of the diagnoses of patients who received >65 Gy is similar to the general study population:

Table 10. Primary Diagnoses of Patients who Received >6500 Gy Total Radiation Dose

Site	A+RT		RT	
	>6500 Gy (n=65)	All Patients (n=150)	>6500 Gy (n=85)	All Patients (n=153)
Oropharynx	35 (54)	77 (51)	41(48)	66 (43)
Larynx	10 (15)	22 (15)	10 (19)	24 (16)
Hypopharynx	5 (8)	13 (9)	9(11)	15 (10)
Oral Cavity	7 (11)	28 (19)	13 (15)	33 (22)
Nasopharynx	4 (6)	5 (3)	5 (6)	6 (4)
Others	3 (5)	1 (1)	–	–
Unknown	1(2)	4 (3)	7(8)	9 (6)

Reviewer's comment: Type of Radiation vs. Doses Received

Patients were prospectively stratified according to the intent of radiation. All post-operative patients were assigned to a high or low risk group depending on the stage of tumor, positivity of tumor margins, etc. The distribution of actual total doses received by patients according to the three dose strata and intent of radiation shows that a majority of the definitive and inoperable patients received doses >65 Gy. The bar graphs below show that there were more patients in the RT arm who received >65Gy, particularly patients in the high dose post-operative group. This could have an impact on both the incidence of toxicity and on tumor control.

Figure 2. Distribution of Patients According to Type of Radiation and Dose Strata (A+RT Arm)

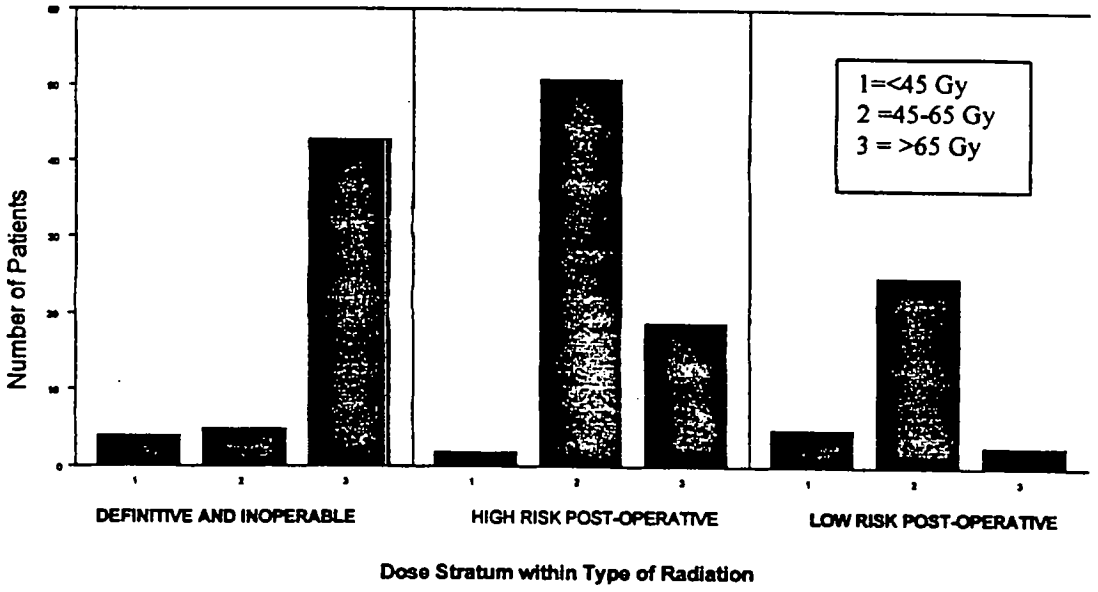
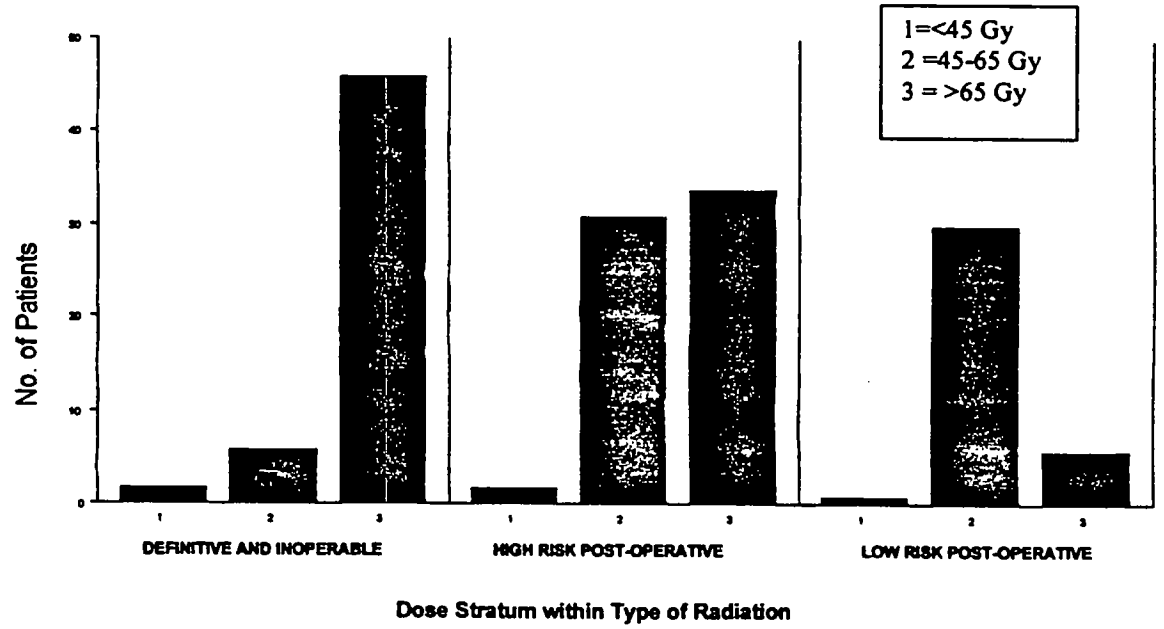


Figure 3.Distribution of Patients According to Type of Radiation and Dose Strata (RT Arm)



Reviewer's comment 7: Baseline Hemoglobin Levels

Hemoglobin levels may affect local control of head and neck tumors and anemia found to be present at baseline should be corrected.[3] *Baseline hemoglobin and hematocrit levels were similar in both treatment arms at baseline.*

Patient Disposition

A total of 315 patients were randomized. However, the intent-to-treat analyses include available data only from patients treated, 150 patients in the A+RT arm, and 153 patients in the RT arm.

Table 11. Sponsor's Summary of Disposition of Patients Randomized to Receive RT ± Amifostine for Head and Neck Cancer

	A + RT	RT Alone
Patients Randomized	**157**	**158**
Patients Not Treated	7	5
Reasons Not Treated		
Patient withdrew consent	4	5
Concomitant illness	1	0
Time at hospital too long	1	0
Refused daily injections	1	0
Patients Treated	**150**	**153**
Patients Discontinued Study	6	1
Patients Who Completed Radiation Therapy	**144**	**152**
Patients Discontinued Amifostine*	**29**	—
Reasons Discontinued		
Adverse events	26	—
i.v. access problems	1	—
Patient requests withdrawal	2	—
Prior to receiving 40 Gy	**18**	—

* All patients who discontinued amifostine prematurely continued to receive their prescribed radiation treatment until completion

[3] Blitzer P et al. Blood pressure and hemoglobin concentration: multivarate analysis of local control after irradiation for head and neck cancer. Int J Radiat Oncol Biol Phys 1984, 10:98

Of the 144 patients who completed radiation treatment, 29 patients discontinued amifostine prior to completing the prescribed radiation schedule. Of these 29, 18 patients discontinued amifostine prior to receiving 40 Gy of radiation.

EFFICACY ANALYSIS

Sponsor's Analysis of Acute Xerostomia

The incidence of acute xerostomia, as assessed using the RTOG Acute Radiation Morbidity Scoring Criteria, was determined according to the worst grade reported within 90 days from the start of radiation treatment. The incidence of Grade 2 or higher acute xerostomia was significantly reduced ($p<0.0001$) in patients receiving amifostine. In addition, the onset of acute xerostomia was calculated from the initiation of radiation to the first occurrence per latest assessment date or study day 90 whichever came first. The cumulative RT dose to onset of Grade 2 or higher acute xerostomia was significantly higher ($p=0.0001$) in the amifostine + RT arm than in the RT alone arm.

Table 12. Sponsor's Analysis of Acute Xerostomia

	A + RT (N=148)		RT Alone (N=153)		p-value
Severity of Acute Xerostomia					
RTOG Grade					
0	16	(11%)	8	(5%)	
1	57	(39%)	25	(16%)	
2	75	(51%)	120	(78%)	**<0.0001[a]** (<0.0001[c])
Onset to Grade 2 Acute Xerostomia					
Median Days	45		30		0.0001[b]
Median Cumulative RT dose (Gy)	60		42		0.0001[b]

[a] Based on Fisher exact test
[b] Based on Kaplan-Meier procedure and log-rank statistic
[c] Adjusted for multiplicity based on a permutation method in SAS PROC MULTTEST

(from sNDA 20-221 vol. 9, p. 13)

Literature citation 4. Acute xerostomia

With standard fractionation schemes, there is a radiation dose-dependent decrease in parotid gland function characterized by a sharp decline in salivary flow during the first week.[4] As the dose increase throughout the radiation course, hyposalivation continues

[4] Wescott WB, et al. Alterations in whole saliva flow rate induced by fractionated radiotherapy. Am J. Roengenol. 1978; 130:145-9

and is persistent and progressive. Patients are generally most concerned about acute side-effects but are generally self-limited.[5]

Reviewer's comment 8. FDA Analysis of Acute Xerostomia

There was no significant difference between treatment arms in the incidence eof Grade 1 and 2 xerostomia (132/150 (90%) in the A+RT arm and 145/153 (94%) in the RT arm) (p=0.07). According to the sponsor's analysis, ethyol may prevent severe acute xerostomia,; however, it does not appear that it prevents overall incidence.

Sponsor's Analysis of Late Xerostomia

Late xerostomia was defined in the protocol as the incidence of Grade 2 or higher late-effect xerostomia as measured by the RTOG Late Radiation Morbidity Scoring Criteria at 9 to 11 months following the completion of radiation or 1 year from the start of radiation. It was defined in the study report as the worst toxicity grade of xerostomia at 365 ± 31 days from the initiation of radiation. Ninety-seven patients in the A+RT arm and 106 patients in the RT arm had late-effect xerostomia data within the 365 ± 31 day time period.

Table 13 Analysis of Late-Effect Xerostomia Using RTOG Late Radiation Morbidity Scoring Criteria

RTOG Grade	A + RT (N=97)		RT Alone (N=106)		p-value
0	16	(16%)	12	(11%)	
1	48	(49%)	34	(32%)	
2	25	(26%)	49	(46%)	
3	8	(8%)	11	(10%)	0.0115[a]
Total Grade 2/3	33	(34%)	60	(57%)	0.0019[b]

[a] Severity analysis based on Mantel-Haenszel Chi-square test
[b] Based on Fisher exact test

Data was missing in approximately one-third of patients in each arm. Reasons for the missing data are as follows: death (n=46), lost to follow-up (n=20), progression data with no further xerostomia data (n=11), assessment of late xerostomia not recorded within the time window of 365±31 days (n=23).

[5] Parsons J. The effect of radiation to normal tissues of the head and neck. Management of Head and Neck Cancer. Philadelphia: JB Lippincot. 1984:173-207

Literature citation 5. Late Xerostomia

Radiation may affect tissues permanently. The extent of damage depends on the daily and cumulative doses of radiation, and the volume of tissues irradiated. Acute lesions occur primarily in epithelial and glandular tissues. Severe late effects in the form of atrophy occur in the alimentary epithelium and salivary glands. However, despite the ability to quantify the radiation dose accurately, the risk of late radiation injury as a function of dose, time and fractionation cannot be calculated with certainty.

Xerostomia usually persists for several months to years and may or may not recover, depending on the total dose and volume of tissue irradiated, daily fraction size and homogeneity of dose. Tumor control is largely dependent on the minimum dose while complications are dependent on the maximum dose. There are interindividual differences in the degree of recovery which is also dependent on the amount of radiation received.[6]

Patients with late xerostomia experience impaired ability to swallow, chew, talk, and/or wear dentures comfortably. Most patients need to change the nature of their diet. Alteration of the normal oral microflora to a more cariogenic one occurs as a result of changes in the salivary contents and lowering of the oral pH.[7]

[6] Cheng V, et al . The function of the parotid gland following radiation therapy for head and neck cancer. Iny J Radiat Oncol Biol Phys. 1981; 7(2) 253-258

[7] Main B. The effect of cytotoxic therapy on saliva and oral flora. Oral Surg 58:545-548, 1984

Reviewer's comment 9. FDA Analysis of Late Xerostomia

Follow-up assessment of radiation reactions after treatment was scheduled one month after termination of radiotherapy , every two months for the first year and every six months thereafter. Late xerostomia was defined in the protocol as the incidence of ≥ Grade 2 late xerostomia 9-12 months after treatment. There were 45 patients (30%) in the A+RT arm and 55 patients (36%) in the RT arm who reported xerostomia (Grade 1-3) during this period. Of these patients, there were 14 (9%) in the A+RT arm and 26 (17%) in the RT arm who reported ≥Grade 2 late xerostomia. (p=0.05, C.I. –0.001,0.152). The incidence of Grades 1-3 late xerostomia was similar between treatment arms; therefore, it appears from the sponsor's and FDA's analyses that ethyol decreases the incidence of severe late xerostomia but does not significantly decrease the overall incidence of late xerostomia.

Table 14 FDA Analysis of Late Xerostomia

	A + RT (N=150)		RT Alone (N=153)	
Patients who reported Post-Treatment Xerostomia	99	(67%)	112	(73%)
Grade 1-3 Xerostomia (>9 months)	45	(30%)	55	(36%)
>Grade 2 Xerostomia (>9 months)	14	(9%)	26	(17%) p=0.05

The total dose of radiation received by patients who experienced late xerostomia was reviewed. There were 27 patients (11 in A+RT and 16 in RT) who received between 45 to 65 Gy and 13 patients (3 in A+RT and 10 in RT) who received >65 Gy.

Although the FDA noted that more patients on the RT arm than the A+RT arm received greater than 65 Gy, when patients were grouped according to radiation dose received, a protective advantage for Ethyol was still apparent for each group:

Table 15. Incidence of Late Xerostomia

RT Dose	A+RT	RT
<45 Gy	0% (0/4)	
45-65 Gy	19% (15/81)	43% (29/67)
>65 Gy	32% (21/65)	40% (34/86)

Sponsor's Assessment of Salivary Gland Function

In an attempt to quantify xerostomia, the WR-0038 study included an assessment of whole saliva production at baseline and at months 1, 5, and 11 post-completion of treatment. Because of variability in saliva collections, three time windows were created to represent month 1 (0-3 months), month 5 (3 to 6 months) and month 11 (6 to 15 months) for the analysis.

Reviewer comment: *The evaluation of saliva collections for month 11 includes a time span of 9 months.*

Unstimulated saliva production was assessed initially. To assess stimulated saliva, the procedure was repeated after chewing on a standardized 5 cm by 5 cm parafilm strip for 2 minutes. Following consultation with [redacted] 0.1 gram was chosen as the cut-off point below which saliva production was considered to be negligible and of little clinical meaning.

Dental Consultant's Comment: *"The consultant cited by the sponsor, [redacted] is an acknowledged expert in the area and, if pre-designated, 0.1 gm/5 min would be an acceptable indicator of clinical efficacy."*

Table 16. Sponsor's Whole Saliva Collection Results

	Amifostine + RT		RT Alone		p-value*
Unstimulated Saliva					
Baseline					
0.1 gram	4	(3%)	6	(4%)	0.7497
>0.1 gram	144	(97%)	143	(96%)	
First follow-up visit					
0.1 gram	29	(25%)	41	(32%)	0.2602
>0.1 gram	88	(75%)	89	(68%)	
1 year following radiation					
0.1 gram	25	(28%)	44	(51%)	0.0033

>0.1 gram	63	(72%)	43	(49%)	
Stimulated Saliva					
Baseline					
0.1 gram	4	(3%)	4	(3%)	1.0000
>0.1 gram	141	(97%)	142	(97%)	
First follow-up visit					
0.1 gram	21	(18%)	25	(20%)	0.7463
>0.1 gram	97	(82%)	103	(80%)	
1 year following radiation					
0.1 gram	29	(33%)	35	(41%)	0.3471
>0.1 gram	58	(67%)	51	(59%)	

* P-value based on Fisher exact test

Significantly more patients pretreated with amifostine were able to produce unstimulated whole saliva at 1 year after radiation as compared to control patients (p=0.0033). In addition, the median saliva production was significantly higher in those patients who received Ethyol (0.26 g vs 0.1 g; p=0.0419) by Wilcoxon rank sum test. There was no difference in the stimulated saliva production.

Reviewer's comment 10. FDA Comments on Sponsor's Analysis of Saliva Collection

The analysis of data using a designated cut-off point (0.1 gm) to determine clinically significant saliva production was assigned retrospectively.

Collection of saliva was scheduled in the protocol at baseline, and post-treatment months 1, 5 and 11. These collection time points were not reflected in the sponsor's analysis which only defined the visit at baseline, first follow-up visit and one year follow-up visit.

Literature citation 6. Salivary Gland Production and the Effect of RT

Typically, the parotid gland contributes 60-65% of normal saliva production, and 20-30% by the submandibular glands. Under resting conditions, the flow from the submandibular glands is at least as great as that from the parotids or possibly greater. If the parotid glands are irradiated and the submandibular glands spared, moisture of the mouth may be preserved. Severe dryness usually results if both parotids, both submandibular and a majority of the minor salivary glands are irradiates (as in nasopharyngeal cancer). [8]

In patients with very low preirradiation salivary flow rates, lesser doses may cause permanent dryness while patients with high pretreatment salivary flow rates develop less dryness following a particular treatment course. The decrease in flow after irradiation

[8] Enfors B. The parotid and submandibular secretion in man: Qualitative recordings of the normal and pathologic activity. Acta Otolaryngol (Suppl) 172, 1962

follows an exponential decay curve. A certain dose reduces the flow by approximately the same percentage, not by the same absolute amount.[9]

If salivary tissue receives more than 3000 to 3500 rads, there is often some loss of function during the six months following therapy. Younger patients are more likely than older patients to recover salivary flow. During treatment planning, one should attempt to limit the volume of salivary tissue irradiated and the dose delivered whenever practical to do so. Minor changes in field size and shape may preserve some salivary flow.

Literature citation 7.Results of Clinical Trials on the Effect of RT on Salivary Production

McDonald, et al evaluated stimulated and unstimulated saliva flow rates in 12 patients with head and neck cancer who were given at least 45 Gy of radiation. Amifostine was given (100 mg/m^2) to 10 patients prior to each radiation treatment. Flow rates of unstimulated whole saliva decreased significantly during radiotherapy, recovering after six months. Stimulated whole salivary flow rates similarly decreased and improved after 3 months. The stimulated parotid flow rates decreased to <1% of pretreatment levels and recovered to 45% of baseline 15-18 months post treatment.[10]

In a study by Takahashi, et al, the long-term radioprotective effect of amifostine on the salivary gland was examined using ^{67}Ga-scintigraphy performed approximately six months after completion of radiation. Accumulation of ^{67}Ga in the salivary gland is believed to result from congestion of saliva due to radiation-induced edema. One hundred fifty-five patients with head and neck cancer were evaluated. A Total of 40 patients received amifostine prior to radiation and 65 treated with radiation alone. Results showed that in glands treated with ≥ 30 Gy, 28 (87%) of 32 glands in the control group had increased uptake versus 23(56%) of 41 glands in patient pretreated with amifostine.[11]

Reviewer's comment 11. FDA Analysis of Saliva Collections

Collection of whole saliva provides important objective documentation of xerostomia. It is unclear from the literature how much saliva is "normal" and how much is required to maintain normal oral function. Many investigators have attempted to establish normal ranges or "cut off" values; however, there is a wide range of salivary function present in healthy individuals. One should be cautious in assigning a single arbitrary "cut-off" value of clinical significance for the following reasons: (1) While there is large variability in the amount of salivary secretions among normal individuals, it is unknown whether such degree of variability exists in patients after radiation; (2) Individual could have suffered a significant decline in the salivary function after radiation but still be considered within the "normal" range, and (3) Individuals with baseline low salivary gland secretions may be able to functionally tolerate further declines despite treatment.

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[9] Mira J, et al. Some factors influencing salivary function when treating with radiotherapy. Int J Radiat Oncol Biol Phys 7, 535-541, 1981

[10] MsDonald S. Amifostine Preserves the Salivary Gland Function During Radiation of the Head and Neck. European Journal of Cancer, vol 31 A supp. 5, November 1995

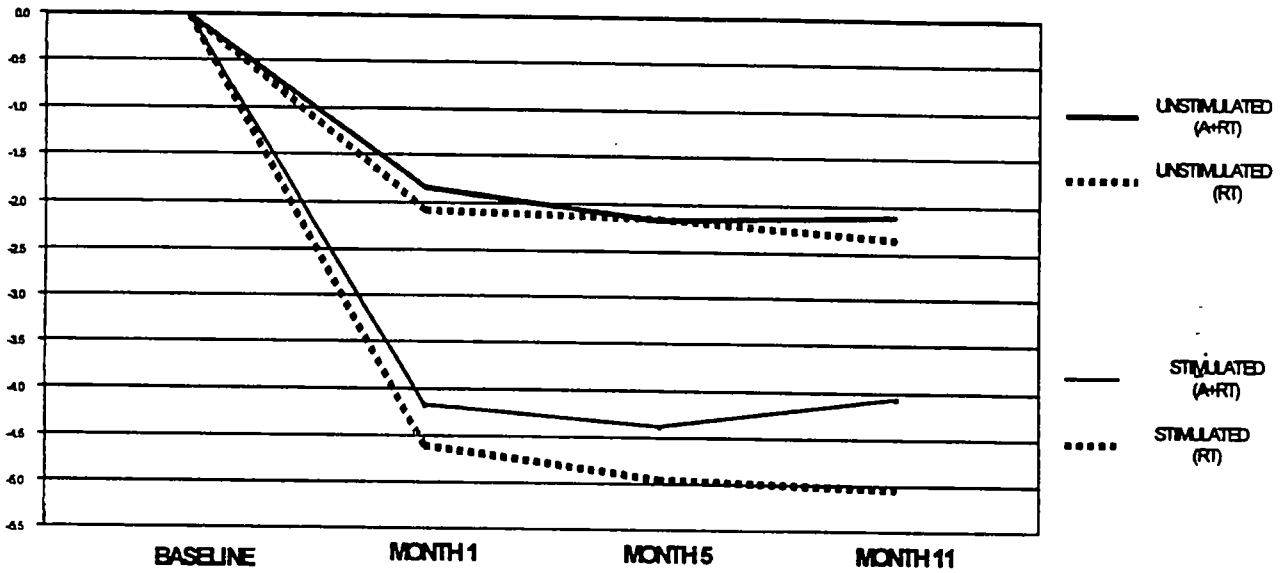
[11] Takahashi, et al., Clinical Study of the Radiatioprotective Effects of Amifostine on Chronic Radiation Injury. I.J. Radiation Oncology, 1986; (12) 935-938

It seems that the change in the salivary flow over time is also an important parameter. As such, a change from the baseline approach was employed by the FDA medical reviewer to assess the effect of RT on whole saliva production. A longitudinal analysis for the data on salivary collections was performed by the statistics reviewer, Dr. Clara Chen. (see review)

Table 17. FDA Summary Table of Salivary Measurements (grams)

	UNSTIMULATED		STIMULATED	
	A+RT (n=150)	RT (n=153)	A+RT N=150)	RT (n=153)
Baseline				
No. of Samples	149	147	145	145
Mean (gm)	2.86	2.97	5.53	6.09
Median (gm)	2.3	2.28	5.1	4.7
Month 1 (0-3 months)				
N(%)	98 (65)	110 (72)	98 (65)	108 (71)
Mean (gm)	1.01	0.9	1.38	1.50
Median (gm)	0.79	0.54	0.9	0.97
Change from Baseline Mean (gm)	1.85	2.07	4.15	4.59
Month 5 (3-6 months)				
N (%)	68 (45)	85 (56)	68 (45)	86 (56)
Mean	0.69	0.82	1.16	1.14
Median	0.34	0.49	0.52	0.50
Change from Baseline Mean (gm)	2.17	2.15	4.37	4.95
Month 11 (6-15 months)				
N (%)	57 (38)	67 (44)	68 (45)	62 (40)
Mean	0.75	0.62	1.48	1.05
Median	0.46	0.35	0.61	0.59
Change from Baseline Mean (gm)	2.11	2.35	4.05	5.04

Figure 4. Change from Mean Baseline Whole Saliva Measurements (grams of saliva)



		# OF PATIENT SAMPLES		
UNSTIM(A+RT)	149	98 (65%)	68 (45%)	57 (38%)
UNSTIM(RT)	147	110 (72%)	85 (58%)	67 (44%)
STIM(A+RT)	145	98 (65%)	68 (45%)	68 (45%)
STIM(RT)	145	108 (71%)	86 (58%)	62 (40%)

The median baseline measurements in the stimulated and unstimulated states were similar between treatment arms. There was a dramatic decline in both unstimulated and stimulated saliva measurements from baseline to one month after treatment. During follow-up, the change from baseline on unstimulated saliva collections was similar between treatment arms. The change from baseline in the stimulated saliva collections seems less in the A+RT arm compared to the RT arm. Note that despite the wide span of time for inclusion during follow-up, only 40-50% of patients had saliva collected on month 5s and 11. Contrary to the results of the sponsor's analysis, the medical officer's analysis suggests that patients in the A+RT arm may have been able to produce more saliva after stimulation compared to patients in the RT arm.

Reviewer's comment 12. FDA Review of Parotid Gland Saliva Collections and Scintigraphy Data

There were only 24 parotid gland saliva collections mostly done at baseline and 51 scintigraphy results. Due to the small numbers, no further analyses were done.

Sponsor's Review of Mucositis:

The primary endpoint to assess mucositis was the incidence of Grade 3 or higher acute mucositis occurring within 90 days from the start of radiation according to the RTOG Acute Radiation Morbidity Scoring Criteria. The onset of acute mucositis was calculated from the initiation of radiation to the first occurrence on the latest assessment date or study day 90 whichever came first. Duration of Grade 3 or higher acute mucositis was calculated from the first occurrence of the defined toxicity during the first 90 days to recovery (<Grade 2) or day 90 whichever came first. Median duration and p-value based on the log-rank test were also reported.

The difference in the incidence of Grade 3 or higher acute mucositis was not statistically significant (p=0.4767).

Table 18. Sponsor's Analysis of Acute Mucositis Using RTOG Acute Radiation Morbidity Scoring Criteria (Intent-to-Treat Analysis)

RTOG Grade	Amifostine + RT (n=148)		RT Alone (n=153)		p-value
0	8	(5%)	1	(1%)	
1	24	(16%)	22	(14%)	
2	64	(43%)	70	(46%)	
3	47	(32%)	57	(37%)	
4	5	(3%)	3	(2%)	0.1442[a]
Total Grade ¾	52	(35%)	60	(39%)	**0.4767**[b] (0.7215[c])

[a] Analysis of severity using Mantel Haenszel Chi-square test
[b] Fisher exact test
[c] Adjusted for multiplicity based on a permutation method in SAS PROC MULTTEST

(from NDA 20-221 v.10, p.71)

Less than 50% of patients on either treatment arm experienced Grade 3/4 mucositis. The median duration of Grade 3 or higher acute mucositis was similar between both treatment arms (p=0.6850).

Literature citation 8. Acute Mucositis

Mucositis is sensitive to changes in daily dose of radiation. At 170 rad to 180 rad five times weekly, the cell-killing and repopulation of mucous membrane stem cells are essentially in equilibrium, and maximal reaction is usually only intense erythema. At daily doses of more than 200 rads in a large treatment volume, the proliferative capacity of the mucous membrane stem cells is exceeded, and almost all patients develop confluent mucositis by the third week. [12] During treatment, symptoms of sore throat are usually maximal 2-3 weeks into the therapy, and thereafter diminish even though therapy is continued.

A randomized study conducted in Argentina was stopped early due to the lack of proof that amifostine provides protection against mucositis. Patients in this study were given amifostine, 200 mg/m^2 ± cisplatin 20 mg/m2 + 5-FU 300 mg/m2 on days 1-4 on weeks 1,4,7 and 10 alternating with RT 2 Gy/d weeks 2,3 and 1.5 Gy in two fractions par day on weeks 5-6, 8-9 with a total dose of 80 Gy. This study showed that among 22 of 29 patients who completed 4 weeks of therapy, the incidence of mucositis was 68.8% in Arm A (+amifostine) and 66.6% in Arm B. The difference for other toxicities and the frequency of delay in treatment was also not significant between the two arms. [13]

Reviewer's comment 13. Protection from Acute Mucositis

Standard dose radiation given in this study as daily, multiportal fractions without potentially radiosensitizing chemotherapy is not expected to result in a greater than usual incidence of severe mucositis. Study WR 9521: "A Phase 3 Randomized Double Blind Placebo Controlled Trial of Carboplatin and Radiation Therapy ± Amifostine in Patients with Head and Neck Cancer", was submitted to the agency on November 1996. This sample size proposed was 30 patients in each arm. It is possible that a difference in acute mucositis between treatment arms may be seen in this pilot phase 3 trial.

Reviewer's comment 14. Use of Prophylactic Medications for Mucositis

Concomitant use of prophylactic medications for mucositis was balanced between treatment arms. A total of 54 patients (35%) in the RT arm and 50 patients (33%) in the A+RT arm were given prophylaxis at the beginning of treatment.

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[12] Coulard H. Principles of x-ray therapy of malignant diseases. Lancet 227,1-8, 1984

[13] . Giglio, R. et al. Alternating Chemotherapy Plus Radiotherapy with Amifostine Protection for Head and Neck Cancer: Early Stop of a Randomized Trial, ASCO Program Abstract 1997

Sponsor's Analysis of Clinical Benefit

The Patient Benefit Questionnaire (PBQ) was used by the patients to rate their symptoms associated with xerostomia. The PBQ was administered at baseline, weekly while receiving therapy, and at follow up visits: month 1, 3, 5, 7, 9, and 11. The mean of the total score was calculated if at least six of eight questions were answered. Otherwise, it was considered missing.

Literature citation 9. Quality of Life Assessment

Saliva produced by the major salivary glands and mucus produced by the minor salivary glands protect the mucous membranes and teeth, lubricate the food bolus and facilitate eating and speaking. Saliva also has additional protective roles in acidity regulation an antimicrobial defense by immunoglobulin and non-immunoglobulin glucoproteins.[14] Decreased secretion of the salivary glands may lead to dry mouth symptoms such as oral pain and burning sensations, the loss of taste and appetite, as well as increased incidence of dental caries. One of the most distressing side effects of radiotherapy is alteration in taste function. As a consequence, patients may lose the desire to eat, reduce food intake, and limit the effectiveness of cancer therapy.[15] The average daily intake was nearly 300 kcal lower in the irradiated patients with dry mouth symptoms than in the control group of 24 patients treated for head and neck malignancies.[16] Saliva plays an important role in mastication, digestion, swallowing and speech. It provides lubrication for the oral tissues and protects them from bacterial infections. It also inhibits enamel decalcification is an important excretory organ.

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[15] Mossman. K. Frequent Short-Term Oral Complications of Head and Neck Radiotherapy.ENT Journal, 73:5 98-102, May 1994

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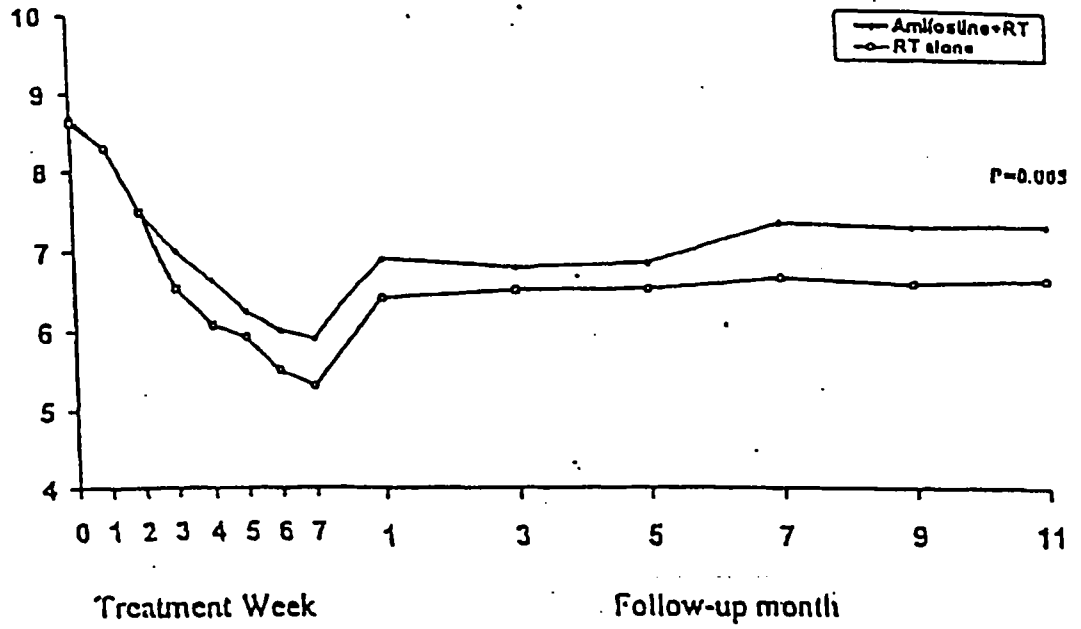

Figure 5 Comparison of overall mean score of PBQ in patients treated with RT ± amifostine for head and neck cancer.

Reviewer's comment 15. Analysis of PBQ Using Mean Scores

The meaning of each numbered response in the PBQ was not adequately described; therefore, a two point difference in the mean also cannot be concretely defined. In addition, calculating the mean score assumes that each question bears equal clinical significance and ignores bias that may be introduced by significant amounts of missing data.

In the table below, there is a deterioration in the mean total scores for both treatment arms, but the difference were mostly not statistically significant. However, there is a trend toward worse change from baseline scores in the RT arm both during treatment and at follow-up.

Table 19. Comparison of Changes in PBQ Mean Scores from Baseline or First Measure at Each Treatment and Follow-up Visit for Patients Treated With RT ± Amifostine for Head and Neck Cancer (Intent-to-Treat Analysis)

	A+ RT (n=150)		RT (n=153)			
Treatment Period	**Mean Change From Baseline**	**n (%)**	**Mean Change From Baseline**	**n**	**Difference in Mean**	**p-value**
Week 1	-0.42	143 (95)	-0.32	146 (95)	-0.10	0.430
Week 2	-1.14	131 (87)	-1.14	141 (92)	0.00	0.993
Week 3	-1.75	128 (85)	*-2.08*	135 (88)	0.33	0.130
Week 4	*-2.10*	128 (85)	*-2.60*	143 (93)	0.49	**0.038**
Week 5	*-2.53*	120 (80)	*-2.70*	140 (92)	0.17	0.518
Week 6	*-2.72*	115 (77)	*-3.16*	128 (84)	0.44	0.114
Week 7	*-2.78*	90 (60)	*-3.22*	95 (62)	0.44	0.198
Last treatment	*-2.84*	146 (97)	*-3.15*	150 (98)	0.31	0.242
Follow-up Period						
Month 1	-1.81	109 (73)	*-2.17*	123 (80)	0.36	0.189
Month 3	*-2.03*	102 (68)	*-2.07*	117 (76)	0.03	0.907
Month 5	*-2.05*	89 (59)	*-2.18*	102 (67)	0.13	0.657
Month 7	-1.59	85 (57)	*-2.06*	89 (58)	0.47	0.129
Month 9	-1.58	91 (61)	*-2.17*	94 (61)	0.60	**0.033**
Month 11	-1.62	83 (55)	-1.99	96 (63)	0.37	0.180

(NDA 20-221, v. 10, p.69)

Dental Consultant Comment: *The common way of using patient benefit questionnaires in this setting is to have a global and specific dryness questions that are treated as variables. They expressed doubts on the validity of the analysis of means and change from baseline.*

Sponsor's Longitudinal Analysis of the PBQ

A longitudinal analysis using the mixed models with spline functions was performed by the sponsor retrospectively in order to account for missingness in the mean scores and change from baseline analyses. Non-completers were defined as those patients with no PBQ data points beyond the month 5 follow-up visit. This cutoff time point was selected as a middle point in the course of 1 year follow-up. Completers had at least one data point beyond the month 5 follow-up visit (i.e., 7 months from the start of treatment). By the data cut-off date, there were 228 (76%) patients (113 patients in the amifostine + RT arm and 115 patients in the RT alone arm) being classified as completers who have some or all data available beyond the month 5 visit and 73 (24%) patients (36 patients in the amifostine + RT arm and 37 patients in the RT alone arm) classified as non-completers who have no data beyond the month 5 visit.

Using the mixed model, the PBQ data for completers was statistically significantly different from non-completers in the time trend analysis (p=0.0001) This indicates that missing data cannot be assumed to be random, and that completers should be analyzed separately from non-completers.

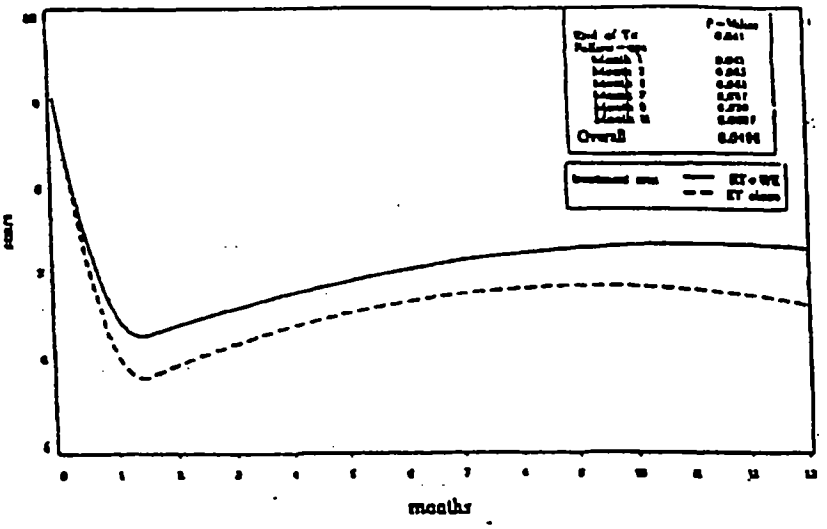

Figure 6. Graph of Mixed Model of Overall PBQ Scores for Completers

The above figure shows the data for completers. The differences at various time points were estimated and tested based on the mixed model. Statistical significance was seen at the end of radiation therapy (p=0.0408) and at the one-year follow-up (p=0.0067).

PBQ mean scores of non-completers were not significantly different between the treatment arms (p=0.2415). (see below)

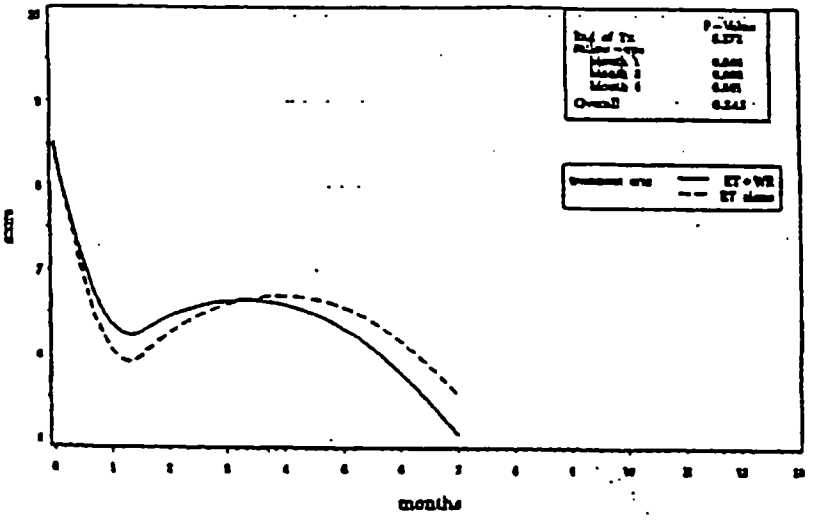

Figure 7.Graph of PBQ Scores for Non-Completers

It cannot be assumed that data is missing at random in the PBQ. The Laird-Ware model shows that the pattern of PBQ score is different in completers versus non-completers. The treatment effect is significant in patients with relatively complete data but not in patients with incomplete data.

Reviewer's comment 16. FDA Reviewer's Longitudinal Analysis of PBQ

Three parameters were identified as most clinically relevant: (1) Functional Well-being, which incorporates the results of questions 4 and 5 on the patient's ability to eat and speak; (2) Global Assessment of Dryness, which considered the results of question 1 on dryness; and (3) Use of External Aids, which incorporated questions 6 and 7. To deal with the pattern of informative dropout, the one year follow-up point was designated to group patients into dropouts and completers.

The FDA statistics reviewers (Drs. Clara Chu, Gang Chen)performed a longitudinal analysis of the PBQ data (see review for details) with the following important observations:

1. *Attrition of patients was significant after one year of follow-up but both treatment arms had similar rates.*
2. *There was no significant difference in treatment effect among drop-outs and completers for functional well-being and use of external aids.*
3. *There was a significant difference in treatment effect among drop-outs in the "general condition" parameter; but no difference among the completers*
4. *There was no evidence of long term clinical benefit in the A+RT group*

Sponsor's Analysis of Locoregional Tumor Control

All intent-to-treat patients (150 patients in the amifostine + RT arm and 153 patients in the RT alone arm) were eligible for the analysis of locoregional control at 1 year defined as time to local failure beyond day 396 (day 365 +31) with at least one record of NED on or beyond day 334 (day 365 + 31), or time to local failure censored between days 334-396 with no documentation of LRF. Patients were excluded from 1 year LRC ratio calculation if their time to local failure was censored before day 334 with no LRF or death with disease.

The primary analysis for antitumor efficacy was the ratio of locoregional tumor control (LRC) rates at 1 year (amifostine + RT/RT alone). Locoregional control was calculated from the start of therapy until documentation of locoregional failure (LRF) or death with disease. LRF was defined as follows:

1) Disease progression with positive local tumor status;
2) Disease progression with no information on tumor status in database.
3) Patients who entered the study with disease and did not experience any NED

4) Patients who entered the study with disease and did not experience any NED before an additional surgery for removing tumor.

For patients who did not experience death with disease or LRF, time to local failure was censored on the latest date with data. If a patient ended with "lost to follow-up", "disease status unknown", or "appointment not kept" without other information, the previous date of review was used as the censoring date.

There is no difference between the treatment arms with respect to locoregional tumor control: 72% (91/127) of the patients on A+RT arm and 71% (96/135) of the patients on the RT alone arm had locoregional control at 1 year (p=1.000). The ratio of the locoregional control rates is 1.008, with a corresponding 95% C.I. of (0.864,1.175).

Table 20. Antitumor Efficacy at 1 Year in Patients Treated With RT ± Amifostine for Head and Neck Cancer

	Amifostine + RT	RT Alone	p-value*
LOCOREGIONAL CONTROL	72%	71%	1.000
Locoregional control ratio	1.008		
Two-sided 95% Confidence Interval	(0.864, 1.175)		
Lower limit of 95% one-sided confidence interval	(0.886)		
Disease-Free Survival Rate[a]	74.6%	70.4%	0.861
Hazard Ratio[b]	1.035		
95% Confidence Interval	(0.702, 1.528)		
Overall Survival Rate[a]	89.4%	82.4%	0.0687
Hazard Ratio[b]	1.585		
95% Confidence Interval	(0.961, 2.613)		

* P-value based on log-rank test
[a] 1 year rates calculated using product-limit method
[b] Hazard ratio >1.0 is in favor of the amifostine + RT arm

Figure 8. Sponsor's Analysis of Disease-free survival

Figure 9. Sponsor's Analysis of Overall Survival

Reviewer's comment 17. FDA Concern Regarding Analysis of Tumor Control

The Agency expressed to the sponsor its concern regarding the adequacy of "the incidence of locoregional recurrence" to show that the addition of amifostine is not tumor protective. At planning meetings, the agency recommended that there should be 195 failure events in a study of 300 patients to yield 80% power to exclude a hazard ratio of 0.7. The FDA is still evaluating the adequacy of the data; however, it appears that they do not have the power to exclude such a possibility. An analysis of the overall survival and disease free survival by the sponsor also did not show a significant difference between treatment arms at one year of follow-up; however, the lack of events limits the power of these analyses. The design of the study also had limited power to detect a difference in antitumor efficacy or survival.

Table 21. Events and Hazard Ratios in Applicant's 18-month Tumor Efficacy Analysis

	Hazard Ratio (RT: A+RT)	Number of Events
Locoregional Failure	0.95 (0.64, 1.39)	103
Disease Free Survival	0.99 (0.69, 1.42)	107
Overall Survival	1.35 (0.87, 2.1)	76

Reviewer's comment 18. Study to Support Absence of Tumor Protection

The study report by Liu, et al summarized below was submitted by the sponsor for additional evidence against tumor protection by ethyol in patients who receive radiation therapy. Two year follow-up of patients treated did not show a significant difference in overall survival. Other efficacy and safety results of the study are not discussed.

Liu, et al[32] (Randomized Trial of Fractionated Radiation ± Amifostine in Patients with Inoperable, Unresectable or Refractory Rectal Cancer, WR-9001)

Study: Randomized, open-label, parallel group Phase III study in patients with advanced inoperable, unresectable or postoperative recurrent rectal adenocarcinoma.
Treatment: whole pelvis radiation with daily fractions of 2.25 Gy 4 days a week for 5 weeks to a total dose of 45 Gy ± amifostine administered at a dose of 340 mg/m^2 prior to each fraction of radiation. Following this, all

patients received a conedown of 7.2 Gy in four fractions. Inoperable and unresectable cases received a second conedown of 7.2 Gy.

Patients: A total of 104 patients were enrolled, of which 100 were evaluable for analysis of efficacy. Of these patients, 49 patients were randomized to the amifostine + RT arm and 51 patients to the RT alone arm.

Preservation of Antitumor Efficacy

Complete responses to treatment were seen in 16% of patients who received amifostine and radiation and in 10% of patients who received radiation alone. At median follow up of 24 months, the median duration of survival for the amifostine + RT arm was 15.0 months (95% confidence interval: 10.5 to 21.2 months) compared to 12.6 months (95% confidence interval: 10.1 to 19.3 months) for the RT alone arm . The hazard ratio is 1.000, with a 95% confidence interval of 0.647, 1.546.

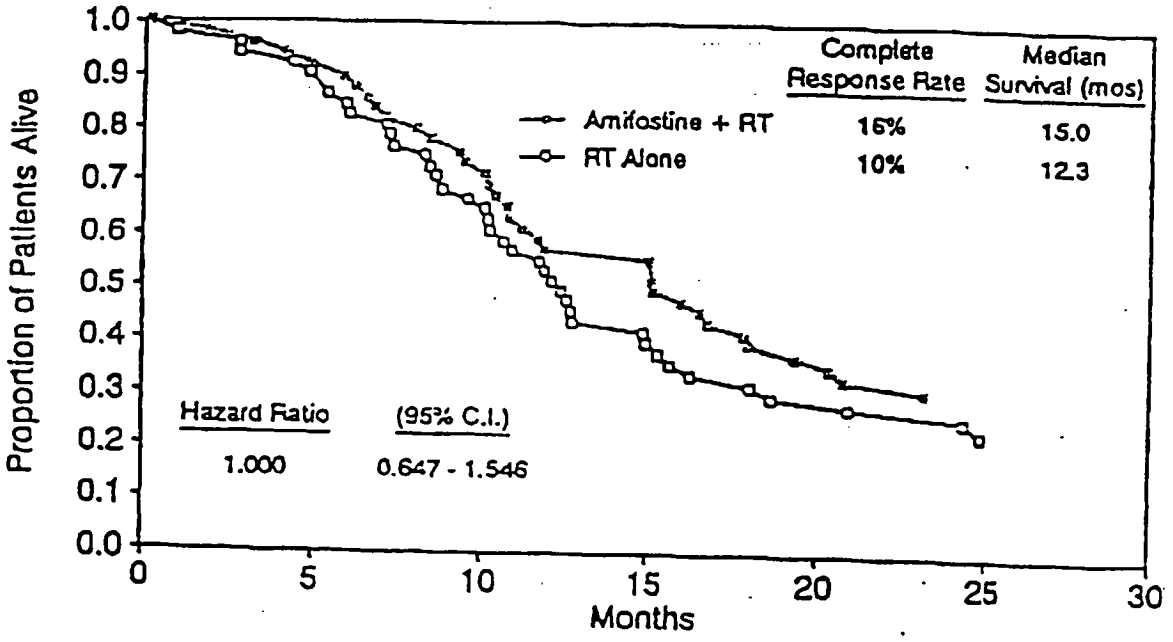

Figure 10. Survival curve for patients with advanced rectal cancer receiving radiation therapy pretreatment with amifostine

SAFETY RESULTS

Listings of all adverse events shows that the following events were reported in the amifostine + RT arm at a greater frequency and/or severity than was reported in the RT alone arm: nausea, vomiting, hypotension, fever, allergic reactions, and dizziness/lightheadedness, with nausea and vomiting being the most prevalent.

Table 22. Sponsor's Summary of the Incidence and Severity of Treatment-Related Adverse Events Associated With Amifostine

Adverse Experience	A+RT (N=150) n	(%)	RT (N=153) n	(%)	P value
Nausea					
Grade 3	4	(3%)	1	(1%)	0.2111
All Grades	66	(44%)	25	(16%)	**<0.0001**
Vomiting					
Grade 3	8	(5%)	0	—	**0.0033**
All Grades	55	(37%)	11	(7%)	**<0.0001**
Hypotension					
Grade 3	4	(3%)	0	—	0.0588
All Grades	22	(15%)	2	(1%)	**<0.0001**
Fever					
Grade 3	3	(2%)	0	—	0.1201
All Grades	12	(8%)	3	(2%)	**0.0174**
Allergic reaction[a]					
Grade 3/4	4[b]	(3%)	0	—	0.0588
All Grades	8	(5%)	0	—	**0.0033**
Dizziness/Lightheadedness					
Grade 3	0	—	0	—	—
All Grades	7	(5%)	0	—	**0.0068**
Fatigue/Lethargy					
Grade 3	1	(1%)	0	—	0.4950
All Grades	15	(10%)	11	(7%)	0.4177
Rigors/Chills					
Grade 3	0	—	0	—	—
All Grades	4	(3%)	1	(1%)	0.2111
Sneezing/Wheezing					
Grade 3	0	—	0	—	—
All Grades	4	(3%)	0	—	0.0588
Sleepiness/Somnolence					
Grade 3	0	—	0	—	—
All Grades	4	(3%)	0	—	0.0588
Flushing/Feeling of Warmth					
Grade 3	1	(1%)	0	—	0.4950

All Grades	3	(2%)	0	---	0.1201
Hypocalcemia					
Grade 3	0	---	0	---	---
All Grades	2	(1%)	0	---	0.2442
Hiccups					
Grade 3	1	(1%)	0	---	0.4950
All Grades	2	(1%)	0	---	0.2442

[a] Includes Patients 2814 (Grade 3 erythema) and 2826 (Grade 2 exanthema).
[b] One Grade 4 reaction was reported by Patient 2706: Following treatment with amifostine + RT from 11 March 1997 to 25 April 1997, an allergic reaction was noted within the radiation port. This patient also received carbamazepine/azalon powder (talcum powder/chamomile). On 26 April 1997, patient was hospitalized with broncho-pneumonia, fever, and generalized erythema multiforme. Investigator felt that RT, amifostine, carbamazepine/azalon powder may have contributed to the allergic reaction.

Discontinuation of Therapy Due to Adverse Events

Twenty-nine (19%) patients discontinued amifostine due to adverse events. All but one of these patients continued to receive radiation treatment until completion. The remaining 25 patients (15 prior to receiving 40 Gy of radiation and 10 after receiving >40 Gy of radiation) discontinued amifostine for the following adverse events: nausea/vomiting (13 patients), allergic reactions/rashes (4 patients), hypotension (3 patients), fever (2 patients), drowsiness (1 patient), cachexia (1 patient), and hand cramps, tingling hands, Trousseau's Syndrome, anxiety, weariness in lower extremities, and increased amylase (1 patient).

Reviewer's comment 19. Discontinuation of Therapy Due to Amifostine Side Effects

This is a large number of amifostine drop-outs despite a lower dose of amifostine used in this study. This may affect the ability to detect a difference in late xerostomia and tumor protection between treatment arms.

Deaths

Four patients, two (Patients 803 and 4001) on the amifostine + RT arm and two (Patients 802 and 1801) on the RT alone arm died during or within 30 days following the completion of protocol therapy. All four of these deaths were considered by the investigator to be unrelated to amifostine or radiation.

Missed Radiation Therapy

Treatment breaks were allowed for healing of severe normal tissue reactions (i.e., confluent mucositis), amifostine-associated reactions, equipment failure, etc. There were 277 treatment breaks (6%) in the amifostine + RT arm and 209 treatment breaks (4%) in the RT alone arm.