

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0315

A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED PHASE III STUDY TO DETERMINE THE EFFICACY OF SANDOSTATIN LAR® DEPOT (OCTREOTIDE ACETATE) IN PREVENTING OR REDUCING THE SEVERITY OF CHEMORADIATION-INDUCED DIARRHEA IN PATIENTS WITH ANAL OR RECTAL CANCER

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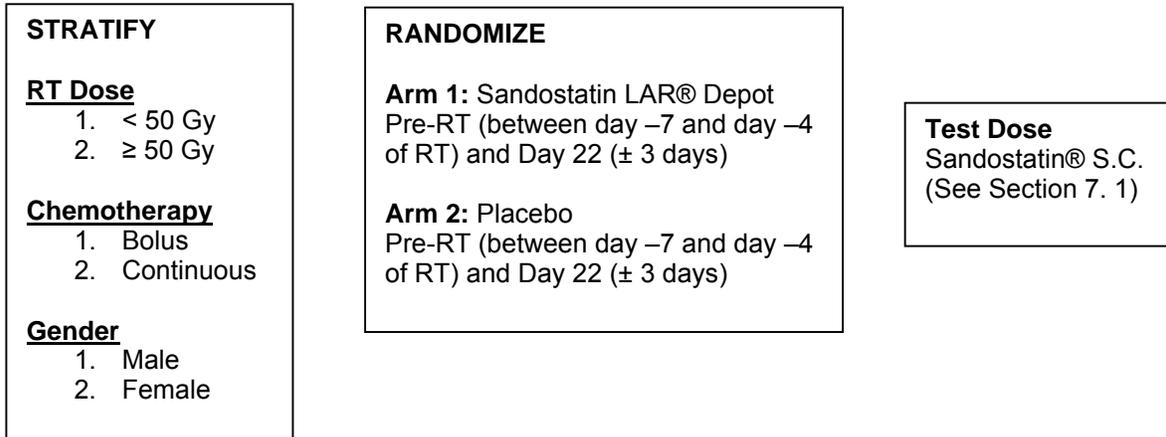
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SCHEMA



Eligibility: (See Section 3.0 for details)

- Current histologic proof of anal or rectal cancer without metastasis beyond pelvic regional nodes
- Planned to receive full course radiotherapy with concurrent chemotherapy as specified in Sections 6.1 and 7.2 (patients who have received prior chemotherapy for any reason are eligible); hyperfractionated, split course radiotherapy, and/or planned brachytherapy prior to completion of external beam radiation therapy is not allowed.
- Patients must ≥ 18 years of age.
- No prior pelvic radiation therapy or radiation for abdominal cancer
- Patients must have no known allergy/hypersensitivity to Sandostatin® (octreotide acetate) or other related drugs/compounds.
- Patients who have previously received Sandostatin® for cancer therapy-related diarrhea are excluded.
- Patients with a history of chronic or acute regional enteritis, malabsorption syndrome(s), or other history of inflammatory bowel disease are not eligible.
- Patients with uncontrolled diabetes or history of cholecystitis or gallstones (unless cholecystectomy was performed) are excluded.
- Patients with a history of hepatic disease are excluded (patients with LFTs < 3x the upper limit of normal are eligible).
- No uncontrolled diarrhea (≥ grade 2) or any incontinence of stool at baseline
- Patients with a colostomy or patients who have had abdominal-perineal resection or other surgery leaving the patient without a functioning rectum are excluded.
- No glucocorticoid therapy, insulin sensitizers, or exogenous growth hormone within 6 months of study entry

(Continued on next page)

- Patients who have received investigational drugs within 30 days of study entry are excluded.
- Pregnant or lactating women are ineligible as treatment involves unforeseeable risks to the participant and to the embryo or fetus.
- Patients who are known to be HIV positive are excluded as the risk of uncontrollable diarrhea is greater in this population.
- Patients must sign a study-specific informed consent prior to study entry.

Required Sample Size: 226

RTOG Institution # _____
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Case # _____

ELIGIBILITY CHECKLIST (12/5/03)
(Page 1 of 3)

- _____(Y) 1. Is the patient 18 years or older?
- _____(Y) 2. Is there current histologic proof of anal or rectal cancer without metastasis beyond pelvic regional nodes?
- _____(Y) 3. Does the planned course of radiation therapy (RT) fall within the parameters outlined in Section 6.1
- _____(Y) 4. Is patient scheduled to receive chemotherapy as specified in Section 7.2? (Patients who have received prior chemotherapy for any reason are eligible.)
- _____(N) 5. Is there uncontrollable (significant) diarrhea at baseline (CTCAE v. 3.0 \geq grade 2)?
- _____(N) 6. Does patient have known allergy or sensitivity to Sandostatin® acetate?
- _____(N) 7. Is there history of chronic or acute regional enteritis, malabsorption syndrome(s) or any other history of inflammatory bowel disease which may exacerbate the radiation toxicity?
- _____(N) 8. Has patient undergone abdominal-perineal resection or other surgical procedure leaving the patient without a functioning rectum?
- _____(N) 9. Uncontrolled diabetes? Controlled diabetics (\leq 250 mg/dL) may participate.
- _____(Y/N) 10. Does patient have a history of cholecystitis or gallstones?
_____(Y) If yes, has a cholecystectomy been performed?
- _____(Y/N) 11. Does patient have a history of hepatic disease?
_____(Y) If yes, are the LFTs $<$ 3x the upper limit of normal?
- _____(Y) 12. Have the pretreatment evaluations specified in Section 3.1.6 been completed?
- _____(N) 13. Is there any medical condition or impairment (including mental that may interfere with the patient's ability to receive planned protocol treatment or comply with study requirements?
- _____(N) 14. Is patient scheduled for hyperfractionated or split course RT (with planned break in-between)?
- _____(N) 15. Any incontinence of stool prior to entry on the study?
- _____(N) 16. Any planned brachytherapy boost prior to completion of all external beam radiation therapy, or following the completion of primary RT?
- _____(N) 17. Has the patient received pelvic irradiation or radiation for abdominal cancer?

(Continued on next page)

RTOG Institution # _____
RTOG 0315
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ELIGIBILITY CHECKLIST (12/5/03)
(Page 2 of 3)

- _____(N) 18. Is the patient pregnant or lactating?
_____(N) 19. Has the patient been diagnosed as HIV positive?
_____(N) 20. Did the patient ever previously receive Sandostatin® for cancer therapy-related diarrhea, or any other investigational drugs in the past 30 days of study entry?

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 Initials (First-Middle-Last) [initials as of 5/03; if no middle initial, use hyphen]
_____ 6. Verifying Physician
_____ 7. Patient's ID Number
_____ 8. Date of Birth
_____ 9. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
_____ 10. Race
_____ 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?

(Continued on next page)

RTOG Institution # _____
RTOG 0315
Case # _____

ELIGIBILITY CHECKLIST (12/5/03)
(Page 3 of 3)

- _____ 16. Medical Oncologist
- _____ 17. Specify RT dose (< 50 Gy or ≥ 50 Gy)
- _____ 18. Specify chemotherapy (Bolus vs. Continuous)
- _____ 19. Treatment Start Date
- _____ 20. Treatment Assignment

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.

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Background

Radiotherapy, a cornerstone in the management of anal canal and rectal cancer, has concomitant acute and late intestinal effects that sometimes result in dose modification or interruption of treatment. Acute radiation enteritis (diarrhea), the most common characteristic of acute radiation effects in pelvic radiotherapy, is an uncomfortable and intolerable side effect. The addition of chemotherapy often exacerbates the onset, severity, and debilitation related to diarrhea, sometimes resulting in dose modification, delay or interruption of treatment.¹ Most critical in the treatment delivery is the ability to deliver planned doses with limited hazardous reactions to normal tissues and without interruption of treatment and possible compromise of the expected curative potential. Acute enteropathy with diarrhea is usually observed after administration of 18 to 22 Gy with conventional fractionation; virtually all patients are affected following radiation doses of 40 Gy or earlier on treatment with combined chemoradiation.²

Diarrhea is often characterized by increased frequency of stools, increased urgency, altered consistency of stools, and abdominal pain or discomfort. Tenesmus, mucus, blood, or dehydration may also be associated with uncontrolled diarrhea. The intensity of these symptoms may vary among individual patients; however, these symptoms may significantly interfere with patients' daily activities and overall quality of life.³⁻⁴ Interruption in treatment may result in clinical as well as financial implications for the patient and the health care system as a whole. Thus, it is crucial to administer the full dose of radiation therapy in the planned timeframe not only to maximize the rate of tumor control, but also to minimize the length of treatment, excess utilization of healthcare resources, and financial costs associated with delays or interruption in treatment.

1.2 Rationale

Unfortunately, to date there are no prophylactic measures effective in preventing the incidence of enteritis during chemoradiation. The diarrhea sometimes responds to such simple measures as low residue diet, administration of Kaopectate, or an adjustment of the daily dose of radiation or modification of chemotherapy dose and timing of administration. However, stronger and repeated measures are frequently required to control the diarrhea such as narcotics (paragoric, codeine phosphate, morphine) and narcotic analogues (diphenoxylate with atropine, loperamide). A recently convened panel of experts identified problems in the assessment (lack of standard tools) and management of cancer treatment related diarrhea. The panel of clinical oncology experts recommended loperamide as initial therapy for low-grade diarrhea (NCI Common Toxicity Criteria [CTC] v. 2.0 grades 1-2) and octreotide (Sandostatin® S.C.) for management of persistent (CTC grades 1-2) and severe (CTC grades 3-4) diarrhea.⁵ However, none of these measures can be administered effectively and continuously for the duration of radiation to prevent diarrhea.

It is obvious that by reducing the chemoradiation-induced bowel symptoms the patient's quality of life during (and following) therapy can be enhanced. Additionally, minimizing the severity of radiation-induced enteritis may increase the probability of completing the planned treatment without interruption. It also is expected that effective management/prevention of severe diarrhea would avoid hospitalization for complications such as dehydration, fluid and electrolyte imbalance, or nutritional decline. Octreotide (Sandostatin®), a drug that inhibits gastrointestinal motility and pancreatic secretion, and increases intestinal absorption, is a promising agent for this setting (see Section 1.4.2). Consequently, we propose a prospective randomized trial to evaluate the efficacy of Sandostatin LAR® Depot in the prevention and management of diarrhea in patients receiving pelvic radiation therapy with chemotherapy as adjuvant or primary treatment for anorectal malignancies. This study will examine the ability of Sandostatin LAR® Depot to prevent or reduce the incidence of severe or life threatening diarrhea and its impact on quality of life.

1.3 Incidence and Severity of Radiation Enteritis in Patients Irradiated for Pelvic Malignancy

In a multi-institutional study involving adjuvant radiation therapy (RT) for rectal cancer, 35% of the patients treated with pelvic RT with concurrent chemotherapy (5-FU) experienced \geq grade 2 diarrhea. The incidence of \geq grade 3 diarrhea was reported at 20% and 5% for RT/5-FU and RT alone patients, respectively.⁶ The toxicities in this study were evaluated using the Mayo Clinic/North Central Cancer Treatment Group Toxicity Criteria. This frequency-based rating scale grades diarrhea based on increase in frequency of stools per day from pretreatment baseline.

The range of scores is from 0 to 4 with 0 being no diarrhea and 4 representing the highest level of diarrhea.

In a review of four studies, Dewit and colleagues reported rates of intestinal complications.⁷ These authors reported rates ranging from 6% to 38% for mild intestinal complications, and 0% to 10 % for severe acute intestinal complications. Each of the studies reviewed used a different instrument to grade acute toxicities, and the definition of intestinal complications was not consistent. More recently, there has been increased attention on characterizing diarrhea and developing management recommendations.^{5,8} A recent review of the literature and panel of experts reported high rates of diarrhea in patients receiving standard doses of 5-FU, cisplatin, or CPT-11 chemotherapy regimens.^{5,8} Rates of diarrhea are estimated to be 50% to 80% depending on disease site and treatment regimen.^{7,9} Rates of severe (CTC or RTOG acute grade 3-4) diarrhea were as high as 18% to 40% depending on chemotherapy regimen.^{5,9} A recent national survey of oncology nurses⁴ reported the following perceived incidence rates of diarrhea by modality:

Chemotherapy	Radiation Therapy	Diarrhea Severity	Incidence
5-FU (+LV)		Any grade	31% to 66%
Cisplatin		Any grade	43%
CPT-11		Any grade	74% to 87%
	pelvis/abdomen	Any grade	20% to 49%

The impact of chemotherapy-related diarrhea in patients treated for colorectal cancer is evident in the following data: Arbuckle reported that 56% of patients required alterations to their treatment regimens.¹ Specifically, 15% discontinued treatment, 22% required dose reduction, 8% experienced delayed dosing administration, 11% experienced more than one adjustment in treatment. These findings, suggest that chemoradiation-induced diarrhea may similarly produce clinically important discontinuation or alterations of treatment.

Overall, these findings on incidence and management of acute radiation enteritis are difficult to compare because of differences in patient selection, sample sizes, total radiotherapy dose, chemotherapy regimens used, measurement tools used, and methods of statistical analysis. Wadler and colleagues provide a comprehensive review of these issues and offer recommendations for managing chemotherapy induced diarrhea and *acknowledge the need for additional studies to elucidate both the assessment and management of diarrhea.*⁵ Additionally, the economic costs and quality of life impact of diarrhea related to uncontrolled diarrhea are not well understood. Nevertheless, the clinical importance of the problem is evident.

1.4 Preliminary and Theoretical Evidence Supporting the use of Sandostatin®

1.4.1 Pathophysiology of Radiation Enteritis

Although the exact pathophysiology of radiation-induced enteritis is not well understood, it has been proposed that radiation enteritis results from intestinal dysfunction and hypermotility related to acute damage of the gastrointestinal mucosa. Acute damage of surface epithelium results in malabsorption of glucose, fats¹⁰ and electrolytes. Decreased fat absorption characterized by high fecal fat values¹⁰ and decreased serum glycerol trioleate, lactase enzyme deficiency¹¹ and fecal bile salt alterations¹²⁻¹³ are important factors in the pathogenesis of diarrhea in pelvic and abdominal irradiation. Excess bile salt in the colon induces water and electrolyte secretion, producing diarrhea. The effect of bile on radiation enteritis was pointed out by researchers who studied this problem in rats.¹⁴ These authors concluded that it was the mucolytic action of bile which contributed to the development of radiation enteritis. Bile salts may deplete the intestinal mucus cap causing increased permeability of the mucosa and subsequent transudation and loss of sodium and water. Cholestyramine, a nonabsorbable ion exchange resin that binds bile acids before their passage into the colon, has been found to be effective in preventing radiation-induced diarrhea.¹⁵⁻¹⁶

Two recent reviews of the literature also suggest that the pathophysiologic factors of chemotherapy-induced diarrhea also are not completely understood. A multifactorial process that results in imbalance between absorption and secretion in the small bowel is described.^{5,9} Some chemotherapy agents including 5-FU and CPT-11 produce acute damage to intestinal

mucosa resulting in loss of epithelium, superficial necrosis, and inflammation of the bowel. This produces a shift in balance between the number of secretory and absorptive cells and leads to abnormal absorption and secretion of fluids and electrolytes. Moreover, opportunistic infections and other inflammatory processes may occur leading to imbalance between secretion and absorption resulting in increased fluid volume and electrolytes in the colon and leads to diarrhea. Persistent or severe loss of fluids and electrolytes due to uncontrolled diarrhea may result in life-threatening dehydration, renal insufficiency and electrolyte imbalances.

1.4.2 Importance of Sandostatin (octreotide acetate) as an Antidiarrheal Agent

Octreotide, a drug that inhibits gastrointestinal motility and pancreatic secretion, and promotes intestinal absorption, is a promising agent for this setting. A handful of published studies have evaluated the efficacy of octreotide in the treatment of patients with chemotherapy-induced diarrhea, short-bowel syndrome, AIDS-associated diarrhea and other conditions with chronic diarrhea not responding to standard treatment. Petrelli et al.¹⁷ treated sixteen patients with colorectal carcinoma receiving 5-FU and high dose leucovorin; the patients had CTC grade 3-4 diarrhea not responding to maximum dose of diphenoxylate. The patients were given octreotide continuous infusion 50 mcg/hr for 12 hours, followed by 100 mcg/hr for 12 hours, and subsequently, to 150 mcg/hr for 12 hours. All patients had bowel rest and intravenous fluid hydration. Complete resolution of diarrhea was seen in 15 of 16 patients (94%). In four patients the resolution of diarrhea was achieved during the 100 mcg/hr infusion, and in 11 patients resolution was achieved during the 150 mcg/hr infusion. Recurrence of diarrhea occurred in two patients after a complete cycle of octreotide infusion. Both patients were restarted on octreotide infusion 150 mcg/hr for 72 hrs with resolution of diarrhea within 36 hrs. No toxicity related to octreotide infusion was reported in this trial.

Cascinu et al. conducted a randomized comparison of octreotide S.C. to loperamide in patients having grade 3 diarrhea secondary to therapy with 5-FU chemotherapy (N=41).¹⁸ Diarrhea resolved within three days of therapy in 19 out of 21 patients in the octreotide arm and only 3 out of 20 patients in the loperamide arm. Ten patients on the loperamide arm and only one on the octreotide arm required hospitalization for parenteral rehydration of fluids and electrolytes. Median frequency of stools over three days of therapy was four, three, and zero for octreotide arm and five, five, and five in the loperamide arm. Cascinu also studied the effect of octreotide in patients with cisplatin-induced diarrhea in 43 patients randomized to receive octreotide S.C. versus placebo and found significant differences ($p<.01$).¹⁹ Ninety-five percent response was observed in the treatment arm, and only 25% response was noted in the placebo arm.

Another recent study by Cascinu et al. found that high-dose loperamine is effective only in patients with mild diarrhea and concluded that octreotide S.C. was more suited for managing severe chemotherapy-induced diarrhea than loperamide in patients with colorectal cancer.²⁰

Gebbia conducted a randomized comparison of octreotide S.C. to loperamide in patients having WHO grade 3-4 diarrhea secondary to therapy with 5-FU chemotherapy (N=40).²¹ Diarrhea resolved (no loose bowel movements) in 80% (16 out of 20) of patients in the octreotide arm and 30% (6 out of 20) of patients in the loperamide arm. These differences were statistically significant ($p<.001$).

In a phase I study to determine the maximum tolerated dose and dose limiting toxicities of octreotide S.C. for treating 5-FU chemotherapy induced diarrhea, Wadler et al. concluded that octreotide was safe and cost effective even at higher doses because of the potential for reduced hospitalization.⁵ Thirty-five patients with CTCAE grade 2 or greater diarrhea were treated with 11 dosage schedules (3 patients at each dose level). Doses ranged from 50 μ g to 2,500 μ g administered t.i.d. for 5 days. Diarrhea was resolved in 57% (28/49), improved in 16% (8/49), and unchanged or worsened in 27% (13/49) of courses delivered. (Some patients who completed a course of therapy were re-treated at higher doses if a new episode of diarrhea occurred). A dose response relationship was noted with more complete responses noted for higher doses of octreotide ($p=.01$) and more patients on higher doses completed therapy ($p=.04$). The following toxicities were documented at doses $>2,000$ μ g: nausea, light headedness, rash, and hypoglycemia.

Goumas observed a higher response rate with a higher dose (500 µg vs. 100 µg) of octreotide S.C. in patients with CTCAE grade 3-4 diarrhea secondary to treatment with the 5-FU regimen.²² Octreotide acetate was well tolerated by all patients. Complete resolution of diarrhea was achieved in 17 of 28 (60.71%) patients treated with 100 µg and in 28 of 31 (90.32%) patients treated with 500 µg of octreotide ($p < 0.05$).

Overall, most studies have shown that octreotide is useful in the management and control of severe diarrhea but not early diarrhea. There are virtually no studies evaluating the ability of Sandostatin LAR® Depot, the long acting, delayed release, formulation of octreotide, in preventing and reducing the onset of grade 3 or 4 diarrhea. A randomized, controlled trial to evaluate the prophylactic use of octreotide in cancer treatment-induced diarrhea is needed.

1.4.3 Pilot data on Sandostatin® S.C. in Radiation-Induced Diarrhea

The role of Sandostatin® in the prevention and treatment of radiation-induced diarrhea is not well established. Kennedy et al. studied the effect of Sandostatin® in patients with colorectal carcinoma receiving 5 FU or 5 FU-leucovorin or pelvic RT.²³ Eleven patients with severe diarrhea unresponsive to lomotil, imodium plus cholestyramine, received Sandostatin® 50 mcg S.C. t.i.d. All patients had total cessation of watery diarrhea within hours (median 12.4 hrs, range 4-34 hrs). Except for pain at the site of injection, no side effects of therapy were noted. Three patients required a higher dose of 100mcg. There was no need to continue Sandostatin® more than 1-3 days.

Yavuz et al. compared Sandostatin® with lomotil (diphenoxylate with Atropine) for the treatment of radiation enteritis.²⁴ Thirty-two patients with grade 2-3 diarrhea during pelvic radiotherapy for cervical (9), bladder (13), endometrial (4), and rectal (6) cancers were entered into the study. Radiation therapy was delivered using high-energy photons to a total of 45 Gy in conventional fractionation. Sixteen patients received Sandostatin® at a dose of 0.1mg S.C. t.i.d., and 16 patients received diphenoxylate 10 mg orally per day. Diarrhea resolved in 13 patients in the Sandostatin® arm (4 within the first day, 6 within the second day and 3 within the third day) versus only 3 (all within the second day of therapy) in the diphenoxylate arm ($p < .005$). Thirteen of 16 patients in the diphenoxylate arm and 3/16 patients in the Sandostatin® arm required discontinuation of radiotherapy for median of 5.4 (+/-4) and 0.6 (+/-1.3) day respectively ($p = .001$). We need a larger randomized study to examine the efficacy and impact of Sandostatin in patients getting chemoradiation for ano-rectal cancer.

1.5 **Problems in Diarrhea Assessment**

A critical component in this study is the accurate assessment of incidence, severity, and duration of diarrhea. This requires active and timely communication with the patient and integration of the patient's and clinician's perspectives of the problem. Since diarrhea is a multifocal problem often attributed to multiple causes including the cancer itself, chemotherapy, radiation therapy, or infection, the problem of diarrhea must be assessed diligently at various points in the spectrum of cancer care. To date there is no adequately validated tools for assessing diarrhea in the patient undergoing cancer treatment.⁸

The Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE) is the most commonly used tool in oncology clinical trials [formerly the Common Toxicity Criteria, (CTC) version 2.0]. This tool classifies diarrhea into four grades (1-4) of severity. The grade of severity is driven by frequency of stool (increase above baseline) for grades 1-3 and by physiologic consequences for grade 4. The tool also differentiates between patients with and without colostomy. However, the CTCAE has major limitations related to lack of focus on consistency of stools, discomfort, urgency of stools, volume of stools, and impact on the patient's quality of life. A comprehensive, widely-used assessment measuring quantitative frequency, severity, duration, and volume of diarrhea does not exist. Thus, the CTCAE will be used in this study in conjunction with other tools to maximize the assessment of salient aspects of diarrhea; the Diarrhea Assessment Scale (DAS) will be used for concurrent assessment of diarrhea for correlation with CTCAE diarrhea scale. Although use of these two measures still may not adequately address the deficiencies in diarrhea assessment, it is an improved step toward comprehensive assessment of diarrhea.

1.5.1 Diarrhea Assessment Scale (DAS)

The DAS is a four-item tool developed at the applicant institution and has been published.²⁵ This self-administered tool uses a four-point, Likert-type response scale to measure the presence and severity of diarrhea and takes less than five minutes to complete. The tool assesses four main characteristics of diarrhea: consistency, frequency, urgency, and abdominal discomfort. The DAS was developed based on careful review of the literature to include these components of diarrhea. The patient rates each of the components on a 0 to 3 scale; scores are summed, providing a total score ranging from 0 to 12. The total score is empirically categorized as follows: 0-3=No diarrhea, 4-6=mild diarrhea, 7-9=moderate diarrhea, and 10-12=severe diarrhea. This tool has undergone formal psychometric testing among healthy volunteers and patients receiving pelvic radiation therapy. Construct validity of the DAS was studied using the known groups method. Scores of a group of apparently healthy adults (n=20) were compared with those of a group of men receiving radiation therapy for cancer of the prostate (n=20). A significant difference ($p<.0001$) between groups supports the validity of the scale. The mean score for the patient group was 7.85 (SD = 1.35). Reliability was estimated using the combined sample (n=40). Internal consistency reliability yielded a coefficient alpha of 0.87, which is acceptably high.²²

The DAS also was used in an unpublished study of quality of life in patients who received definitive radiotherapy for prostate cancer (n=70).²⁶ Preliminary psychometric testing using data from 70 patients on this study showed adequate reliability. Internal consistency reliability produced a Cronbach alpha of 0.76. Test-retest reliability coefficients for the different areas of the instrument ranged from 0.42 to 0.82.

1.6 Quality of Life Measurement

Cancer therapy has pronounced effects on general health related quality of life as well as selected areas of function (symptoms). Thus, the effect of Sandostatin® in reducing the impact of therapy on quality of life will be assessed using three self-administered tools concurrently: a general health related quality of life tool, the Quality of Life Radiation Therapy Instrument (QOL-RTI), and two bowel and urinary functioning quality of life tools. These tools have been selected for their relevance to the salient aspects of quality of life in this patient population. The salient characteristics and psychometric properties (reliability, sensitivity, validity, and responsiveness to change) are summarized below.

1.6.1 Quality of Life-Radiation Therapy Instrument (QOL-RTI)

The patient-administered, 25-item QOL-RTI is a comprehensive general health-related quality of life instrument designed for patients who are treated with radiotherapy for malignant disease (Appendix VI). The scale uses an 11-point Likert-type scale ranging from 0 to 10 and takes less than 10 minutes to complete. This questionnaire is designed to assess 4 domains of health-related quality of life: general quality of life; functional/health; socioeconomic/family functioning; emotional/psychological functioning. Each domain contains several radiation therapy-specific items intended to assess the impact of the radiation treatment. This instrument has undergone reliability and validity testing. The internal consistency reliability yielded coefficient alpha of ≥ 0.81 and test-retest produced correlation coefficients ≥ 0.75 .²⁶⁻²⁷ This instrument has demonstrated adequate validity based on correlations with the Ferrans and Powers QLI and with the FACT-G, both well validated general quality of life tools.²⁷⁻²⁸ It is expected that the summary quality of life scores will be sensitive to changes in quality of life due to the efficacy of octreotide; higher quality of life scores are expected for the octreotide group. The instrument's sensitivity and responsiveness to change over time were demonstrated.²⁸

1.6.2 The Expanded Prostate Cancer Index Composite (EPIC)

The EPIC is a robust and comprehensive 50-item prostate cancer instrument based on the 20-item Prostate Cancer Index (PCI) and includes separate and distinct urinary and bowel modules that can be administered independently of each other and separate from the rest of the instrument.²⁹ These modules address salient issues relevant to the overarching concerns (patient function and bother) of patients receiving pelvic irradiation. The EPIC bowel and urinary subscales require approximately five minutes to complete and will be used to assess disease-specific quality of life prospectively. Reliability and validity were assessed by test-retest correlation, Chronbach's alpha coefficient, interscale correlation, and EPIC correlation with other validated health related quality of life instruments including the FACT-P, AUA-Symptom

Index, and the Medical Outcomes Short Form (SF-12). The instrument demonstrated high test-retest and internal consistency reliability for the subscales (urinary, bowel, sexual, and hormonal domain summary scores) with $r \geq .80$ and Chronbach's alphas ≥ 0.82 . However, other than prostate patients, the tool has not been tested with other male patients or female patients receiving pelvic irradiation. Thus, another disease-targeted questionnaire, albeit less comprehensive, the Functional Alterations due to Changes in Elimination (FACE) developed by Watkins-Bruner³⁰ will be used in this study in combination with the EPIC bowel and urinary subscales.

1.6.3 Functional Alterations due to Changes in Elimination (FACE)

The FACE, designed to measure the construct of intrusion on daily functioning caused by changes in elimination as measured by two subscales, has been used in a phase III study of Pentosanpolysulfate (PPS) in treatment of GI tract sequelae of radiotherapy, RTOG 98-09. This study includes male and female patients who have received prior abdominal or pelvic radiotherapy. The two subscales of FACE are Changes in Urinary Function (CUF) and Changes in Bowel Function (CBF). This tool has demonstrated adequate reliability and validity. Correlations between CUF and the Functional Assessment of Cancer Therapy (FACT) range from 0.35 to 0.79 (RTOG 98-09). The psychometric properties of the CBF have not been established.²⁹ This one-page tool requires less than five minutes to complete.

1.7 Study Hypotheses

The primary endpoint of this trial is the effectiveness of Sandostatin LAR® Depot in reducing the incidence of severe or life-threatening (CTCAE grade 3 or 4) diarrhea. The efficacy hypothesis is that Sandostatin LAR® will result in statistically significant reduction in grade ≥ 3 diarrhea compared to placebo.

Two secondary hypotheses will be evaluated, one related to quality of life outcomes and the other related to economic impact. The quality of life hypothesis is that the reduction in the severity of diarrhea will result in statistically significant changes in quality of life that are meaningful to the patient. The QOL-RTI and FACE scores will be used to determine the patient's self-assessment of the impact of diarrhea and interference in daily activity. Since patients are still undergoing radiotherapy, it is expected that the active treatment group will have better scores than patients in the placebo control group on the QOL-RTI (higher total score) and the FACE (lower CBF scores).

The economic impact hypothesis will assess whether the reduction in severity of diarrhea is associated with fewer hospitalizations due to complications of diarrhea, and lower utilization of other anti-diarrheal medications. The treatment group is expected to be associated with lower health care resource utilization because of better diarrhea control during and after treatment.

In addition, the QOL-RTI, FACE (CBF), EPIC-Bowel, DAS, and the CTCAE diarrhea scale will be correlated with each other to assess validity of the DAS and the EPIC Bowel Function subscale in this population. This study also should help to determine whether the DAS, FACE-CBF, and EPIC Bowel Function scale are sensitive to change over time.

2.0 OBJECTIVES

2.1 Primary Objective

2.1.1 To determine the ability of Sandostatin LAR® Depot to prevent the incidence of severe or life-threatening diarrhea (CTCAE v 3.0 grades 3-4)

2.2 Secondary Objectives

2.2.1 To assess differences in quality of life outcomes between the treatment and placebo group

2.2.2 To determine number of hospitalizations and use of antidiarrheal agents (Imodium), related to diarrhea (or its complications)

2.2.3 To assess treatment delays (interruptions) and/or dose reductions (chemotherapy and radiation therapy)

2.2.4 The validity of the Functional Alterations due to Changes in Elimination (FACE-CBF), the Diarrhea Assessment Scale (DAS), and the Expanded Prostate Cancer Index Composite (EPIC-Bowel) questionnaires will be assessed based on comparisons of the instruments and correlated with the Quality of Life-Radiation Therapy Instrument (QOL-RTI) and CTCAE v 3.0 diarrhea scale.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

- 3.1.1 Current histologic proof of primary anal or rectal cancer without metastasis beyond pelvic regional nodes;
- 3.1.2 The planned course of conventional radiation therapy (RT) must fall within the parameters in Section 6.1;
- 3.1.3 Patient must be scheduled to receive chemotherapy as specified in Section 7.2; patients who have received prior chemotherapy for any reason are eligible;
- 3.1.4 Patients must be registered/randomized prior to the administration of the Sandostatin® Test Dose (See Section 7.1);
- 3.1.5 Patients must be ≥ 18 years or older;
- 3.1.6 Pretreatment evaluations required for eligibility include: (1/12/04)
 - CBC with differential, hepatic panel (SGOT, SGPT, LDH, total bilirubin), and chemistry panel (sodium, potassium, chloride, BUN, creatinine, glucose) to evaluate hydration status within 2 weeks of randomization;
 - Serum pregnancy test for women of childbearing potential.
- 3.1.7 Patients must sign a study-specific informed consent (Appendix I) prior to study entry.

3.2 Conditions for Patient Ineligibility

- 3.2.1 Patients with known history of allergy/hypersensitivity to Sandostatin® or other related drug or compound;
- 3.2.2 Patients who have previously received Sandostatin® (octreotide) for cancer therapy-related diarrhea;
- 3.2.3 History of chronic or acute regional enteritis, malabsorption syndrome(s) or any other history of inflammatory bowel disease that may exacerbate the radiation toxicity;
- 3.2.4 Any incontinence of stool prior to entry on the study; Uncontrollable diarrhea at baseline (NCI-CTCAE v 3.0 Grade ≥ 2).
- 3.2.5 Patients who have undergone abdominal-perineal resection or other surgical procedure leaving the patient without a functioning rectum; patients using colostomy;
- 3.2.6 Patients with uncontrolled diabetes; fasting serum glucose > 250 mg/dL;
- 3.2.7 Patients with a history of cholecystitis or gallstones, unless a cholecystectomy has been performed;
- 3.2.8 Patients with a history of hepatic disease (patients with LFTs $< 3x$ the upper limit of normal are eligible);
- 3.2.9 Patients who have received glucocorticoid therapy within the past 6 months, insulin sensitizers (e.g. metformin, pioglitazone, rosiglitazone), or exogenous growth hormone therapy;
- 3.2.10 Patients who have received other investigational drugs administered or received within 30 days of study entry;
- 3.2.11 Planned hyperfractionated or split course radiation; a planned break in treatment would influence the resolution of acute bowel toxicity and potentially confound the study end points;
- 3.2.12 Planned brachytherapy prior to completion of all external beam radiation therapy;
- 3.2.13 Prior pelvic radiation therapy; acute toxicity in previously irradiated bowel is likely to be increased;
- 3.2.14 Patients being irradiated for abdominal cancer have been excluded as it is felt that these patients are likely to experience severe diarrhea due to the large volume and oversensitivity of small bowel included in radiation portal. Additionally, the majority of these patients commonly receive combined chemoradiation treatment. When the dose and timing questions have been answered with a homogenous group of patients receiving pelvic radiation therapy alone, it would be feasible to include patients receiving abdominal radiation in future studies;
- 3.2.15 Patients with any medical condition that may interfere with their ability to receive protocol treatment including mental impairment limiting their ability to comply with study requirements;
- 3.2.16 Patients who are pregnant or lactating as treatment involves unforeseeable risks to the participant and to the embryo, fetus, or child; patients with childbearing potential must practice appropriate contraception.
- 3.2.17 Patients who are known (previously diagnosed) to be HIV positive since the risk of uncontrollable diarrhea is greater in this population.

4.0 PRETREATMENT EVALUATIONS

4.1 Required Pretreatment Evaluations

- 4.1.1 Patients will complete the quality of life assessments, QOL-RTI, EPIC-Bowel, DAS, and FACE, before initiation of any therapy;
- 4.1.2 CTCAE-Diarrhea Scale.

4.2 Recommended Pretreatment Evaluations

- 4.2.1 History and physical exam (H & P) within 2 weeks before randomization. If the full H & P is performed more than 2 weeks before registration, a limited re-evaluation including a record of height, weight, vital signs, diarrhea assessment with DAS scale and the CTCAE v 3.0 diarrhea scale, and *documentation of number of stools/day* will suffice, as long as the patient had a valid physical exam within the prior 6 weeks;
- 4.2.2 Documentation of concomitant medications immediately prior to start of treatment;
- 4.2.3 Nutrition consultation by registered dietician to provide usual dietary teaching at baseline.

5.0 REGISTRATION PROCEDURES

5.1 Study Agent Shipment Form Pre-Randomization Requirement

Each institution must submit a Study Agent Shipment Form (Appendix III) as soon as the individual responsible for the study agent has been identified and the site has institutional IRB approval for the study. The Shipment Form must be submitted in order to receive initial Sandostatin® S.C. test kits and prior to registration of the institution's first case.

U.S. sites must submit the Shipment Form to the CTSU Regulatory Office (FAX 215-579-0206). Canadian sites must submit the Shipment Form to RTOG Headquarters (FAX 215-574-0300). Allow adequate processing time before calling to register the first case or scheduling test dose administration.

5.2 Sandostatin® Test Kit Distribution (6/15/04)

Biologics, Inc., will provide two Sandostatin® S.C. test kits to each participating center when the Study Agent Shipment Form (Appendix III) is received at CTSU or RTOG.

5.3 Registration/Randomization

Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to the Sandostatin® S.C. Test Dose and 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 randomized 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.

5.4 Study Drug and Additional Test Kit Distribution (6/15/04)

After each randomization, RTOG Headquarters will provide the double-blinded treatment assignment to Biologics, Inc. who will ship the 2 doses of Sandostatin LAR® depot/placebo needed to complete the study and 2 more Sandostatin® S.C. test kits by next day shipment (Priority Overnight) to the institution. NOTE: Sites must plan ahead due to the following shipping schedule: Study agent/placebo for patients randomized after 4 p.m. ET will be shipped the following business day. Study agent/placebo will be shipped to U.S. sites Monday to Thursday only. Study agent/placebo will be shipped to Canadian sites Monday to Wednesday only. For example, study agent/placebo for a patient randomized to a U.S. site on Thursday after 4 p.m. will be shipped on the following Monday (or Tuesday, if Monday is a holiday). Study agent/placebo will not be shipped on holidays or December 23rd through January 2nd. Each institution is responsible for notifying the RTOG Regulatory Associate at 215-574-3185 if study agent/placebo does not arrive on the expected date.

6.0 RADIATION THERAPY NOTE: Intensity modulated RT (IMRT) is not allowed.

6.1 Radiation Dose

- 6.1.1 Patients participating on another RTOG protocol will be treated in accordance with the protocol specific radiotherapy parameters. However, these parameters must meet the basic minimum

and maximum dosing parameters specified below. Patients who are not participating on another clinical trial protocol also must meet the following treatment parameters:

- Patients must be scheduled for a continuous course of definitive or adjuvant external beam pelvic radiation therapy to a minimum dose of 45 Gy.
- Patients should receive one treatment per day and daily fraction should be ≥ 1.5 Gy and ≤ 2 Gy per day given 4-5 times per week.
- The radiotherapy portal (AP/PA) should be more than 10 X 10 cm. The superior border may not lie superior to the L4-5 interspace.
- The total planned dose to the central axis midplane (for AP-PA parallel opposed fields) or isocenter (for 3- or 4-field techniques) for the whole pelvic field must be in the range of 45-50.4 Gy. Subsequent to completion of treatment to the whole pelvic field, a boost to primary tumor or tumor bed may be planned.

6.2 Radiation Adverse Event Reporting — RTOG AE TELEPHONE LINE (215) 717-2762

All acute and late adverse events from radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). **Please note that this study will not be using separate toxicity scales for acute and late radiation adverse events.**

6.2.1 Documentation

Patients will receive radiation therapy combined with chemotherapy; therefore, ALL serious adverse events are reported using the appropriate reporting form (MedWatch) as stated in section 7.0 of this protocol.

6.2.2 Summary of AE Reporting Involving Radiation Treatment With Chemotherapy Administration

- Report Grade 4/Grade 5 AEs;
- Telephone report within 24 hours of discovery;
- Document using the appropriate report — MedWatch within 10 days (a dictated summary and CRF's may also be indicated);
- Institutional reporting as required;
- For **DEATH WITHIN 30 DAYS OF COMPLETION OF TREATMENT:**
 - Telephone report to RTOG within 24 hours of discovery;
 - Follow guidelines outlined in section 7.0 of this protocol for AE reporting.

7.0 DRUG THERAPY

7.1 Sandostatin® Test Dose

7.1.1 Biologics, Inc. will provide two Sandostatin® S.C. test kits to each participating center when the Study Agent Shipment Form (Appendix III) is received at CTSU or RTOG Headquarters (See Section 5.1).

7.1.2 After meeting eligibility criteria and signing a study-specific consent form, the registered patient will receive a test dose of Sandostatin® 100mcg S.C. injection to assess for sensitivity or allergy to the study drug prior to the first study drug dose administration. Patients who exhibit symptoms of intolerance within 4 hours of the 100mcg test dose will not receive study medication but will be followed per protocol and the forms submission schedule (See Sections 11.1 and 12.1). Patient reactions/symptoms will be reported on the Initial Evaluation Form (**I1**).

Possible reactions to look for include anaphylactic reaction, skin rashes, nausea, vomiting, and any other disorders or reactions occurring within 4 hours after administration of test dose. Patients will be monitored in clinic with vital signs, including BP, pulse, respirations, and temperature, immediately before test dose and 30 minutes afterwards. If no reaction is noted, the patient may go and return for evaluation 4 hours after test dose. This assessment also may be completed by phone as long as the assessment is documented. In previous studies, no significant reactions were noted.

7.2 Sandostatin® Treatment Plan (6/15/04)

7.2.1 Eligible, consenting patients that have demonstrated tolerance to the Sandostatin® S. C. test dose will receive Sandostatin LAR® Depot 30 mg or placebo, by intramuscular injection (I.M.) at the gluteal site as specified in the treatment schema and treatment plan below.

7.2.2 For eligible, randomized patients with no demonstrated sensitivity/allergies to Sandostatin® acetate (after test dose, see Section 7.1 above): (6/15/04)

- Treatment Start Date: Patients must start study drug within 5-7 working days of randomization. Delays must be documented and called into RTOG Headquarters.
- Patients will receive either Sandostatin LAR® Depot 30 mg or placebo by intramuscular injection at the gluteal site.
- First dose is given before the first treatment (chemo or radiation fraction), between Day – 7 and Day – 4 of RT (i.e., 4 to 7 days prior to the start of RT) as there is a latent period before the drug is fully effective.
- Second dose is given on calendar day 22 (\pm 3 days) of RT.
- The total number of injections to be administered is 2. Each patient must receive 2 injections of 30 mg each.

7.3 Sandostatin® (octreotide acetate) [6/15/04]

7.3.1 Sandostatin® is a synthetic, long acting, octapeptide analogue of the natural hormone, somatostatin.³¹ Like somatostatin, Sandostatin® exerts inhibitory effects on the release of pituitary and gastroenteropancreatic hormones (i.e. GH, TSH, insulin, glucagon, CCK, VIP and gastrin) inhibits gastric acid, pancreatic enzyme secretion and bile flow; prolongs intestinal transit time, and decreases gallbladder contractility. Sandostatin® is a specific and potent somatostatin-receptor type 2 agonist. Relative to native somatostatin, Sandostatin® is 45 times more potent in terms of inhibition of growth hormone (gh) secretion, 11 times more potent in inhibition of glucagon, but only 1.3 times as active in inhibition of insulin secretion. Importantly, the half-life of Sandostatin® (113 minutes) is prolonged relative to somatostatin (3 minutes).³¹ Sandostatin® is normally administered subcutaneously (S.C.) either twice or three times per day.

7.3.2 Sandostatin LAR® depot is a long-acting formulation that was developed for patients requiring long-term Sandostatin® therapy. It consists of octreotide acetate microencapsulated by a biodegradable polymer, poly(dl-lactide-co-glycolide) d-(+)glucose. Drug release occurs slowly as cleavage of the polymer takes place primarily through tissue fluid hydrolysis. Sandostatin LAR® is approved for the treatment of acromegaly and for the treatment of symptoms of malignant carcinoid syndrome, vipoma, and in some countries for other gastroenteropancreatic (gep) neuroendocrine tumors. The Sandostatin LAR® Depot 30 mg dose was selected for this study instead of 20 mg, which may be equally effective and less expensive, in order to maximize the protection especially for patients receiving chemotherapy regimens known to be more diarrheagenic.

For more complete information regarding the clinical use of Sandostatin LAR®, including contraindications, adverse reactions, and precautions, please refer to the full prescribing information contained within the package insert. To facilitate correct administration, each site will receive a booklet titled “Injecting With Confidence – How to Prepare and Administer Sandostatin LAR® Depot” (slr-8049; copyright Novartis 2001).

7.3.3 Pharmacokinetics

After single I.M. injections of Sandostatin LAR®, the serum octreotide concentration reaches a transient initial peak within 1 hour after administration, followed by a progressive decrease to a low undetectable octreotide level within 24 hours. After this peak on day 1, octreotide remains at sub-therapeutic levels in the majority of the patients for the following 7 days. Thereafter, octreotide concentrations increase again, reach plateau concentrations at around day 14 and remain relatively constant during the following 3 to 4 weeks. The peak level during day 1 is lower than levels during the plateau phase, and no more than 0.5% of the total drug release occurs during day 1. After about day 42, the octreotide concentration decreases slowly, concomitant with the terminal degradation phase of the polymer matrix of the dosage form. Following multiple doses of Sandostatin LAR® given every four weeks, steady-state octreotide serum concentrations are achieved after the third injection. With this regimen, serum octreotide concentrations are maintained and the day 2-7 post-injection trough seen after a single initial dose does not occur.

7.3.4 Sandostatin® Packaging

This is a double-blind study. To minimize bias, the patient’s assigned treatment group will not be known to the patient, investigator, study coordinator, pharmacist, and study monitors.

Matching placebo will be identical in appearance to active drug substance. All study drug kits will be packaged identically.

7.3.5 Randomization

Randomization data are kept strictly confidential, accessible only to authorized persons, until the time of unblinding. At the conclusion of the trial, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis. Only when the study has been completed, the data file verified, and the protocol violations determined will the drug codes be broken and made available for data analysis.

7.3.6 Storage

For prolonged storage, Sandostatin LAR® depot should be stored at refrigerated temperatures 2°C-8°C (36°F-46°F) and protected from light until the time of use. Sandostatin LAR® depot kits should remain at room temperature for 30-60 minutes prior to preparation of the drug suspension. However, the drug suspension must be administered immediately.

Drug supplies must be kept in an appropriate, secure area (e.g. locked cabinet) and stored in accordance with the conditions specified on the drug labels. The investigator must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which will be provided to Novartis at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. All drug supplies are to be used only for this protocol and not for any other purpose.

7.3.7 Toxicity

Local injection site reactions to Sandostatin LAR® may occur and are usually mild and of short duration. They include local pain and, rarely, swelling and rash. Gastrointestinal complaints are the most common adverse events. Approximately one third of patients experience diarrhea and abdominal pain. Flatulence and constipation are also common. Gastrointestinal events generally begin with the first injection with some increase during the second and third months during steady state build up of octreotide levels. Newly occurring gastrointestinal events are uncommon after the third month.

Prolonged use of Sandostatin LAR® may result in gallstone formation. Development of gallstones has been reported in 15-30% of long-term recipients of Sandostatin® S.C.³³ The incidence in the general population is about 5-20%.³⁴ Long-term exposure to Sandostatin LAR® of patients with acromegaly or gastro-entero-pancreatic neuroendocrine tumors suggests that treatment with Sandostatin LAR® does not increase the incidence of gallstone formation, compared with S.C. treatment. Ultrasonic examination of the gallbladder before and at about 6-monthly intervals during Sandostatin LAR® Depot therapy is recommended. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids (e.g. Chenodeoxycholic acid [CDCA] 7.5 mg/kg per day together with ursodeoxycholic acid [UDCA] 7.5 mg/kg per day) or by surgery.

7.3.7.1 Adverse effects that are more frequent include: abdominal pain; diarrhea/loose stools; flatulence; steatorrheic stools; nausea and vomiting; transient pain; redness, bleeding, or swelling at the injection site; hyperglycemia; and hypothyroidism.

7.3.7.2 Adverse effects that are less frequent include: gallbladder and biliary tract abnormalities including asymptomatic or symptomatic gallstones, sludge, biliary duct dilatation, gallbladder dilatation; hypoglycemia; bradycardia; reversible thrombocytopenia; dizziness; vasomotor flushing (hot flashes); elevation in liver function tests; hair loss, rash; headaches.

7.3.7.3 Adverse effects that are rare include: hypertension, pancreatitis; hepatitis; galactorrhea; fatigue; anxiety; depression; shortness of breath; heartbeat irregularities; heart failure; chest pain; dry mouth; numbness; visual disturbances; fever; throat discomfort.

7.4. Supply and Distribution

Sandostatin LAR® depot/placebo will be provided free of charge to patients on study by Novartis Pharmaceuticals in 30 mg vials. Novartis also will supply the 100 mcg Sandostatin® S.C. test dose. Sandostatin LAR® depot/placebo and Sandostatin® S.C. test kits will be distributed by Biologics, Inc.

Each institution must submit a Study Agent Shipment Form (Appendix III) as soon as the individual responsible for the study agent has been identified and the site has institutional IRB

approval for the study. The Shipment Form must be submitted in order to receive the initial Sandostatin® S.C. test kits and prior to registration of the institution's first case. U.S. sites must submit the Shipment Form to the CTSU Regulatory Office (FAX 215-579-0206). Canadian sites must submit the Shipment Form to RTOG Headquarters (FAX 215-574-0300). Allow adequate processing time before scheduling test dose administration or calling to register the first case.

- 7.4.1** After each randomization, RTOG Headquarters will provide the double-blinded treatment assignment to Biologics, Inc. who will ship the 2 doses of Sandostatin LAR® depot/placebo needed to complete the study and 2 more Sandostatin® S.C. test kits by next day shipment (Priority Overnight) to the institution. **NOTE: Sites must plan ahead due to the following shipping schedule:** Study agent/placebo for patients randomized after 4 p.m. ET will be shipped the following business day. Study agent/placebo will be shipped to U.S. sites Monday to Thursday only. Study agent/placebo will be shipped to Canadian sites Monday to Wednesday only. For example, study agent/placebo for a patient randomized to a U.S. site on Thursday after 4 p.m. will be shipped on the following Monday (or Tuesday, if Monday is a holiday). Study agent/placebo will not be shipped on holidays or December 23rd through January 2nd. Each institution is responsible for notifying the RTOG Regulatory Associate at 215-574-3185 if study agent/placebo does not arrive on the expected date.
- 7.4.2** Biologics will label each vial of Sandostatin LAR® depot/placebo with the treatment-specific, double-blinded reference number, the study and case number, and the expiration date. The label will comply with legal requirements of the country in which the study is performed and will be printed with the local language. The Sandostatin® S.C. test dose also will be labeled with the expiration date. Sites will use Appendix IV to report on-site destruction of expired Sandostatin® S.C. test kits and to request replacement of Sandostatin® S.C. test kits.
- 7.4.3** The individual responsible for the Sandostatin LAR® depot/placebo and the Sandostatin® S.C. test kits must maintain a careful record of the inventory and disposition of all drugs received. At the end of the study, institutions will destroy on site unused Sandostatin LAR® depot/placebo as well as all expired and/or unused Sandostatin® S.C. test kits that have not expired. The individual responsible for the Sandostatin LAR® depot/placebo and the Sandostatin® S.C. test kits will complete the Drug Destruction Form (Appendix IV) and fax it to:

Leigh Hancock, CPhT
Clinical Trials Manager
Biologics Inc.
Fax 919-546-9816
800-850-4306, ext. 106
lhancock@biologicstoday.com

7.5 Chemotherapy (6/15/04)

Institutional participation in chemotherapy studies must be in accordance with the medical oncology quality control guidelines stated in the RTOG procedures manual.

- 7.5.1** Chemotherapy must be given concurrently with radiotherapy (i.e. given between day 1 and the last day of radiotherapy).
- 7.5.2** This protocol doesn't define specific chemotherapy administration schedules in order to remain as broad as possible to capture any combinations of chemotherapy that would produce significant diarrhea.
- 7.5.3** Allowable chemotherapy agents include (but are not limited to) fluoropyrimidines (*iv* or oral), captothecins, or platinols.
- 7.5.4** Each drug, dose, frequency, and total amount administered must be documented accordingly.

7.6 Criteria for Removal from Therapy

Patients may refuse to participate in the study at any time and it will be documented whether or not each patient completed the clinical study. Reasons for refusal will be documented in the medical record and data forms for data analysis purposes. Any patient who receives at least one dose of trial medication will be included in the safety analysis. It is agreed that, for reasonable cause, either the investigator or the sponsor may terminate this trial, provided that timely written notification is provided.

- 7.6.1** Refusal to participate in this project will have no impact on the delivery of medical care to the patient.

7.6.2 Patients that experience severe or life threatening hyperglycemia (diabetic ketoacidosis, hyperosmolar coma) develop jaundice, hepatitis, or other primary hepatic dysfunction will be discontinued from protocol treatment but will be followed as specified in Sections 11.1 and 12.1, unless the patient withdraws consent.

7.6.3 Reasons that a patient may discontinue participation in a clinical study are considered to constitute one of the following:

- adverse event(s)
- abnormal laboratory value(s)
- abnormal test procedure result(s)
- unsatisfactory therapeutic effect
- subject's condition no longer requires study treatment
- protocol violation
- subject withdrew consent
- lost to follow-up
- administrative problems
- death

7.7 Adverse Event Reporting (10/6/04)

Sites will follow the same guidelines for reporting adverse events (AEs) for this protocol as apply to any NCI/RTOG research protocol that uses commercial anticancer agents. The following AEs experienced by patients accrued to this protocol and attributed to Sandostatin® octreotide/placebo, radiation therapy, or chemotherapy (**definitely, probably, or possibly related**) should be reported:

- Any AE which is both serious (life-threatening [grade 4] or fatal [grade 5]) and **unexpected** (not listed as a known toxicity or is of greater severity or specificity than the listed toxicity);
- Any increased incidence of a **known** (listed in the drug information, background, or informed consent form section of the protocol) AE;
- Any **death on study** if clearly related to Sandostatin® octreotide/placebo, radiation therapy, or chemotherapy or **within 30 days after treatment** must be reported. Any death more than 30 days after treatment, which is felt to be treatment related, must also be reported.

7.7.1 The following steps must be taken to report serious adverse events that occur while the patient is on this trial:

- Within **24 hours of discovery** of the adverse event, **call** the RTOG Headquarters Adverse Events (AE) telephone line, (215) 717-2762, or to 1-800-227-5463, X4189;
- Within **10 working days**, **send** to RTOG Headquarters: a copy of the FDA form 3500 (MedWatch) **including the investigator's attribution** (event is definitely not, unlikely, possibly, probably or definitely related) to Sandostatin® octreotide/placebo, radiation therapy, or chemotherapy **in item 5 on the form**; copies of the appropriate case report forms/flowsheets recording the event and any other data/items as requested during the telephone report.

7.7.2 The completed FDA Form 3500 must be **mailed or faxed to ALL** the following addresses:

FDA	Investigational Drug Branch	RTOG Headquarters
MedWatch	P.O. Box 30012	1818 Market St., Suite 1600
5600 Fishers Lane	Bethesda, MD 20824	Philadelphia, PA 19103
Rockville, MD 20852	301-230-2330 (24 hrs.)	215-717-2762 (24 hrs.)
Fax 800-332-0178	Fax 301-230-0159	Fax 201-928-0153
FDA only via internet: www.fda.gov/medwatch		

All MedWatch forms submitted to RTOG Headquarters **must include the RTOG study and case numbers**; the non-RTOG intergroup study and case numbers must be included, when applicable.

7.7.3 **Death from any cause while the patient is receiving protocol treatment or up to 30 days after the last protocol treatment, must be telephoned to the RTOG Headquarters** AE phone line within 24 hours of discovery to ensure proper reporting of adverse events.

7.8 Special Reporting for this Study

7.8.1 All \geq grade 4 adverse events attributable to Sandostatin® (octreotide)/placebo and all \geq grade 4 nonhematologic adverse events attributable to chemotherapy must be reported to RTOG by telephone (215-717-2762) within 24 hours.

7.8.3 Data submission must adhere to the timetable specified by the patient calendar and Section 12.0.

8.0 SURGERY

Not applicable to this study.

9.0 CONCOMITANT AND ANCILLARY THERAPY

9.1 Patients should continue to take their usual chronic maintenance medications (such as anticonvulsants, antisecretory agents, antihypertensives, thyroid replacement therapy, vitamin or mineral supplements) during the course of the study other than those contraindicated by the inclusion criteria.

9.2 Interventional use of standard antidiarrheal medications (e.g., Imodium, Lomotil) except for Sandostatin® (octreotide) S.C. is permitted in both study arms for grade $>$ 1 diarrhea. A patient diary will be used to track concomitant medications.

9.3 Prophylactic use of antidiarrheal medications is not allowed.

9.4 **(1/12/04, 4/19/04)** Rescue therapy with Sandostatin® S.C. 0.3 mg tid (or qid per investigator discretion) subcutaneously and/or rehydration therapy is appropriate only for patients who have Grade \geq 3 diarrhea. A recently convened panel of experts recommended Sandostatin® S.C. for management of persistent and severe (CTCAE v 3.0 grades 3-4) diarrhea.⁷ Rescue therapy will be continued at the investigator's discretion until clinically stable using medications or measures of choice. Patients who receive rescue therapy will continue participation and evaluations to the end of the study (at 12 months from the start of radiation therapy). Study drug will be continued as prescribed in patients who receive rescue therapy.

9.5 In both arms, patients will be instructed in appropriate dietary measures at baseline as well as throughout the radiation therapy treatment as needed to reduce or control diarrhea per institutional practice (same for both arms). In order to minimize bias, the nutritional instruction should be standardized for both arms at each participating center.

9.6 **(3/23/04)** Additional chemotherapy is allowed, after the planned radiotherapy with concurrent chemotherapy (as specified in Sections 6.1 and 7.2) is completed. However, these patients need to be assessed for diarrhea before the first chemotherapy cycle post radiotherapy.

10.0 PATHOLOGY

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

Assessments	Pre-Study	Weekly During RT	At Completion of RT	Follow Up ^f
History/Physical ^a	X	X ^g		X
Performance Status	X			X
CBC, diff, Hepatic Panel (SGOT, SGPT, LDH, total bilirubin)	X			
Serum chemistry (e.g. Chem 20: sodium, potassium, chloride, BUN, creatinine, glucose)	X			
Adverse Event Evaluation		X		X
Pregnancy test ^d	X			
CTCAE toxicity evaluation	X	X ^g		X
DAS	X ^c	X	X	X
QOL-RTI	X ^c		X ^e	X
EPIC-bowel	X ^c		X ^e	X
FACE	X ^c		X ^e	X
Economic Data (See Section 11.3.2)		X		X
Patient Diary (to document diarrhea, concomitant medications)	X	X		X
Nutrition Instruction	X	X ^d		X ^d

- Include history of hemorrhoids, diverticulosis, fecal impaction, intestinal obstruction, malabsorption, regional enteritis, cholecystitis, gallstones, or cholecystectomy, allergies/hypersensitivities, medications
- For women of childbearing potential only
- Patients must complete prior to start of radiation therapy; if RT does not start within 1 week (seven days) of randomization these instruments must be re-administered immediately prior to first RT treatment
- As clinically indicated (according to institutional practices) during radiation therapy and in follow up
- To be completed at the end of RT only (NOT WEEKLY).
- Follow-up will be done at 3, 6, 9, and 15 months from start of RT
- Number of stools per day, diarrhea, rectal bleeding, abdominal or rectal cramping, treatment modification or interruption

11.2 All baseline patient assessments will be performed no more than 2 weeks prior to randomization, unless specified otherwise. Demographic and clinical information to be recorded will include: age, sex, race, education, income, site of primary tumor, stage of disease, radiation therapy dose (total), field size, radiation fraction size, diet and nutrition information, body weight.

11.3 Evaluation During Treatment

11.3.1 *Diarrhea Monitoring*

Patients will be evaluated for toxicity using the CTCAE version 3.0 once a week during treatment by a physician. Patients will also complete the DAS scale once a week during radiation therapy for correlation with CTCAE scale. The research associate will review the DAS to determine completeness. For data reporting and analysis purposes weekly CTCAE and DAS scores (during radiation therapy) will be reported on data collection forms.

Patients will be asked to use a diary to document diarrhea and concomitant medication use on a daily basis. A clinician or research associate will review the diary during the weekly clinic visit.

11.3.2 Economic Data

To assess economic impact we will collect data on health care resource utilization during radiation therapy and in follow-up. The research assistant will interview patients weekly during radiation therapy and at each follow-up visit regarding the following [to be recorded on the Treatment Form (TF) and Follow-up Form (F1)]:

- Use of Imodium or other medical regimens to control diarrhea or its complications;
- Any outpatient or hospital-based care for management of enteritis or its complications;
- Follow-up care for diarrhea during the 12 month follow-up period

11.4 Follow up

11.4.1 Because symptoms of diarrhea and other related sequelae may persist after the end of RT, the patient will be evaluated at 3, 6, 9, and 15 months from start of radiation therapy. This follow-up period is believed to be sufficient to observe resolution of acute diarrhea related to primary therapy.

11.4.2 During the follow-up period, the study assessments and quality of life questionnaires will be conducted according to the schedule specified in Section 11.1.

11.4.3 If a patient is not evaluated in clinic, follow-up evaluations can be carried out by phone or by mail if the patient is unable to come in for an appointment, for both toxicity assessment and quality of life questionnaires (including the CTCAE, DAS, QOL-RTI, FACE and EPIC scales).

12.0 DATA COLLECTION (10/6/04)

Data should be submitted to:

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

12.1 Summary of Data Submission (10/6/04)

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 wks of study entry
Initial Evaluation Form (I1)	
QOL-RTI questionnaire (RI)	
EPIC-bowel (BA)	
FACE questionnaire (FA)	
DAS (DA)	
Pathology Report (P1)	
QOL-RTI questionnaire (RI)	Within 2 weeks of RT end
EPIC-bowel (BA)	
FACE questionnaire (FA)	
*DAS (DA)	
Treatment Form (TF)	
Protocol Calculation Form (TL)	
Follow-up Form (F1)	At 3, 6, 9, 15 months from start of RT
QOL-RTI questionnaire (RI)	
EPIC-bowel (BA)	
FACE questionnaire (FA)	
DAS (DA)	

* Submit DA form from the week that corresponds to the worst grade CTCAE (diarrhea) reported on the TF form.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

- 13.1.1** The primary endpoint is to prevent the incidence of severe or life-threatening diarrhea (grade 3-5)
- 13.1.2** Quality of Life (QOL) will be assessed.
- 13.1.3** Economic measures will be compared between the treatment and placebo group.
- 13.1.4** The validity of the FACE-CBF, QOL-RTI, and the EPIC-Bowel questionnaires will be assessed based on comparisons of the instruments.

13.2 Sample Size

The study is designed to test whether Sandostatin LAR® Depot reduces the incidence of severe or life-threatening diarrhea (grade 3 or above) that cause dose modification, delay or interruption of the treatment. Patients will be randomized between Sandostatin LAR® Depot and placebo. The previously published paper³⁵ and RTOG agenda reports on rectum and anal canal showed to have a 20 – 35% grade 3 or above diarrhea rate, which will be assumed to be the placebo arm. It is hypothesized that the rate of diarrhea will have a relatively 50% reduction for the experimental arm. The required sample size for 90% statistical power and one-sided 0.05 type I error, is 107 patients per arm by Chi-square test using the normal approximation.³⁶ This assumes the placebo arm will have 35% grade 3 or above diarrhea. Assuming 5% of the patients are either retrospectively ineligible or invaluable due to never starting any therapy, then **a total of 113 patients per arm or 226 randomized patients will be required.**

13.3 Quality of Life

This study will test whether Sandostatin® provides better QOL compared to patients receiving placebo. The QOL-RTI scale will be used to assess QOL in this patient group. The standard error of measurement (SEM)³ will be used to classify patients as having improved, stable, or deteriorated from pretreatment levels. It is estimated that 60% of the placebo group will have deteriorated in their QOL score at three months. A sample size of 107 evaluable patients per arm will provide at least 87% statistical power to detect a decrease in the proportion of patients having a deterioration in QOL on the Sandostatin® arm to 40% at three months, using a 0.05 significance level (one-sided).

13.4 Patient Accrual

The patient accrual is projected to be 10 patients per month. At that rate this study will complete accrual in 2 years. If the monthly accrual is less than 5 patients per month, the study will be re-evaluated with respect to feasibility.

13.5 Randomization Scheme

The treatment allocation will be one using a randomized permuted block to balance for institution.

13.6 Analyses Plans

13.6.1 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 have been submitted. In general, the interim reports will contain information about:

- a. The patient accrual rate with projected completion date for the accrual phase;
- b. The distribution of patients with respect to pretreatment characteristics;
- c. The frequency and severity of the toxicities, not split by treatment

13.6.2 Interim Analyses of Study Endpoints

There will be two interim analyses of the primary study endpoint (incidence of grade 3 or above diarrhea) when 50% and 75% of patients have been accrued and followed for a minimum of 3 months. If the rate of grade 3 or above diarrhea in placebo arm is lower than 35% at the interim analysis, the required sample size will be recalculated. The interim analyses will proceed according to the following table:

<u>Total Accrual</u>	<u>Significance Level</u>
50%	.006
75%	.023
100%	.042

If a significance level is smaller than the value listed above, then the null hypothesis will be rejected. The significance level was calculated to ensure an overall significance level of 0.05

(type I error). The results of these interim analyses only will be reported, in a blinded fashion, to the RTOG data monitoring committee as privileged communications. A report with recommendations will be given to the study chairman. Any problems or recommendations identified by the data monitoring committee, not results, will be reported to the CCOP committee, which is responsible for this study and, if necessary, the RTOG executive committee, so that corrective action can be taken.

13.6.3 Analysis and Reporting of Initial Treatment Results

This major analysis will be undertaken when each patient has been potentially followed for a minimum of three months. The usual components of this analysis are:

- a. Tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion
- b. Reporting institutional accrual
- c. Distribution of important prognostic factors by assigned treatment
- d. Observed results with respect to the study endpoints

The final analysis will use a p-value of 0.0421, which accounts for the prior interim analysis. The incidence of diarrhea toxicity will be tested to show the effect of Sandostatin LAR® Depot using chi-square test. Analysis will also be performed by means of logistic regression so that categorical response (diarrhea toxicity – yes versus no) can be appropriately associated with important prognostic variables. Further subgroup analyses may be conducted (depending upon the sizes within the subgroups) for the purpose of identifying patterns of treatment responses.

The SEM will be computed using reliability coefficients from the literature for the QOL-RTI, EPIC-Bowel, and FACE-CBF. The standard deviations for these three measures will be computed from pretreatment assessments. The SEM will be computed for each instrument and used to determine whether there has been significant change in the scores at follow-up. These changes will be categorized as improved, stable, and deteriorated. Proportions of patients in each of these groups will be compared by treatment arm using the Wilcoxon rank-sum test. Each time point will be considered an independent test. Patients with follow-up assessment and pretreatment assessment will be used in the analysis.

The number of hospitalizations will be tallied by treatment arm. The proportion of hospitalizations will be compared using Fisher's exact test. Treatment compliance will be assessed as the average treatment time on both arms and the number of dose reductions of chemotherapy. A z-test will be used to compare the average treatment time for both arms, while a Fisher's exact test will be used to compare the proportion of patients requiring dose adjustments for chemotherapy.

FACE-CBF, DAS, and EPIC-Bowel results will be compared to the QOL-RTI and diarrhea scale of CTCAE. These comparisons will be used to determine the relationship between QOL and symptom scales and the relationship between the symptom scales and toxicity scale.

13.7 Inclusion of Minorities

In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interaction between race and treatments. Based on the latest accrual statistics from RTOG 9403 and 9811, we project that 89% of patients in the study are white, 5% are black (not of Hispanic origin), 3% are Hispanic, 1% are Asian or Pacific Islander, 1% are American Indian or Alaskan Native, and 1% are others and unknown. In those studies, 53% of the patients were women. The following table lists the projected accrual for each racial and gender group:

Gender/Minority Table

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	4	3		7
Not Hispanic or Latino	116	103		219
Unknown				
Ethnic Category: Total of all subjects*	120	106		*226
Racial Category				
American Indian or Alaskan Native	1	1		2
Asian	1	1		2
Black or African American	6	6		12
Native Hawaiian or other Pacific Islander				
White	111	97		208
More than one race	1	1		2
Unknown				
Racial Category: Total of all subjects*	120	106		*226

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APPENDIX I

RTOG 0315

SAMPLE CONSENT FOR RESEARCH STUDY

A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED PHASE III STUDY TO DETERMINE THE EFFICACY OF SANDOSTATIN LAR® DEPOT (OCTREOTIDE ACETATE) IN PREVENTING OR REDUCING THE SEVERITY OF CHEMORADIATION-INDUCED DIARRHEA IN PATIENTS WITH ANAL OR RECTAL CANCER

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. 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.

You are being asked to take part in this study because you have anal or rectal cancer and you will be undergoing treatment with radiation and chemotherapy.

WHY IS THIS STUDY BEING DONE?

A side effect of treatment with radiation to the abdominal area and chemotherapy is diarrhea, which can be severe. Currently, there are no medications to prevent such diarrhea from occurring.

The purpose of this study is to see if taking the drug, Sandostatin LAR® (long-acting form), while undergoing treatment with radiation and chemotherapy will prevent severe diarrhea. Sandostatin® (short-acting form) has been approved by the United States Food and Drug Administration (FDA) for patients who have carcinoid (a specialized tumor) of the gastrointestinal tract for the very severe diarrhea and flushing that can occur with that disease. In earlier studies, Sandostatin® also was shown to work well in controlling diarrhea in patients receiving chemotherapy. It has not been used to prevent or reduce diarrhea in patients receiving combined chemotherapy and radiation.

This study will compare the effects (good and bad) of Sandostatin LAR® (long-acting form) with the drugs commonly used to treat diarrhea after diarrhea occurs to see which is better in preventing or reducing diarrhea, in patients receiving both radiation and chemotherapy.

Your disease, the treatments you receive for the disease, and the side effects of treatment can affect the quality of your daily life and also have an impact on your finances. In order to study these effects, the researchers will ask you to complete some questionnaires and also take part in short interviews about any additional costs you may have while undergoing treatment for your cancer.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 226 patients will take part in this study.

WHAT IS INVOLVED IN THE STUDY? (2/23/04, 3/23/04)

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. You will be placed in one of the groups by a computer. 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 two groups.

If you agree to participate in this study and you are randomized, you will be given a test dose of the study drug, Sandostatin® S.C. The test dose is given with a needle under your skin and contains a very small amount of the study drug, not large enough to have any treatment effect. Your doctor will take your blood pressure, pulse, and temperature and will check your breathing immediately before the test dose and 30 minutes afterwards to make sure you do not have a serious or allergic reaction. Although allergic reaction to Sandostatin LAR® is uncommon, the test dose is a good way to check if you are likely to experience serious reaction to the larger doses of Sandostatin LAR®.

If no reaction is noted, you may leave your doctor’s office and return 4 hours later for evaluation or your doctor will telephone you 4 hours after test dose to evaluate you. If you have no reaction to the test dose (for example, rash, fever, itching, or other signs and symptoms of allergic reaction), you will begin your study treatment. If you experience a reaction to the test dose, you will not receive treatment on this study. You will be seen in follow-up visits at 3, 6, 9, and 15 months, and you will receive usual medical care.

Group 1

If you are randomized to this study group, you will be given Sandostatin LAR® with a needle into your buttock for a total of 2 injections. The injections will be given before radiation begins (at least 4 to 7 days before), then 3 weeks later during radiation therapy. During the time you are being treated with Sandostatin LAR®, your doctor also will be able to give you any other standard drugs that are routinely given for diarrhea. These medications may include the short-acting form of Sandostatin®.

Group 2

If you are randomized to this study group, you will be given a placebo with a needle into your buttock for a total of 2 injections. The injections will be given before radiation begins (at least 4 to 7 days before), then 3 weeks later during radiation therapy.

The placebo contains no active agents. It will look like Sandostantin LAR® but does not have a treatment effect. During the time you are being treated with the placebo, your doctor also will be able to give you any other standard drugs that are routinely given for diarrhea. These medications may include the short-acting form of Sandostatin®.

Both Groups (6/15/04)

If you take part in this study, you will have the following tests and procedures:

Schedule

Procedure

Before study entry

- Physical exam with medical history
- Blood tests, including a CBC, chemistries, and pregnancy test (for women who can bear children)
- Nutrition consultation
- Completion of quality of life questionnaires

Once a week during radiation treatment

- Physical exam
- Nutrition consultation (as needed)

Daily during radiation treatment

- A diary in which you will record diarrhea, medications and financial costs

Weekly during radiation therapy

- Completion of diarrhea questionnaire

At each follow-up appointment (2/23/04)

- Physical exam
- Nutrition consultation (as needed)
- Completion of quality of life questionnaires

You will be asked to complete a questionnaire about the presence and severity of your diarrhea once a week during radiation therapy. This questionnaire will take about 5 minutes each time you are asked to complete it.

You will be asked to complete 3 questionnaires about the quality of your life; these questionnaires will need to be filled out at the following times: a) before

you start receiving radiation therapy; b) after completing radiation therapy; c) at each follow-up appointment at 3, 6, 9, and 15 months from the start of radiation therapy. The questionnaires will take about 20-25 minutes to fill out, each time you are asked to complete them.

In addition, once a week during radiation therapy and at each follow-up appointment, you will be asked briefly about any additional costs you may have while undergoing treatment for your cancer. Answering these questions will take about 5 minutes each time you are asked to respond.

HOW LONG WILL I BE IN THE STUDY?

You will be in this study for about 16 months. Active treatment will last about 2 months. Follow-up visits with the study doctor will be scheduled at 3, 6, 9, and 15 months from the start of radiation therapy.

The researcher may decide to stop your treatment if it is in your medical best interest, your condition worsens, or new information becomes available, and this information suggests the treatment will be ineffective or unsafe for you; however, you still will be seen in follow-up visits, and data about your treatment will be included in the study results.

It is unlikely, but the study may be stopped 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 study doctor first.

WHAT ARE THE RISKS OF THE STUDY?

Sandostatin LAR® has been found to be associated with the following side effects. Although you will receive Sandostatin LAR® for a short period of time in this study, you are at risk for these side effects. Receiving radiation therapy to the abdominal area and/or chemotherapy involves similar side effects to those associated with Sandostatin LAR®, but the side effects from these treatments may be more or less likely or severe than those listed below.

You should discuss these side effects with the study doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable.

Sandostatin®

Very Likely

- Nausea and/or vomiting
- Loss of appetite

- Diarrhea/loose stools
- Cramping abdominal pain
- Abdominal bloating
- Flatulence (gas)
- Pain, redness, swelling, or bleeding at the injection site
- High blood sugar
- Decreased thyroid function, which may result in tiredness, weakness, or swelling of the legs or feet

Less Likely (2/23/04)

- Headaches
- Dizziness
- Lightheadedness
- Flushing (hot flashes)
- Hair loss
- Rash
- Formation of gallbladder stones or other changes in gallbladder function
- Slower heart rate
- Decreases in blood sugar
- Low platelet blood counts, which is temporary but which may lead to an increased risk of bleeding and bruising easily
- Changes in liver function, which may result in tiredness, itching of the skin, or yellow discoloring of the skin, eyes, and inside of the mouth (jaundice)

Rare

- Dry mouth or throat discomfort
- Fever
- Changes in vision, such as blurring of vision
- Nervousness
- Depression
- Numbness of hands or feet
- Insulin dependent diabetic patients may need to have their dose of insulin adjusted

Rare, but Serious

- High blood pressure
- Chest pain
- Shortness of breath
- Irregular heartbeat or heart failure
- Inflammation of the pancreas or liver, which may result in low blood sugar, abdominal pain, nausea and/or vomiting
- Severe allergic reactions, which may cause difficulty breathing, heart failure, or even death

(1/12/04) Although the study drug, Sandostatin LAR®, may prevent or reduce diarrhea, it could cause loose stools or diarrhea in some patients. This type of diarrhea is not expected to be severe, and if it occurs, your doctor will monitor

you closely. We are using Sandostatin LAR® in this study to test its value in preventing severe diarrhea caused by your cancer treatments.

Reproductive Risks

The risks to an unborn human fetus or a nursing child from Sandostatin LAR® are not known. Receiving radiation therapy and/or chemotherapy also involves risks to a nursing infant or an unborn child. Women who are pregnant or nursing a child may not take part in this study. You must have a negative pregnancy test before you join the study. You must not become pregnant or father a child during this study. If you are able to bear children, your doctor will discuss appropriate birth control measures with you. If you suspect that you have become pregnant during the trial, you must notify your doctor. If you are pregnant, you will be withdrawn from the trial.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may be direct medical benefit to you. The treatment could manage and/or control your diarrhea and improve the quality of your life. However, these benefits are not certain or guaranteed. We hope the information learned from this study will benefit other cancer patients in the future.

WHAT OTHER OPTIONS ARE THERE?

You may choose not to participate in this study. You may choose to receive the standard medications for control of diarrhea in patients receiving chemotherapy and radiation. Your doctor can tell you more about these medications.

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 the Radiation Therapy Oncology Group (RTOG) and groups such as the Food and Drug Administration (FDA), The National Cancer Institute (NCI), qualified representatives of Novartis Pharmaceuticals Corporation and its authorized agents, governmental agencies

in other countries where the study drug may be considered for approval, and the Institutional Review Board (IRB).

The results and other information from this study may be submitted to the FDA and governmental agencies in other countries where the study drug may be considered for approval; however, you will be identified by initials and patient study number only. You will not be identified by name in any reports or publications resulting from this study.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

You or your insurance company will be charged for continuing medical care and/or hospitalization. Medicare should be considered a health insurance provider.

The study drug and placebo will be provided free of charge to patients on this study by the pharmaceutical company, Novartis.

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; Novartis will not provide payment for any medical expenses that you may incur as a result of your participation in this study. No other type of compensation will be provided by Novartis.

You must notify your doctor immediately of any research related injury. If you have questions concerning the availability of medical care or if you think you have experienced a research related illness, injury, or emergency contact [investigator's name and phone and/or pager number].

By signing this form, you have not give up any of the legal rights that you otherwise would have as a participant in a research study.

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

WHAT ARE MY RIGHTS AS A PARTICIPANT? (3/23/04)

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. If you choose to stop participating in the study, you should first discuss this with your doctor. 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, will 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:

(OHRP) 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 information at **www.cancer.gov/clinicaltrials** or for accurate cancer information including PDQ (Physician Data Query) visit **www.cancer.gov/cancerinfo/pdq**

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*).
- 5 Death

APPENDIX III (10/6/04)

RTOG 0315

STUDY AGENT SHIPMENT FORM

The Sandostatin® S.C. test kits and study drug/ placebo will be shipped only to institutions who have identified a single individual associated with the investigational drug unit of the institution and only if the site has institutional IRB approval for the study. This information must be recorded on this form, and the form must be submitted in order to receive the initial Sandostatin® S.C. test kits. U.S. sites must submit the Shipment Form to the CTSU Regulatory Office. Canadian sites must submit the Shipment Form to RTOG Headquarters. Allow adequate processing time before calling to register the first case and before scheduling test dose administration.

SHIP TO:

Name: _____

Address: _____

(no P.O. Box addresses)

Telephone: _____

E-mail: _____

Fax#: _____

RTOG Institution#: _____

Institution Name: _____

IRB Approval Date: _____ **RTOG HQ Confirmation:** _____

Investigator (PI) Signature _____ Date: _____

Investigator Name (Print) _____

Investigator NCI # _____

Send Completed Form to:

U.S. Sites

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX 215-569-0206

Canadian Sites

RTOG Headquarters
1818 Market Street, Suite 1600
Philadelphia, PA 19103
FAX 215-574-0300

RTOG Headquarters Approval _____

Date: _____

APPENDIX IV



BIOLOGICS

DELIVERING TOMORROW'S MEDICINES TODAY

RTOG 0315
Replacement of Test Kit(s)/Drug Destruction Form
(Check boxes as appropriate)

Fax to:
Biologics Inc.
Attn: Leigh Hancock, Clinical Trials Manager
Fax: (919) 546-9816
Phone: 800-850-4306

Destruction of Sandostatin® S.C. Test Kit(s)

Quantity	Item/Lot Number	Expiration Date

Replacement of Test Kit(s)
Quantity needed: _____

Drug Destruction Only (Replacement of Sandostatin LAR® Depot/placebo is not necessary)

Quantity	Item/Lot Number	Expiration Date	Case Number

Name: _____
Institution Name: _____
Institution Number: _____
Telephone: _____ Ext: _____
Fax: _____

Notes: