SUMMARY OF CHANGES
Amendment 5, Version Date: November 4, 2005

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"

Study Chair: Babu Zachariah, MD, 813-972-7667, bzachariah2001@yahoo.com

RTOG 0315 was amended to change the primary endpoint from grade 3-4 diarrhea to grade 2-4 diarrhea, as all grades of diarrhea impact patient treatment and quality of life. The following changes were made to the protocol for this change:

Section 1.1: The text after the fourth sentence in the first paragraph was amended to provide background for why grade 2 toxicity is clinically important.

Section 1.2: New text, including a new reference, was added to the beginning of the second paragraph, providing the rationale for the changes being made in this amendment. The original first sentence of the paragraph was revised as "It is obvious that by reducing both low- and high-grade chemoradiation-induced bowel symptoms that the patient's quality of life during (and following) therapy can be enhanced."

Section 1.4.2: In the first sentence of the second paragraph, "2 to" was added to grade 3 diarrhea; a new second sentence was added.

Section 1.7: In the first sentence, "moderate" was added and CTCAE "grade 3" was changed to "grade 2-4." In the second sentence, "grade > 3" was changed to "grade > 2."

Section 2.1.1: The word, "moderate", was added, and "grade 3-4" was changed to "grade 2-4."

Sections 2.2.5 and 13.1.5: These sections were added to keep grade 3-4 diarrhea as a secondary objective/endpoint.

Section 13.1.1: The word, "Moderate", was added, and "grade 3" was changed to "grade 2" in "grade 2-5."

The following changes were made in Section 13.2:

- In the first sentence, "moderate" was added.
- The third sentence was amended to refer to three citations, and "20-35%" was amended to "25-50%".
- In the fourth sentence, "50%" was amended to "42%".
- In the sixth sentence, "35%" was amended to "45%".
The phrase, "grade 3" was changed to "grade 2" in the first, third, and sixth sentences.

**Section 13.6.2:** In the first sentence, "grade 3" was changed to "grade 2." The second sentence was deleted. In the table below the paragraph, the three significance levels were amended.

**REFERENCES:** Citation number 6, referred to in Section 1.2, was added, and subsequent citations were appropriately renumbered in REFERENCES and throughout the protocol.

**Other Changes**

**Title Page:** The contact information for Babu Zachariah, MD was changed.

An amended protocol is available on the RTOG Web site, [www.rtog.org](http://www.rtog.org)
RTOG 0315, “A Randomized, Double Blind, Placebo-Controlled Phase III Study To Determine The Efficacy Of Sandostatin LARÒ Depot (Octreotide Acetate) In Preventing Or Reducing The Severity Of Chemoradiation-Induced Diarrhea In Patients With Anal Or Rectal Cancer”

Study Chair: Babu Zachariah, MD, 813-972-8424, zacharb@moffitt.usf.edu

RTOG 0315 has been amended as follows:

The observation period for monitoring patients’ reactions to the test dose of Sandostatin® S.C. has been lengthened from 4 hours to 24 hours. This amendment is based on more than one report of patients experiencing diarrhea with cramping (a grade 3 reaction) after the four-hour observation period but within 24 hours of administration of the test dose.

The following sections were amended: Section 7.1 and Appendix I (under “What Is Involved In The Study?”).

An amended protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
SUMMARY OF CHANGES
Revision 3, Version Date: October 6, 2004

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”

Study Chair: Babu Zachariah, MD, 813-972-8424, zcharb@moffitt.usf.edu

RTOG 0315 has been revised as follows:

Section 7.7.2: The address for RTOG Headquarters was updated. This change also was made in Section 12.0 and in Appendix III.

Section 12.1: The Protocol Calculation Form (TL) was added to collect the field size of radiation. This information will be used as an adjustment factor in a secondary, exploratory analysis to determine if poor response (diarrhea) is related to field size.

A revised protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
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

Study Chair: Babu Zachariah, MD, 813-972-8424, zacharb@moffitt.usf.edu

RTOG 0315 has been revised as follows:

The following changes were made to Sections 5 and 7 in order to make the sequence of the procedures clearer to those registering patients:

Section 5: Section heading 5.1 added (Study Agent Shipment Form Pre-Randomization Requirement); Sandostatin Test Kit Distribution moved from Section 7.1.1 to become Section 5.2; wording from old Section 7.5.6.1 repeated in new Section 5.4 (Study Drug and Additional Test Kit Distribution) for clarity; old 5.3 and 5.4 wording deleted because it already occurs in Sections 7.1.1, 7.1.2, and 7.2.1.

Section 7: Old Section 7.2 Chemotherapy moved to just before Criteria for Removal from Therapy (now new section 7.5); old Section 7.3.2 and 7.3.3, concerning Sandostatin packaging and randomization, were moved to become Sections 7.3.4 and 7.3.5 just before 7.3.6 Storage; old Sections 7.3 Sandostatin Treatment Plan and Section 7.4 Study Drug Administration were combined and re-numbered as Sections 7.2 (and 7.2.1); old Section 5.4 Treatment Start Date was moved to new Section 7.2.1 as the first bullet.

Treatment Start Date: (first bullet in new Section 7.2.1): the wording has been changed to “Patients must start study drug within 5-7 working days of randomization.” The previous number of days (3) was too short.

Consent: Under What is Involved in the Study: Both Groups: Delete “Blood tests (as needed) to include a CBC, chemistries,” because these tests are done as Pre-Study Assessments only.

Study Chair Contact Information: The fax # for Dr. Babu Zachariah has been changed to 813-978-5805.

A revised protocol is available (no password required) on the RTOG website, http://www.rtog.org
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

Study Chair: Babu Zachariah, M.D., 813-972-8424, zacharb@moffitt.usf.edu

RTOG 0315 has been updated as follows:

Section 9.4 – Corrected typo .3 mg changed to 0.3 mg.

NOTE: This is an editorial/administrative change to the protocol. NCI requires that these changes be documented on the protocol title page with the date of the update noted as “Update Date”, not as a revision.

An updated protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
SUMMARY OF CHANGES
Update Date: March 23, 2004

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

Study Chair: Babu Zachariah, M.D., 813-972-8424, zacharb@moffitt.usf.edu

RTOG 0315 has been updated as follows:

Added Section 9.6 for clarification.

In the Consent, Under What Is Involved In The Study – Second paragraph, corrected typo "Sandostatin LAR® (long-acting form)" to read "Sandostatin® S.C."

In the Consent, Under What Are My Rights As A Participant – First paragraph, deleted sentences four and five as it is incorrect to imply that additional permission is needed from the patient in order for follow-up data to be submitted for analysis.

NOTE: This is an editorial/administrative change to the protocol. NCI requires that these changes be documented on the protocol title page with the date of the update noted as “Update Date”, not as a revision.

An updated protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
SUMMARY OF CHANGES
Update Date: February 23, 2004

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

Study Chair: Babu Zachariah, M.D., 813-972-8424, zacharb@moffitt.usf.edu

RTOG 0315 has been updated as follows:

In the Consent, Under What is Involved in the Study: In order to clarify that the
patient is registered and randomized and then receives a test dose of the study drug, the
following wording changes to the Consent were made:

- Paragraph Two, first sentence: delete the word “before.” The new wording of the
sentence is the following: “If you agree to participate in this study and you are
randomized, you will be given a test dose of the study drug….”

- Paragraph Three, second sentence: delete the words “be randomized into one of the
study groups described below.” The new wording of the sentence is the following: “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.”

- Page 24 under heading Both Groups: under section “At each follow-up appointment”,
deleted the phrase “Ultrasound of the gall bladder (as needed)” from the procedure list.

In the Consent, Under What Are the Risks of the Study, Under Sandostatin, Less
Likely: Delete the item “Dry mouth or throat discomfort.” It was inadvertently listed
both here and under “Rare.”

NOTE: This is an editorial/administrative change to the protocol. NCI requires that these
changes be documented on the protocol title page with the date of the update noted as
“Update Date”, not as a revision.

An updated protocol is available (no password required) on the RTOG Web site,
http://www.rtog.org
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

Study Chair: Babu Zachariah, M.D., 813-972-8424, zacharb@moffitt.usf.edu

RTOG 0315 has been updated as follows:

Informed Consent page 24 — Under “What is involved in this Study?”, “Both Groups”, “At each follow-up appointment”, deleted the phrase “Ultrasound of the gall bladder (as needed)” from the procedure list.

NOTE: This is an editorial/administrative change to the protocol. NCI requires that these changes be documented on the protocol title page with the date of the update noted as “Update Date”, not as a revision.

An updated protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
SUMMARY OF CHANGES
Revision 1, Version Date: January 12, 2004

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

Study Chair: Babu Zachariah, M.D., 813-972-8424, zacharb@moffitt.usf.edu

IRB Review Requirements:
(   ) Full board review required
(X) Expedited review allowed; however, site IRB requirements take precedence.
(   ) No review required

RTOG 0315 has been revised as follows:

Section 3.1.6 — For clarity, the phrase “for women of childbearing potential” was added
to the required pretreatment serum pregnancy test.

Section 9.4 — In the first sentence, “Grade > 3 diarrhea” was corrected to “Grade ≥ 3
diarrhea”.

Appendix 1, sample consent — Under “What Are The Risks Of The Study?”, in the last
paragraph under the risks associated with Sandostatin®: The phrase, “in rare cases”, was
deleted from the first sentence. The sentence now reads “Although the study drug,
Sandostatin LAR®, may prevent or reduce diarrhea, it could cause loose stools or
diarrhea in some patients”. This correction was made to make this sentence consistent
with “Diarrhea/loose stools” listed under the “Very Likely” risks of Sandostatin®.

A revised protocol is available (no password required) on the RTOG Web site,
http://www.rtog.org
RTOG 0315, A Randomized, Double Blind, Placebo-Controlled Phase III Study To Determine The Efficacy Of Sandostatin LARÒ Depot (Octreotide Acetate) In Preventing Or Reducing The Severity Of Chemoradiation-Induced Diarrhea In Patients With Anal Or Rectal Cancer

Study Chair: Babu Zachariah, M.D., 813-972-8424, zacharb@moffitt.usf.edu

RTOG 0315 has been updated as follows:

Eligibility Checklist — Question 16, page 2 and question 20, page 3 were deleted from this demographic/operational section of the checklist, and subsequent questions were appropriately renumbered. The patient’s gender will be specified in Question 11, and the treatment start date will be specified in question 19.

Section 12.1 — A “Pathology Report (P1)” was added to the forms due “Within 2 wks of study entry”.

NOTE: This is an editorial/administrative change to the protocol. NCI requires that these changes be documented on the protocol title page with the date of the update noted as “Update Date”, not as a revision.

An updated protocol is available (no password required) on the RTOG Web site, http://www.rtog.org