TITLE PAGE

Oral Mucositis

Protocol Number: SAN005-01

A Single-Center, Open-Label, Proof of Concept Trial to Evaluate the Efficacy, Safety and Tolerability of SAN005 for the Prevention and Treatment of Oral Mucositis Induced by Radiation Therapy with or without Concurrent Chemotherapy

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Supported by: Santalis Pharmaceuticals

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Title	A Single-Center, Open-Label, Proof of Concept Trial to Evaluate the Efficacy, Safety and Tolerability Trial of SAN005 for the Prevention and Treatment of Oral Mucositis Induced by Radiation Therapy with or without Concurrent Chemotherapy
Setting and Trial Center(s)	This trial will be a single-center study conducted in the United States
Objectives	The objectives of this proof of concept trial are: • To evaluate the efficacy of SAN005 when administered to adults for the prevention and treatment of radiation induced oral mucositis • To evaluate the safety of SAN005 when administered to adults for the prevention and treatment of radiation induced oral mucositis • To evaluate the tolerability of SAN005 when administered to adults for the prevention and treatment of radiation induced oral mucositis
Trial Design and Subject Population	This trial will be a single-center, open-label, proof of concept trial to evaluate the efficacy, safety and tolerability of SAN005 treatment regimen when administered to adults at least 18 years of age for the prevention and treatment of oral mucositis. Subjects will enter the Screening Period once the informed consent process has been completed. Subjects who are scheduled to receive radiation with or without concurrent chemotherapy and meet all of the inclusion criteria and none of the exclusion criteria will be eligible for the study: Once subject eligibility is confirmed the subject will start SAN005 treatment on Day 1 of their radiation treatment. All subjects will receive active medication in the study with the first dose administered on Day 1. Subjects will be instructed on the administration of study medication thrice daily throughout the duration of radiation therapy. Subjects will be evaluated by the physician once a week while receiving radiation therapy and then every other week once their radiation therapy has been completed, until their mucositis has resolved for the Final Study Visit.

Inclusion Criteria

Subjects will be included in the trial if they meet all of the following criteria:

1. Subjects with head and neck cancer involving the oropharynx or oral cavity, who are expected to undergo high dose radiation therapy (i.e., ≥ 60 Gy) that typically results in oral mucositis, with or without concurrent chemotherapy or biologic targeted therapy.
2. At least 18 years of age
3. Estimated survival of at least 6 months.
4. No prior radiation therapy to the head and neck area, and no chemotherapy within the last year except for induction chemotherapy delivered (or to be delivered) prior to the current course of radiation therapy
5. Female subjects of child-bearing potential must agree to use an adequate form of contraceptive (e.g., hormonal, barrier method or abstinence) prior to study entry and for the duration of the trial.
6. Are willing to refrain from using other treatments for oral mucositis until they consult with the study investigator(s).
7. Are able to give written informed consent in a manner approved by the Institutional Review Board and comply with the requirements of the study.

Exclusion Criteria

Subjects will be excluded from the trial if they meet any of the following criteria:

1. Have preexisting mucositis from other causes.
2. Are immunosuppressed or in chronic use of immunosuppressive drugs.
3. Have a known sensitivity to any of the constituents of the test product including sensitivities to sandalwood oil, fragrances or any member of the Compositae family of vascular plants (e.g., sunflowers, daisies, dahlias, etc.).
4. ECOG performance status ≥ 3
5. Unwilling or unable to follow the protocol requirements.
6. Have any condition that in the opinion of the investigator would confound the efficacy, safety and tolerability assessments, such as oral thrush.
7. Have participated in any clinical trial in the previous 30 days.
8. Are pregnant, breastfeeding, or unwilling to practice an acceptable form of birth control during the study.

Screening – Pretreatment Period

Visit 1

Eligible subjects will be asked to read and sign an informed consent form. No study procedures will be conducted until the informed consent form is signed.

The study investigator will review inclusion and exclusion criteria to ensure the subject qualifies for the study.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled, then the following study procedures will be performed:

- Record the subject's demographic data including height, weight PEG tube usage, quality of life questionnaire (QoL) and ECOG performance status
- Review and update the subject's pertinent medical history and current medications
- If the subject is a female of childbearing potential, perform a serum pregnancy test before radiotherapy simulation
- Instruct the subject to return for the next study visit

It is allowed that the above procedures to be completed on separate visits, as long as they are done before initiation of radiotherapy.

Treatment Period

Visit 2: Baseline (Day 1 of treatment or at Validation)

The following procedures will be completed at Visit 2 (Baseline).

- Review and update the subject's medications and PEG tube usage
- Inspect the oral cavity for any abnormalities that could potentially confound study results
- Administer the Numerical Rating Pain Scale (NRPS) as related to mouth pain and pain with swallowing. The NRPS will be recorded daily by the subjects between study visits.
- Administer the QoL Questionnaire
- Provide the subject with the products, directions for use and diary. Be sure to weigh the study medication container(s) to ensure an accurate weight of the unused medication is obtained at Visit 3 and for future comparisons
- Request the subject to complete Day 1 of the diary and review for completeness and accuracy

Visit 3 to 8

Clinic visit with a radiation oncologist once a week till the end of treatment.

All study visits will have a ± 2 day visit window during the radiotherapy.

- Query for adverse events
- Update concomitant medications and PEG tube usage
- Review the diary for the previous week
- Query for treatment regimen compliance
- Collect the study medication and weigh the study medication to determine usage
- Administer the QoL Questionnaire
- Administer the Numerical Rating Pain Scale (NRPS) as related to mouth pain and pain with swallowing. The NRPS will be recorded daily by the subjects between study visits
- Inspect the oral cavity and grade mucositis according to the RTOG Scale
- Record the subject's tolerability to the study drug
- Instruct the subject to return for the next study visit with study medication container and diary

Follow-up Period

Visit 9 to 10

Clinic visit with a radiation oncologist every other week after completion of radiotherapy until either mucositis resolves or it reaches Visit 10, whichever is earlier.

All study visits will have a ± 2 day window during the follow-up period.

- Query for adverse events
- Update concomitant medications and PEG tube usage
- Review the diary for the previous week.
- Query for treatment regimen compliance
- Collect the study medication and weigh the study medication to determine usage
- Administer the QoL Questionnaire
- Administer the Numerical Rating Pain Scale (NRPS) as related to mouth pain and pain with swallowing. The NRPS will be recorded daily by the subjects between study visits.
- Inspect the oral cavity and grade mucositis according to the RTOG Scale
- Record the subject's tolerability to the study drug
- Instruct the subject to return for the next study visit with study medication container and diary

Trial Contacts

Name	Affiliation / Address	Responsibility
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse drug reaction
AE	Adverse event
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
Eg	For example
EOS	End of Study
EOT	End of Treatment
ERB	Ethical Review Board
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good clinical practice
GRAS	Generally recognized as safe
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IGA	Investigator Global Assessment
IRB	Institutional Review Board
ITT	Intent to treat
IUD	Intra-uterine device
MedDRA	Medical Dictionary for Regulatory Activities
OTC	Over-the-counter
PP	Per protocol
QA	Quality Assurance
RTOG	Radiation Therapy Oncology Group
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard operating procedure
SPF	Sun protection factor
w/w	Weight/weight

1 INTRODUCTION

1.1 Oral Mucositis

Oral mucositis is an acute injury to the mucosal lining of the head and neck region associated with radiotherapy and chemotherapy. The inflammatory response to injury can cause pain and discomfort that result in dysphagia and odynophagia, excessive secretions and associated nausea. Patients often require a temporary feeding tube to go through radiotherapy. The severity of radiation-induced mucositis is associated with the volume of mucosa irradiated, radiation dose and fractionation, concomitant use of chemotherapy, and patient factors such as tobacco and alcohol use, genetic predisposition and comorbidities. It has a negative impact on patients' quality of life and compliance with treatment that often result in unintended radiation treatment breaks. It can also cause weight loss making radiation dose delivery less optimal secondary to significant tissue volume changes. These can unfavorably affect radiotherapy local control rates.

Currently there have been no agents that are clinically proven to prevent radiation-induced mucositis. The management strategies for oral mucositis are mainly supportive care including adequate pain control, use of protective coating agents or devices, feeding tube use to bypass the irradiated oral mucosa for nutrition and hydration, and other symptomatic management strategies.

Topical and systematic administration of analgesics is the most commonly used first-line therapy. There are many oral agents (various mouth rinses or coating devices) for the management of mucositis symptoms, but none have shown convincing benefits in treating radiation-induced mucositis. The FDA has approved several products not as active pharmacologics but as devices to relieve mucositis symptoms. Among those approved are Gelclair, MuGard, Mucatrol, and Caphasol. Other approaches, such as growth factor GM-CSF, Amifostine, antiseptic and antimicrobial agents, and anti-inflammatory agents have been tested but are mostly negative in trials[1].

1.2 Santalis Oral Mucositis Treatment

East Indian sandalwood is a tall evergreen tree native to southern India. The oil derived from this tree is composed almost exclusively of closely related sesquiterpenoids. The alcohols, alpha- and beta-santalol, are primarily responsible for the oil's odor and comprise approximately 70% of the oil. Both the wood (in powder form) and oil of the East Indian sandalwood tree have been used to treat a variety of skin and general health conditions. In traditional Indian (Ayurvedic) medicine, East Indian sandalwood oil (EISO) was used as a

treatment for inflammatory and eruptive skin diseases [2,3]. Traditional Chinese medicine also lists sandalwood as a treatment for gonorrhea [4], as well as for epigastric pain, chest pain, and vomiting[5]. In Europe, sandalwood has been used to treat fever and pain.

Sandalwood oil is a widely available item of commerce with minimal restrictions on the claims that vendors can make as to its potency, safety, and efficacy. Most sandalwood oils offered for sale are poorly characterized and may be of low grade and often contain residual solvents, adulterants, other essential oils, synthetic fragrances, and/or bulking or extending agents. Such materials are not generally manufactured and tested in accordance with the US FDA's 2004 Botanical Drug Development Guidelines and do not comply with the ISO specifications for EISO. There are a number of websites and documents that support the safe use of many essential oils, including sandalwood oil, on babies and children. It is not uncommon for consumers/parents to consult these sources, purchase sandalwood oil from any number of sources, and formulate their own treatments (sandalwood oil diluted in carrier oils), again with no regulation or controls for use on their children. Nevertheless, there have been very few reports of safety issues in the public domain.

Santalis plans to evaluate the safety and efficacy of their proprietary medical grade EISO, as the active ingredient in an oral mucositis treatment, in subjects with a high risk of developing oral mucositis during cancer therapy in a highly controlled environment consistent with prescription drug development guidelines. The initial observation of EISO as an efficacious preventive and therapeutic agent for oral mucositis came from a cancer patient who was undergoing chemotherapy (personal communications). It is Santalis' interest and belief that this observation may carry much further implications. As oral mucositis significantly affects patients' quality of life and therapeutic outcome, and there are few preventive and therapeutic agents with clinically proven efficacy available, a new treatment in managing radiation and chemotherapy induced oral mucositis, if proven efficacious, would benefit cancer patients tremendously.

The initial proposed clinical study will be conducted in adult head and neck cancer patients. This will be an open-labeled, proof of concept trial to evaluate the efficacy, safety and tolerability of EISO in a form of oral rinse as adjunctive therapy to standard of care. Santalis believes that the proposed study is a prudent and appropriate approach to investigate the potential of their product to prevent or improve oral mucositis symptoms commonly seen in patients undergoing radiotherapy with or without chemotherapy.

2. OBJECTIVES

The objectives of this trial are:

- To evaluate the efficacy of SAN005 when administered to adults for the prevention and treatment of radiation-induced oral mucositis

- To evaluate the safety of SAN005 when administered to adults for the prevention and treatment of radiation-induced oral mucositis
- To evaluate the tolerability of SAN005 when administered to adults for the prevention and treatment of radiation-induced oral mucositis

3. STUDY PLAN

3.1 Overall Study Design

This trial will be a single-center, open-label, proof of concept trial to evaluate the efficacy, safety and tolerability of SAN005 treatment regimen when administered to adults at least 18 years of age for the prevention and treatment of oral mucositis.

Subjects will enter the Screening Period once the informed consent process has been completed. Subjects who are scheduled to receive radiation with or without concurrent chemotherapy and meet all of the inclusion criteria and none of the exclusion criteria will be eligible for the study:

Once subject eligibility is confirmed the subject will start SAN005 treatment on Day 1 of their radiation treatment. All subjects will receive active medication in the study with the first dose administered on Day 1.

Subjects will be instructed on the administration of study medication thrice daily till oral mucositis resolves. Subjects will return to the clinic once a week while receiving radiation and then once every two weeks once their radiation has been completed and then until their mucositis has resolved for the Final Study Visit.

Preliminary Efficacy Evaluation will be the severity of pain rated by the NRPS and mucositis grade by RTOG criteria at Visit 7 (Day 36). Additional secondary efficacy evaluations will include the severity of pain rated by the NRPS and mucositis grade by RTOG criteria at each study visit, frequency of the PEG tube for feeding during the duration of treatment and weight loss from baseline through Visit 5 and 7. The time of mucositis onset and duration will also be used in assessing efficacy. Additional secondary and exploratory endpoints will be outlined in the statistical analysis plan. The overall efficacy is determined by comparing the data to historical controls.

Safety will be assessed by evaluating adverse events (AEs) with respect to severity, duration, and relationship to study drug. In addition tolerability evaluations will be performed at each study visit.

During the active treatment period, subjects will return to the study site according to the study schedule for interim assessments, review of subject dosing diaries, and assessment of concomitant medication and adverse events (AEs).

The study design is summarized in Figure 3-1.

Figure 3–1 Study Design

Pretreatment	Treatment		Follow-up
Day 0	Day 1 Baseline	Day 8,15,22,29,36,43 (± 2 day, weekly)	Every other week until mucositis resolves or it reaches Visit 10
Visit 1	Visit 2	Visit 3 to 8	Visit 9 and 10

3.2 Study Endpoints

Primary efficacy will be assessed by the numerical rating pain scale (NRPS) and RTOG mucositis grade at Visit 7 (Day 36).

4. SELECTION OF STUDY POPULATION

4.1 Number of Subjects Required

An estimated number of 15 patients at least 18 years of age will be enrolled in this study to ensure 10 analyzable patients who complete the study. Dropouts secondary to poor compliance or patients who have more than two weeks of radiation treatment break will be excluded and will be replaced by enrolling more patients.

4.2 Inclusion Criteria

Patients will be included in the trial if they meet all of the following criteria:

1. Subjects with head and neck cancer involving the oropharynx or oral cavity, who are expected to undergo high dose radiation therapy (i.e., ≥ 60 Gy) that typically results in oral mucositis, with or without concurrent chemotherapy or biologic targeted therapy.
2. At least 18 years of age
3. Estimated survival of at least 6 months.
4. No prior radiation therapy to the head and neck area, and no chemotherapy within the last year except for induction chemotherapy delivered (or to be delivered) prior to the current course of radiation therapy
5. Female subjects of child-bearing potential must agree to use an adequate form of contraceptive (e.g., hormonal, barrier method or abstinence) prior to study entry and for the duration of the trial.
6. Are willing to refrain from using other treatments for oral mucositis until they consult with the study investigator(s).
7. Are able to give written informed consent in a manner approved by the Institutional Review Board and comply with the requirements of the study.

4.3 Exclusion Criteria

Patients will be excluded from the trial if they meet any of the following criteria:

1. Have preexisting mucositis from other causes.
2. Are immunosuppressed or in chronic use of immunosuppressive drugs.
3. Have a known sensitivity to any of the constituents of the test product including sensitivities to sandalwood oil, fragrances or any member of the Compositae family of vascular plants (e.g., sunflowers, daisies, dahlias, etc.).
4. ECOG performance status $\geq$ 3
5. Unwilling or unable to follow the protocol requirements.
6. Have any condition that in the opinion of the investigator would confound the efficacy,

safety and tolerability assessments, such as oral thrush.

7. Have participated in any clinical trial in the previous 30 days.
8. Are pregnant, breastfeeding, or unwilling to practice an acceptable form of birth control during the study.

5.0 Patient Enrollment

The Investigator or designee will be expected to maintain a log of screened patients and an Enrollment Log of all patients enrolled in the study indicating their assigned study number.

This is an open-label study so there is no randomization. Each patient will receive active product.

As noted in Section 8.1.2, each potential patient will sign and date an informed consent form before any study specified procedures are performed.

Once a potential patient is determined to be eligible for inclusion in the study, site personnel will dispense study medication according to this protocol.

6.0 VISIT SCHEDULE AND ASSESSMENTS

6.1 Study Procedures

The visit schedule and assessments are summarized in Table 5-1. A patient will have a maximum of 10 visits: a pretreatment Visit (Visit 1), weekly treatment visits (Visit 2 – 8), and if the mucositis persists, follow-up visits (Visit 9 -10) every other week until the patient's mucositis has resolved which is estimated out to be approximately 9 to 11 weeks after Day 1 treatment initiation.

Source documents will be completed at each patient's visit, and the data captured in the source documents will be subsequently entered into the case report forms (CRFs) by the Investigator or designee.

Table 6–1 Time and Events

Procedure	Pretreatment	Treatment							Follow-up	
	Visit 1 Pretreatment (Up to -42 days)	Visit 2 Day 1 or Validation (± 2 days)	Visit 3 Day 8 (± 2days)	Visit 4 Day 15 (± 2 days)	Visit 5 Day 22 (± 2 days)	Visit 6 Day 29 (± 2 days)	Visit 7 Day 36 (± 2 days)	Visit 8 Day 43 (± 2 days)	Visit 9 Day 57 (± 2 days)	Visit 10 Day 71 (± 2 days)
Obtain Informed Consent[a]	X									
Review Inclusion/Exclusion Criteria	X									
Record Demographics and ECOG status	X									
Record Medical History[b]	X									
Record Concomitant Medications Including Chemo- and Radiation Treatment(s)	X	X	X	X	X	X	X	X	X	X
Conduct a Serum Pregnancy Test[c]	X									
Inspect the Oral Cavity and Grade Level of Mucositis	X	X	X	X	X	X	X	X	X	X
Administer NRPS and QoL	X	X	X	X	X	X	X	X	X	X
Teaching Correct Use of Study Drug		X								
Record Subject's Tolerability to Study Drug		X	X	X	X	X	X	X	X	X
Weigh Study Drug to Determine Usage			X	X	X	X	X	X	X	X
Dispense Study Drug as needed and Directions for Use with Diary		X	X	X	X	X	X	X	X	
Record Adverse Events		X	X	X	X	X	X	X	X	X

Footnotes to Table 1: Time and Events

[a] Site staff will follow the requirements of the local IRB if required to obtain informed consent from the subjects.

[b] Only pertinent medical history will be recorded for each subject including smoking history and alcohol intake.

[c] A serum pregnancy test will be completed for all women of child-bearing potential before radiotherapy simulation.

[d] Adverse events will be collected after the subject's first treatment and throughout the trial.

6.2 Study Visits and Contacts

6.2.1 Treatment Period: Visit 2 Baseline (Day 1 or at Validation)

The following procedures will be completed at Visit 2 (Baseline) after the informed consent process has been completed and the informed consent form signed.

- Review and update the subject's medications and PEG tube usage
- Inspect the oral cavity for any abnormalities that could potentially confound study results
- Administer the Numerical Rating Pain Scale (NRPS) as related to mouth pain and pain with swallowing. The NRPS will be recorded daily by the subjects between study visits.
- Administer the QoL Questionnaire
- Provide the subject with the products, directions for use and diaries. Be sure to weigh the study medication container(s) to ensure an accurate weight of the unused medication is obtained at Visit 1 and for future comparisons
- Review Day 1 of the diary for completeness and accuracy

6.2.2 Treatment Period: Visit 2 to 8

During the treatment period, subjects will be evaluated by the treating physician once a week. If it is not possible for the subject to come in for the scheduled study visit, the visit can be conducted 2 days earlier or later, but the study personnel should attempt to get the subject back on schedule at the next study visit.

The following procedures will be completed.

- Query for adverse events
- Update concomitant medications and PEG tube usage
- Review the diary of the previous week
- Query for treatment regimen compliance
- Collect the study medication and weigh the study medication to determine usage
- Dispense study medication, as necessary
- Administer the QoL Questionnaire
- Administer the Numerical Rating Pain Scale (NRPS) as related to mouth pain and pain with swallowing. The NRPS will be recorded daily by the subjects between study visits.
- Inspect the oral cavity and grade mucositis according to the RTOG Scale
- Record the subject's tolerability to the study drug
- Instruct the subject to return for the next study visit with study medication container and diary

6.2.3 Follow-up Period: Visit 9 to 10

Clinic visits with a radiation oncologist every other week after completion of radiotherapy until mucositis has resolved.

Study visits will have a ± 2 day window during the follow-up period.

- Query for adverse events
- Update concomitant medications and PEG tube usage
- Review the diaries of the previous week.
- Query for treatment regimen compliance
- Collect the study medication and weigh the study medication to determine usage
- Dispense study medication, as necessary
- Administer the QoL Questionnaire
- Administer the Numerical Rating Pain Scale (NRPS) as related to mouth pain and pain with swallowing. The NRPS will be recorded daily by the subjects between study visits.
- Inspect the oral cavity and grade mucositis according to the RTOG Scale
- Record the subject's tolerability to the study drug
- Instruct the subject to return for the next study visit with study medication container and diary

6.3 Interruption or Discontinuation of Treatment

Every subject has the right to refuse further participation in the study at any time and without providing reasons (see also Section 8.1.2). A subject's participation is to be terminated immediately upon his/her request. The investigator should seek to obtain the reason and record this on the case report form (CRF).

Should the subject, during the course of the study, develop conditions which would have prevented his/her entry into the study according to the safety related medical exclusion criteria, he/she must be withdrawn immediately.

The subject may be withdrawn from the study at any time at the discretion of the investigator for medical reasons and/or due to non-adherence to the treatment scheme and other duties stipulated in the study protocol. The reasons are to be fully documented on the CRF.

In addition, the sponsor and the investigator reserve the right to end or suspend the study at any time (see Section 8.2.3).

6.4 Withdrawals

The following medical and other reasons justify a premature termination (by subject or investigator) of any of the study products:

- Adverse event (including any SAE, clinically significant AE, intercurrent illness, or other medical condition that indicates to the investigator that continued participation is not in the best interest of the subject);
- Death;
- Lost to follow-up;
- Noncompliance with study medication dosing regimen, protocol requirements, or study-related procedures;
- Investigator discretion in case of occurrence of any medication condition, requirement for prohibited concomitant medication or treatment, or circumstances that would not allow the subject to adhere to protocol requirements;
- Pregnancy;
- Study terminated by Sponsor;
- Withdrawal of consent;

If a subject withdraws from the study, all efforts will be made to complete a final evaluation, if possible. Subjects discontinued due to an AE will be followed until the AE is resolved, a reasonable explanation is provided for the event, or the subject is referred to his/her own primary medical doctor. The specific AE in question will be recorded on the appropriate CRF. All subjects who are withdrawn should complete return to the clinic for a final assessment.

6.5 Withdrawal Procedures

Protocol-specified withdrawal procedures are the same as those to be performed at the last study visit (Section 6.2.9).

6.6 Subject Replacement

Subjects who prematurely discontinue the study will not be replaced. Up to 15 subjects will be enrolled to ensure 10 subjects complete the trial.

6.7 Subject Re-screening

Subjects previously denied entry into the study may be re-screened for enrollment once all inclusion (Section 4.2) and no exclusion criteria (Section 4.3) are met.

7 STUDY TREATMENT

7.1 Formulation

The product ingredients are consistent with other retail and OTC products at acceptable concentrations.

Formulation information is presented below in Table 7-1.1

Table 7–1. Santalis Mouth Rinse

Active ingredient	0.5% EISO
Inactive ingredients	Polysorbate-80 NF, Poloxamer 407 NF, Xylitol NF, Sorbitol 70% Solution USP, Menthol USP, Peppermint Oil NF, Sodium Saccharin USP, Purified Water USP
Dosing schedule	30 mL to be used thrice daily for approximately 10 weeks or until mucositis resolves.
Manufacturer	Pam Lewis and Associates, Boerne TX
Packaging	1 Liter bottles
Storage requirements	Store at controlled room temperature[a] (20°C to 25°C [68°F to 77°F])

a: Controlled room temperature indicates a temperature maintained thermostatically that encompasses the usual and customary working environment of 20°C to 25°C (68°F to 77°F). Excursions are allowed between 15°C and 30°C (59°F and 86°F).

7.2 Packaging and Labeling

The study product labels will contain, at minimum, the following information:

- Sponsor name and address;
- Protocol number;
- Subject number (may be hand printed on the label);
- Product description;
- Lot number;
- Storage conditions;
- Expiry or retest date, if applicable;
- "Investigational use only. Keep out of reach of children"

Study product(s) will be provided in study kits containing the mouth rinse.

7.3 Dosing Regimen

Subjects are to administer the treatment regimen according to the following schedule and order:

The following treatment products will be provided:

- Mouth Rinse– Take 30 ml by mouth each time. Swish for 30 seconds and spit. Use the rinse three times daily, including weekends when radiotherapy is not delivered, ideally 15 minutes after meals and refrain from eating or drinking for one hour after rinsing.

The investigational products contain ingredients commonly found in other oral products. The site staff will initially be responsible for teaching how to use SAN005, and then the subject will be instructed on the procedure for self- administration at home.

Subjects will be supplied with a patient dosing diary during the treatment period and will be instructed to answer several questions about their experience with the treatment regimen. The investigator or designee should collect and review the diary with the subject at every visit.

7.3.1 Dose Modification

In the event a subject experiences any health issue in the treatment area during the study, the subject should be examined by the study physician. All AEs should be recorded in the case report forms (CRFs) and any reactions to study product must be reported to the study coordinator.

If a subject experiences an allergic reaction to the study drug oral diphenhydramine may be administered according to package labeling if necessary.

Upon resolution of any reaction (localized or generalized), the subject may be re-challenged with study treatment at the discretion of the treating physician after careful analysis of the possible cause of the reaction. The investigator or designee must stress the importance of using the study treatment according to the instructions provided. In the absence of further reactions, study treatment may resume. If a reaction recurs, treatment should be stopped. Subjects should report to the study physician, and they will be discontinued from the study.

7.3.2 Assignment to Treatment

This is an open label study and all subjects will receive the active study medication. No randomization is required.

7.3.3 Subject Numbering

Each subject who signs an informed consent form and successfully completes the screening procedures will be enrolled in the study. Each subject will be assigned a unique subject number that will be written on the products and used on all CRFs.

7.4 Prior and Concomitant Therapy

All medications, including over the counter (OTC) drugs, mouth washes or rinses, taken within 30 days prior to the start of the study will be recorded at Pretreatment Visit (Visit 1). Information regarding the total daily dose, route of administration, start and discontinuation dates, and indication are to be recorded on the subject's CRF.

7.5 Treatment Compliance

Records of study product used and intervals between visits will be kept during the study. Product accountability will be noted by the study monitor during site visits and at the completion of the trial.

Subjects will be asked to return all partially used and empty products to the study site at each visit. The products will be weighed prior to dispensation and at each study visit and the weight difference will be analyzed as a measure of product usage. Subjects who are consistently noncompliant (ie, < 80% of required doses) will be counseled and may be withdrawn from the study. Subjects will be asked to return all unused product at the end of the study.

7.6 Efficacy Assessment

Efficacy is assessed by the patient's self-reporting of pain using Numerical Rating Pain Scale (NPRS) and the physician's assessment of oral mucosal changes using RTOG grading of mucositis.

7.6.1 Pain Assessment

At each Study Visit the NRPS will be recorded for mouth pain and pain upon swallowing. For the primary efficacy assessment the NRPS scale at baseline will be compared to Week 5. Subjects that complete at least 80% of treatments as determined by the diary and confirmed by the weight of the returned study product will be included in the efficacy analysis.

If possible, the same investigator who completes the scoring at Baseline should complete all subsequent assessments for the patient.

7.7 Tolerability Assessment

The number and percentage of subjects reporting burning or tasting irritation (Grade 1 or higher) will be tabulated by severity.

7.8 Safety Assessment

7.8.1 Safety Reporting

7.8.1.1 Definitions

Adverse event - An adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., and abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, without judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of

administration, formulation, or dose, including an overdose.

Adverse reaction - An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

Suspected adverse reaction - Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the drug caused the event. Inherent in this definition (of suspected adverse reaction), and in the requirement to report them is the need for the sponsor to evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the adverse event.

Unexpected Adverse Event - An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the literature for East Indian sandalwood oil.

Serious - An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the outcomes listed in Section 6.4.

Life-threatening - An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

If either the sponsor or investigator believes that the event meets the definition of life-threatening, it must be considered life-threatening.

7.8.1.2 Adverse Events

Information about all AEs, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, or other means, will be collected and recorded on the Adverse Events page of the CRF and followed as appropriate. Adverse events will be coded using an internationally recognized dictionary (see Section 7.8.1).

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (ie, any procedures specified in the protocol). Adverse events occurring before starting study treatment, but after signing the informed consent form, are recorded on the Medical History/Current Medical Conditions page of the CRF.

As far as possible, each AE will also be described by:

- its duration (start and end dates),
- the severity grade (mild, moderate, severe),
- its relationship to the study product (definite, probably, possibly, unlikely, or not related),
- the action(s) taken, and,
- the outcome, as relevant.

Severity of adverse events

The investigator is to classify the severity of an AE according to the CTCAE 4.0 definitions.

Relationship of adverse event to study treatment

The investigator is to classify the relationship of the AE to the investigational product according to the definitions outlined in Table 7-8.

Table 7–8 Terms for Defining Relationship of Adverse Event to Study Product

Association	Definition
Not related	(1) the existence of a clear alternative explanation (eg, mechanical bleeding at surgical site) or (2) non-plausibility, eg, the subject is struck by an automobile or develops cancer a few days after product administration.
Unlikely related	A clinical event, including laboratory test abnormality (if applicable), with an improbable time sequence to product administration and in which other drugs, chemicals for underlying disease provide plausible explanations.
Possibly related	A clinical event, including laboratory test abnormality (if applicable), with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably related	A clinical event, including laboratory test abnormality (if applicable), with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal.
Definitely related	A clinical event, including laboratory test abnormality (if applicable), with an established temporal or other association (eg, re-challenge) and the event is not reasonably explained by the subject's known clinical state or any other factor, based on available information.

7.8.1.3 Serious Adverse Events

An AE can be severe, but not necessarily serious. A serious adverse event (SAE) or suspected adverse reaction as 'serious' if, in the view of either the investigator or sponsor, results in any of the following outcomes:

- death;
- a life-threatening adverse events
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly or a birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered to be serious AEs are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen; and/or
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

If either the sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the sponsor.

Information about all SAEs will be collected and recorded on the Serious Adverse Event Report Form and reported to the Medical Monitor:

Ying Li, M.D., Ph.D.
Dept. Of Radiation Oncology
7979 Wurzbach Rd.
San Antonio, TX 78229
Telephone: 210-450-1719
Email: liy8@uthscsa.edu

To ensure subject safety each SAE must also be reported to the sponsor within 24 hours of learning of its occurrence and, if applicable, to the responsible Institutional Review Board (IRB) according to their reporting requirements.

Pregnancy, although not itself an SAE, should also be reported on a Serious Adverse Event Report Form.

A death occurring during the study, or which comes to the attention of the investigator within 4 weeks after stopping treatment, must be reported.

Any serious adverse event occurring in a subject after providing informed consent and until 4 weeks after stopping study drug treatment must be reported

8. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

8.1 General Considerations for Data Analysis

All statistical processing will be performed using the SAS® system (Version 9.12 or higher). Up to 15 subjects will be enrolled in this study to ensure a minimum of 10 subjects complete the study. The primary efficacy analysis of the study will be the determination of the NPRS from baseline to Visit 7 (Day 36).

Secondary efficacy endpoints will be evaluated using descriptive statistics. No interim or subgroup analyses are planned.

8.2 Sample Size and Power Considerations

This study is not designed or powered for statistical considerations.

8.3 Treatment Assignment and Blinding

This is an open-label study therefore, no blinding is required.

8.4 Analysis Populations

8.4.1 Intent-to-Treat Analysis Set

The Intent-to-treat (ITT) Analysis Set is defined as all subjects enrolled and that receive at least one treatment of the investigative study regimen.

8.4.2 Full Analysis Set

The Full Analysis Set (FAS) is defined as all subjects who receive at least one administration of the investigative study regimen and who had at least one post-Baseline efficacy assessment. The FAS population will be the primary population used for efficacy analysis.

8.4.3 Per Protocol Analysis Set

The Per Protocol Analysis Set (PP) is defined as all subjects in the FAS who do not have any major protocol violations, including:

- Violations of inclusion/exclusion criteria;

- Use of prohibited concomitant medications;
- Noncompliance (ie, <80% compliant with study treatment);
- Failure to provide a clinical observation at Week 5 (± 2 day, Visit 7);

The PP will be a secondary population used for efficacy analysis.

8.4.4 Safety Analysis Set

The Safety Analysis Set is defined as all enrolled who received at least one dose of study treatment.

8.5 Planned Methods of Analysis

8.5.1 Background and Demographic Characteristics

Descriptive statistics will be used to summarize demographic characteristics (age, gender, and race) and background characteristics for the enrolled subject population. Past/coexistent medical history information for all subjects will be presented in a by-subject listing.

8.5.2 Study Product/Visit Compliance

The number and percentage of subjects attending each study visit will be presented. Compliance to study treatment and extent of exposure will be summarized by descriptive statistics of total number of uses, total weight of product used, and average weight per application of product. The number and percentage of subjects who received fewer than 80% will be presented.

8.5.3 Prior and Concomitant Therapy

Prior and concomitant medication information for all treated subjects will be presented in a by-subject listing.

8.5.4 Efficacy Analysis

The primary data analysis set for efficacy analyses will be the PP defined in Section 8.4.3. The primary analysis will be the determination of the severity and intensity of mucositis from Baseline to Visit 7 (Day 36).

The secondary efficacy endpoints analysis will be summarized using standard statistical methods and outlined in the Statistical Analysis Plan (SAP). In general, categorical endpoints will be tabulated by number, percentage, and a 95% 2-sided confidence interval (exact methodology) will be estimated. Continuous endpoints (i.e., percent change from baseline) may be summarized using descriptive statistics (N, mean, median, standard deviation, and range).

8.5.5 Safety Evaluations

Adverse events

The assessment of safety will be based on the frequency of AEs and the severity of AEs according to the CTCAE Version 4.

Adverse events may be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Adverse events will be summarized by presenting, for each treatment group, the number and percentage of subjects having any AE, having an AE in each body system and having each individual AE. Any other information collected (e.g., severity or relatedness to study medication) will be listed as appropriate.

8.6 Interim Analyses

No interim analyses are anticipated.

9.0 ADMINISTRATIVE PROCEDURES

9.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with standard operating procedures (SOP) of the clinical site.

9.1.1 Institutional Review Board (IRB)

Before implementing this study, the study site must determine if this study requires local IRB approval of the protocol, the proposed informed consent form. If required a signed and dated statement that the protocol and informed consent form have been approved by the IRB must be received before study initiation. All IRB procedures must be followed e.g.

approval of the informed consent document, advertising materials, any amendments to the protocol, other than administrative ones, and the reporting of serious adverse events.

9.1.2 Subject Information and Consent

The investigator or designee must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and he/she should be given a copy of the signed document. No subject can enter the study before informed consent has been obtained from him or her.

9.1.3 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the CRF, and if the subject name appears on any other document it must be obliterated before a copy of the document is supplied to the sponsor. As part of the informed consent process, the subjects will be informed in writing that representatives of the sponsor, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that subject confidentiality will be maintained at all times.

9.2 Changes in the Conduct of the Study or Planned Analyses

9.2.1 Protocol Amendments

With the exception of administrative changes, any changes or additions to this clinical study protocol require a written protocol amendment that must be approved by the Sponsor and the investigator before implementation.

9.2.2 Other Changes in Study Conduct

Deviations from the planned study conduct are not permitted; any unforeseen changes in study conduct must be reported within 5 days to the sponsor.

9.2.3 Termination or Suspension of Study

The sponsor reserves the right to terminate or suspend the study at any time. If applicable, the IRB will be notified of the termination/suspension and the reason(s).

9.3 Data Handling and Record Keeping

9.3.1 Recording of Data

Case report forms will be designed to identify each subject by number and subject's initials, the protocol number, and the results observed. Data on subjects collected on CRFs during the study will be documented and properly coded, and the subject will only be identified by the subject number, and by his/her initials, if also required. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, both the study sponsor, and the investigator are bound to keep this information confidential.

All CRFs must be completed legibly and accurately using a black ballpoint pen. Pencils and correction fluids may not be used. If corrections are necessary, an authorized member of the investigator's staff will enter them in the following manner: the wrong entry will be crossed out (however, it must remain legible) and the correct entry will be placed next to it. Corrections will be initialed and dated. The CRFs will be kept in order and current, so that they reflect the latest observations on the subjects enrolled in the study.

In addition to the case report forms, individual subject source documents will be maintained. These documents may include the visit dates, the clinical study number, the name or initials of the subject, medical history or previous physical examinations, demographic and medical information, including, concomitant medications/treatments, etc, any AEs encountered, and other notes, as appropriate. All information on CRFs must be traceable to the source documents kept in the subject's file, including reasons for corrections on the CRF or source documents. These reasons must be initialed and dated by the individual who made the correction. Data without a written or electronic record will be defined before the start of the study and will be recorded directly on the CRFs by the investigator or his/her designee, which will be documented as being the source data.

The lead investigator at each site must sign the designated page(s) of the CRFs, thereby stating that he/she takes responsibility for the accuracy of the data in the entire case record book. All records will be kept in conformance to applicable U.S. laws and regulations.

The original signed informed consent form will be attached to each subject's file. When the study treatment is completed, the informed consent form will be in the appropriate file folder; otherwise a note indicating where the records can be located will be made.

9.3.2 Retention of Documents

Essential documents, as listed below, must be retained in a secure place by the investigator for a minimum of 5 years from completion of the study (and must inform the Sponsor prior to destruction), or as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

- the study protocol and any amendments;
- IRB approvals for the study protocol and all amendments;
- all source documents;
- CRF originals or copies;
- subjects' informed consent forms (with study number);
- Product inventory
- any other pertinent study document (e.g., investigator's brochure, correspondence, study reports, etc.).

9.3.3 Database Management

Data will initially be entered into an acceptable database for review and analysis.

9.3.4 Coding of Concomitant Medications and Adverse Events

Concomitant medications entered into the database may be coded using the World Health Organization (WHO) Drug Reference List which classifies the medications according to the Anatomic Therapeutic Chemical classification system. Coexistent diseases and AEs may be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

9.3.5 Database Lock

When the database has been declared to be complete and accurate, the database will be locked.

9.4 Product Handling and Accountability

All product supplies are to be used only for this clinical study and not for any other purpose. Study product supplies must be kept in an appropriate, secure area (eg, locked cabinet) and stored according to the conditions specified on the product labels.

The investigator site must maintain a full record of the shipment and dispensing of study product in a product accountability ledger. This log must be kept current and should contain the following information:

- identification of the subject to whom the study product was dispensed,
- date(s) and quantity of the study product dispensed to the subject,
- date(s) and quantity of the study product returned by the subject (if applicable), and
- initials of the study site representative(s) dispensing and receiving returned study product.

The inventory must be available for inspection by the study monitor. Any discrepancy and/or deficiency must be accounted for.

The investigator must not destroy any product labels, or any partly used or unused product supply. At the conclusion of the study and, as appropriate, during the course of the study, all study product supplies, including partially used or empty containers, must be returned or destroyed according to the designation of the sponsor. Any missing supplies will be indicated on the inventory.

If requested in writing by the sponsor, unused product supplies may be destroyed by the Principal Investigator, provided such disposition does not expose humans to risks from the drug. **Records shall be maintained by the principal investigator of any such alternative disposition of the investigational product.** These records must show the identification and quantity of each unit disposed of, the method of destruction (taking into account the requirements of local law), and the person who disposed of the products. Such records will be retained in the principal investigator's records for this clinical study and copies will be submitted to the sponsor.

9.5 Quality Control and Quality Assurance

9.5.1 Monitoring Procedures

During the study, a study monitor may visit the study site(s) regularly to check the completeness of subject records, the accuracy of entries on the CRFs, adherence to the protocol and to the principals of ICH-GCP guidelines, the progress of enrollment, and also to ensure that study product is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the study monitor during these visits.

The data required by the protocol must be recorded on the appropriate CRFs. The CRFs and any source documents will be available to the study monitor who will perform a 100% data check (comparison of the data recorded in the CRF with those in the source documents). The CRFs and source data will also be available for an audit by the sponsor, or sponsor representative, at any time.

The investigator must give the monitor and auditor access to relevant hospital or clinical records, to confirm their consistency with the CRF entries. No information in these records about the identity of the subjects will leave the study site(s). Additional checks on the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. The completed CRFs and all other records will be kept on file as outlined above (see Section 9.3.2 on retention of documents).

9.5.2 Auditing Procedures

In addition to the routine monitoring procedures, a study center may be audited in depth for study quality assurance by the sponsor, an external auditor on behalf of the sponsor, and/or by regulatory authorities. This audit may include a review of all source documents, drug records, and original CRFs at some or all of the study sites used in the study. Subject confidentiality will be maintained at all times and consent for this will be obtained before

entry of the subject into the clinical trial (see Section 8.1.2 on informed consent). If an inspection is requested by a regulatory authority, the investigator must immediately inform the study sponsor that this request has been made.

9.6 Study Funding

The costs necessary to perform the study will be agreed with the investigator and/or the management of the study center, and will be documented in a separate financial agreement that will be signed by the investigator and the sponsor, or designee.

9.7 Confidentiality and Publication Policies

9.7.1 Disclosure and Confidentiality

By signing the protocol, the investigator agrees to keep all information provided by the sponsor in strict confidence and to request similar confidentiality from his/her staff and the IRB. Study documents provided by the study sponsor (i.e. protocols, investigators' brochures, CRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by the sponsor to the investigator may not be disclosed to others without direct written authorization from the sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial.

9.7.2 Communication and Publication of Results

Any formal presentation or publication of data from this study will be considered as a joint publication by the investigator(s) and appropriate sponsor personnel. Authorship will be determined by mutual agreement. The sponsor must receive copies of any intended communication in advance of publication (at least 30 working days for an abstract or oral presentation and 60 working days for a journal submission). The sponsor will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently divulged and provide any relevant supplementary information.

10. REFERENCE LIST

1. Rosenthal DI, Trotti A: Strategies for Managing Radiation-Induced Mucositis in Head and Neck Cancer. Seminars in Radiation Oncology 19:29-34, 2009
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5. The PDR for Herbal Medicine(3rd ed.) ontvale, NJ:702–703, 2004

Appendix 1 – Numerical Rating Pain Scale (NRPS) and Tolerability

Numerical Rating Pain Scale (NRPS)

Date:

My oral pain on swallowing today (on a scale of 0-10)
(please circle the appropriate number)

0	1	2	3	4	5	6	7	8	9	10
No Pain										**Worst Possible Pain**

I have taken pain medication today (circle one)? Yes No

The name of the pain medication?

What is the daily dose you are taking?

How do you take your pain medication (by mouth, patch?)

How often do you take your pain medication (once daily, twice daily, etc.)?

Tolerability assessment: (Please circle your selection)

Taste	Poor	Fair	Good	Excellent
Burning/irritation	None	Mild	Moderate	Severe

Appendix 2 - RTOG Grading Scales for Acute Radiation Mucositis

Grade	Mucous Membrane
0	No change over baseline
1	Injection/may experience mild pain not requiring analgesic
2	Patchy mucositis which may produce an inflammatory serosanguinitis discharge/may experience moderate pain requiring analgesia
3	Confluent fibrinous mucositis/may include severe pain requiring narcotic
4	Ulceration, hemorrhage or necrosis