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Rose Geranium in Sesame Oil Nasal Spray as an Agent to Improve Symptoms of Nasal Vestibulitis: A Phase III Double Blinded Randomized Controlled Trial

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Mayo Clinic Cancer Center

MC19C1, Rose Geranium in Sesame Oil Nasal Spray as an Agent to Improve Symptoms of Nasal Vestibulitis: A Phase III Double Blinded Randomized Controlled Trial

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Drug Availability:
Commercial Agents: Gateway Pharmacy; Bismark, ND

MNCCTN institutions will enter patients on this clinical trial

Document History	**(Effective Date)**
Activation	November 13, 2020
MCCC Amendment 1	pending

Protocol Resources

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*No waivers of eligibility allowed

Table of Contents

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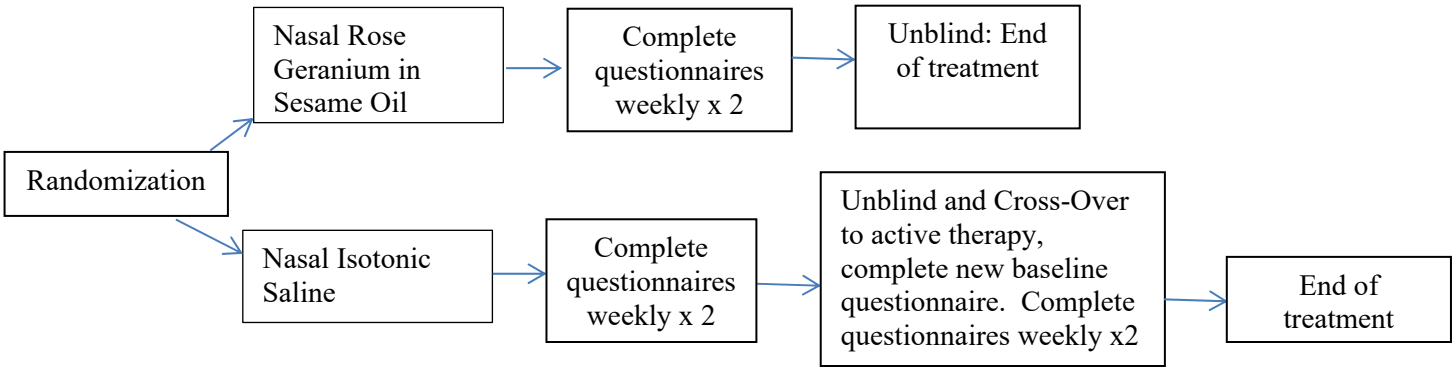
Schema



Cycle length= 14 days

Generic name: Nasal Rose Geranium in Sesame Oil Brand name(s): N/A Availability: Gateway Pharmacy	Generic name: Nasal Isotonic Saline Brand name(s): N/A Availability: Gateway Pharmacy

1.0 Background

Dryness, crusting, pain, and bleeding of the nostrils due to inflammation, termed nasal vestibulitis, is infrequently reported in the literature as a side effect of cancer-directed therapy, but recent reports support that this is a common clinical problem for which patients desire an effective intervention. One retrospective study described 115 patients who developed nasal vestibulitis while undergoing targeted therapy (1). Recently, a Mayo study surveyed 100 patients, who had undergone at least 6 weeks of cancer-directed therapy, regarding the presence of nasal symptoms (2). Forty-one percent of the 100 surveyed patients reported nasal symptoms, including dryness, pain, bleeding, and scabbing. Higher frequencies were reported among those who had received taxanes (71%), and VEGF-related therapies (78%).

The current literature does not guide providers as to how best to treat nasal vestibulitis. Topical antibiotics may offer some benefit for nasal vestibulitis associated with cancer-directed therapy. Of the 115 patients undergoing targeted therapy and evaluated by Ruiz et al, 95% of patients were treated with topical or oral antibiotics by a dermatology provider, and 60% reported symptom resolution (1), but this has not been prospectively studied.

Another potential therapy for nasal vestibulitis is rose geranium in sesame oil nasal spray. This compound was initially evaluated in a small study, which showed that it decreased epistaxis severity among patients with hereditary hemorrhagic telangiectasia (2-4). After rose geranium in sesame oil nasal spray was anecdotally noted to improve nasal vestibulitis symptoms, a retrospective evaluation of its potential benefit in breast cancer patients undergoing cancer-directed therapy at Mayo Clinic was conducted. Of the 20 patients who used the nasal spray product and responded to surveys, all reported symptomatic benefit, and 8 (40%) reported dramatic or complete resolution of symptoms.

While very rare cases of lipoid pneumonia have been reported after ingestions of large amounts of sesame oil, this compound was generally well tolerated; although two patients reported unpleasant effects: one commented that it was “messy” and another noted that it left an “oily coating at the back of the throat” (5, 6). A prospective study of rose geranium in sesame oil nasal spray is needed to better determine the potential benefit of this compound.

The current trial is designed to prospectively evaluate the utility of a rose geranium in sesame oil nasal spray for treating established nasal vestibulitis.

Nasal isotonic saline has not been studied in nasal vestibulitis. Limited data report that nasal isotonic saline mildly improves symptoms of rhinosinusitis, but it is most efficacious when utilized as a part of high-volume nasal irrigation (7-9). While it is frequently used to treat dry nasal passages, isotonic saline nasal spray was used as a placebo control in a trial evaluating a sesame oil nasal spray for weather-related dry nasal mucosa (4).

1.1 Treatment

1.11. Dosing and scheduling of rose geranium in sesame oil nasal spray

This trial will be an evaluation of rose geranium in sesame oil nasal spray versus nasal saline. Rose geranium in sesame oil nasal spray is a compounded preparation, containing 0.2 mL (4 drops) of pharmaceutical grade rose geranium oil to 119.8 mL of pharmaceutical grade sesame oil and then put into 30mL bottles. This is the same compound that was used in the aforementioned study of patients with hereditary hemorrhagic telangiectasia (2). Isotonic nasal saline will contain 0.9% sodium chloride with benzalkonium chloride, as a preservative, in a 30 mL bottle.

1.12 Treatment duration

The therapy will be given for two weeks. This should give us adequate time to determine whether rose geranium in sesame oil nasal spray can decrease nasal vestibulitis. Following that two week period, participants taking the saline spray will be allowed to cross over to the other spray. Subjects may cross over within two weeks after completion of treatment and be on therapy for an additional two weeks such a patient must still be receiving chemotherapy or within 2 weeks of the last chemotherapy dose, at the time of crossover.

2.0 Goals

2.1 Primary Goal

To determine the ability of rose geranium in sesame oil nasal spray to alleviate nasal vestibulitis in patients undergoing systemic, antineoplastic therapy when compared with isotonic nasal saline.

2.2 Secondary Goals

To assess toxicities related to rose geranium in sesame oil nasal spray in this study situation.

3.0 Registration Patient Eligibility

3.1 Registration - Inclusion Criteria

3.11 Age ≥18 years and be diagnosed with cancer and receiving chemotherapy

3.12 Ability to provide informed consent

3.13 Willingness to complete questionnaires

3.14 ECOG Performance Status (PS) 0, 1, 2

3.15 One or more of the following nasal symptoms for which the patient reports they would appreciate treatment. Symptoms must have started after the initiation of systemic, antineoplastic therapies, be attributed to the systemic, antineoplastic therapies, and symptoms must be reported as being moderate (corresponding to a score of 2) or worse on a scale from mild (1) to very severe (4) on at least one of the items below.

a. Dryness

b. Discomfort/Pain
c. Bleeding
d. Scabbing
e. Sores

3.2 **Registration - Exclusion Criteria**

3.21 Predisposition to epistaxis prior to the initiation of cancer-directed therapy (more than once a month over the previous year).

3.22 Planned initiation or continuation of any topical nasal treatment other than the studied nasal spray,(such as nasal steroids, Ayr nasal gel, Neosporin ointment or nasal administration of petroleum jelly). Taking Imitrex for migraines is acceptable.

3.23 Previous exposure to rose geranium in sesame oil nasal spray.

3.24 Concurrent upper respiratory tract infection

3.25 History of allergic or other adverse reactions to sesame oil or essential rose geranium oil

3.26 Any other reason that the study clinician or investigator feels precludes safe or appropriate inclusion in this study

3.27 Vulnerable populations: pregnant women, prisoners, mentally handicapped.

3.3 Re-Registration:

3.31 The patient will be un-blinded and determined to have been on the saline arm, when initially randomized.

4.0 Test Schedule

Tests and procedures	Active Monitoring Phase		
	≤ 14 days prior to Registration	**Baseline (Day 1)**	**Days 7 and 14**
Window			±3 days
History and appropriate physical exam	**X**		
Adverse event assessment		X	X
Baseline pre-nasal spray questionnaire (App I)		**X[2]**	
Nasal symptom and patient experience questionnaire (App II). Nurse should ensure that this contains a record of patient's most prominent nasal symptom at baseline			**X**
Nurse/research staff call[1]			**X**

1. Phone evaluation once weekly, to remind patients to complete questionnaires and evaluate AEs.
2. Administer questionnaire on the same day nasal spray starts, making sure that the patient completes the questionnaire prior to receiving the study spray

Cross-Over Continuation Phase (For Initial Saline participants only)		
Tests and procedures	**Baseline (Day 1)**	**Days 7 and 14 after cross-over**
Window	±14 days	± 3 days
Patient contact (Nurse visit/call)	X	
Adverse event assessment		X
Baseline pre-nasal spray questionnaire (App I)	X[2]	
Nasal symptom and patient experience questionnaire (App II). Nurse/research staff should ensure that this contains a record of patient's most prominent nasal symptom at baseline		**X**
Nurse/research staff call[1]		**X**

1. Phone evaluation once weekly, to remind patients to complete questionnaires and evaluate AEs
2. Administer questionnaire on the same day nasal spray starts, making sure that the patient completes the questionnaire prior to receiving the study spray

4.1 Survival Follow-up: N/A

5.0 Stratification Factors

5.1 **Gender:** Male vs. Female

5.2 **Age:** ≤ 50 vs. > 50

5.3 History of **Seasonal Allergies and/or Asthma:** Yes vs. No

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

To register a patient, access the Registration Application at registration.mayo.edu. The Registration Application is available 24 hours a day, 7 days a week. If unable to access the application, contact the Mayo Clinic Site Management Team (ResearchSiteManagement@mayo.edu, 507-284-2753) between the hours of 8am and 4:30pm Central Time, Monday through Friday.

Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC Subject ID number (R######) must be assigned. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent.

All Institutions:

6.2 Verification of materials

Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.3 Documentation of IRB approval

Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: 507-284-0885). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.4 Treatment start

Treatment cannot begin prior to registration and must begin ≤14 days after registration.

6.5 Baseline symptoms

Only nasal symptoms are required to be documented at baseline, within one day prior to starting the spray.

6.6 Study drug

Study agent will have been sent to the institution entering the patient.

6.7 Patient questionnaire booklets

Patient questionnaire booklets are available on site. Copies are not acceptable for these submissions. Booklets should be ordered using the Patient Questionnaire Order Form

6.8 Study Conduct

The clinical trial will be conducted in compliance with regulations (21 CFR 312, 50, and 56), guidelines for Good Clinical Practice (ICH Guidance E6), and in accordance with general ethical principles outlined in the Declaration of Helsinki; informed consent will be obtained from all participating patients; the protocol and any amendments will be subject to approval by the designated IRB prior to implementation, in accordance with 21 CFR 56.103(a); and subject records will be stored in a secure location and subject confidentiality will be maintained. The investigator will be thoroughly familiar with the appropriate use of the study drug. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

6.9 Randomization Procedures

6.9a1 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.9a2 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups saline vs rose geranium in sesame oil using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups (Pocock-Simon ref – see below).

Procedures for Double Blinding the Treatment Assignment

After the treatment assignment has been ascertained by the registration/randomization application, the patient's study medication code number will be displayed on the confirmation of registration screen.

MCCC Registration Office personnel will monitor the supply of coded bottles at each participating institution and will arrange for the research pharmacist to send further supplies to the participating institutions as needed.

6.9b Crossover Registration (Step 2)

To register a patient, access the Registration Application at registration.mayo.edu. The Registration Application is available 24 hours a day, 7 days a week. If unable to access the application, contact the Mayo Clinic Site Management Team (ResearchSiteManagement@mayo.edu, 507-284-2753) between the hours of 8am and 4:30pm Central Time, Monday through Friday.

Prior to initiation of protocol treatment, this process must be completed in its entirety.. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent.

6.9b3 Treatment cannot begin prior to registering to the crossover phase and will ideally begin ≤14 days after registration for the crossover phase.

7.0 Protocol Treatment

7.1 Treatment Schedule

7.12 Treatment medication table

Arm	Agent	Dose Level	Route	Days	Cross-over continuation phase
A	Rose Geranium in Sesame Oil Nasal Spray	1 spray into each nostril twice daily. One additional spray can be administered if the first spray is not a full spray	Intranasal	1-14 twice daily	N/A
B	Nasal Saline	1 spray into each nostril twice daily. One additional spray can be administered if the first spray is not a full spray	Intranasal	1-14 twice daily	Administer the cross-over nasal preparation, in the same manner as the first randomization.

Participants should not be taking other topical nasal preparations at the same time as the provided nasal sprays. If the patient develops a concurrent infection or allergic episode involving the nasal passages (i.e. sinusitis or allergic rhinitis) after enrollment, the treating physician should provide the appropriate treatment for this infection.

7.2 Breaking Codes in Double–Blinded Studies

Emergency Unblinding Procedures
In the event of an emergency, call the MCCC Registration Office at (507) 284–2753 to break the code on Monday through Friday, 8:00 a.m. to 4:30 p.m. Central Time. If the code must be broken after hours, assume the patient was assigned to active treatment and treat accordingly. Place a call to the MCCC Registration Office and leave a message informing them of the need to un-blind a patient. Provide your contact information so that MCCC Registration Office personnel can return the call the next business day.

Protocol-Specific Unblinding Procedures
Trial participants who complete initial protocol treatment may be unblinded. To unblind the patient, call the MCCC Registration Office (507-284-2753) Monday through Friday, 8:00 a.m. to 4:30 p.m. Central Time to find out if the patient was receiving nasal rose geranium in sesame oil or nasal isotonic saline. Upon confirmation by the nurse/research staff call that all questionnaires have been completed and sent in the mail, the treatment assignment may be unblinded. Patients who were assigned nasal isotonic saline may proceed with the crossover phase and must be re-registered per the instructions in Section 6.9b.

8.0 Dosage Modification Based on Adverse Events

If the patient develops any Grade 2 or higher Adverse Event (AE) attributed to rose geranium in sesame oil nasal spray or isotonic nasal saline, it should be recorded on the AE Form and the study spray should be reduced to once a day or be stopped per clinician discretion. The patient should continue to be followed according to protocol criteria.

9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care:

Other treatment as necessary for control of chemotherapy related symptoms is allowed, with the exception of utilization of other topical nasal therapies.

10.0 Adverse Event (AE) Monitoring and Reporting

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf	Mayo Sites – attach to MCCC Electronic SAE Reporting Form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 Will automatically be sent to CANCERCROSAFETYIN@mayo.edu and RSTP2CSAES@mayo.edu Non Mayo sites – complete and forward to RSTP2CSAES@mayo.edu

Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form: http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56	Will automatically be sent to CANCERCROSAFETYIN@mayo.edu and RSTP2CSAES@mayo.edu
Non-Mayo Clinic Sites	MedWatch 3500A: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf	RSTP2CSAES@mayo.edu and MCCCCRO@mayo.edu

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0 A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

a. Identify the grade and severity of the event using the CTCAE version 5.0.
b. Determine whether the event is expected or unexpected (see Section 10.2).
c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
e. Determine if other reporting is required (see Section 10.5).
f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.
An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.
NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.32 **EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting**

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*

*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

*Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry

- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.

10.4 Expedited Reporting Requirements for Commercial or Commercial Imaging Agents (Non-IND) Agent(s) ONLY:

10.41 Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND trial within 30 Days of the Last Administration of a Commercial Agent[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

NOTE: Refer to Section 10.32 for exceptions to Expedited Reporting

10.42 General reporting instructions

The Mayo IND and/or MCCC Compliance will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 for investigational agents or commercial/investigational agents on the same arm. Will automatically be sent to CANCERCROSAFETYIN@mayo.edu and RSTP2CSAES@mayo.edu

Non-MCCC Institutions:

Use form MedWatch 3500A http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

Submit copies to MCCCCRO@mayo.edu, RSTP2CSAES@mayo.edu and

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide the appropriate documentation and use the Mayo Clinic Cancer Center Expedited Event Report form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56, to submit to CANCERCROSAFETYIN@mayo.edu. The Mayo Clinic Compliance Unit will review and process the submission to the Mayo Clinic IRB and work with the IND Coordinator for submission to FDA.

Non-MCCC Institutions*:*

Submit to your IRB as required by your institutional policies.
Submit copies to FDA, RSTP2CSAES@mayo.edu and

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
    - Death due to progressive disease should be reported as **Grade 5 "General disorders and administration site conditions-Disease progression"**under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND will be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

10.55 Pregnancy, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.6 Required Routine Reporting

10.61 **Baseline and Adverse Events Evaluations**

Pretreatment symptoms/conditions other than nasal symptoms do not need to be graded.

10.62 All other AEs

Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.621 Grade 1 and 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

11.0 Treatment Evaluation/Measurement of Effect

Effect of nasal preparation will be measured by differences in reported nasal symptoms before and after, utilizing responses to questionnaires in Appendix 1 and 2.

12.0 Descriptive Factors

12.1 Prior different treatments tried for nose symptoms: 0 vs 1 vs 2 vs 3+

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. If the patient received treatment, the patient may continue treatment at the discretion of the

physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol.

- If the patient never received treatment, on-study material must be submitted.

13.2 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol.

13.3 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens: None

15.0 Drug Information

15.1 Rose Geranium Extract (genus *Pelargonium*) in Sesame Oil Nasal Spray

15.11 **Background**: Rose geranium in sesame oil nasal spray is a compounded product utilizing essential rose geranium oil and sesame oil.

15.12 **Formulation**: We will obtain Rose Geranium from Professional Compounding Centers of America (PCCA).

0.2 mL of Rose Geranium oil will be mixed with 119.8 mL of Sesame Oil. After mixing the compounded product will be aliquoted into nasal spray bottles (30 mL / bottle). The study agent will be compounded by Gateway Pharmacy (Bismarck, ND).

The lot number of all components used per batch of agent will be recorded on a Formula Worksheet (Each batch will be assigned a unique log number on the day the compound is mixed.

The nasal spray containers with screw cap closure will be purchased from Professional Compounding Centers of America (PCCA). The contents of each container will be 30 ml.

Each spray will deliver about 0.1ml of drug to the patient.

15.13 **Preparation and storage**: The rose geranium in sesame oil should be stored in its original closed container at room temperature 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C to 30°C (59°F to 86°F) and protected from light.

15.14 **Administration:** Instill 1 spray into each nostril twice daily. One additional spray can be administered if the first spray is not a full spray.

15.15 **Pharmacokinetic information**: None available.

15.16 **Potential Drug Interactions**: None

15.17 **Known potential toxicities**: Lipoid pneumonia (rare).

15.18 **Study agent procurement:**
Gateway Pharmacy (Bismarck, ND) will supply Rose Geranium Oil Nasal Spray to the registered sites participating on the trial.

Mayo and each participating MNCCTN site will order a starter supply of blinded Rose Geranium in Sesame Oil Nasal Spray/Placebo and open label supply from Gateway Pharmacy. Fax the Drug Order Form to:

Gateway Pharmacy
Bismarck, ND
FAX: 701-258-6391
Phone: 701-354-7591

Registration Office personnel will monitor the supply of blinded Rose Geranium in Sesame Oil Nasal Spray/Placebo at each participating site and will coordinate with Gateway Pharmacy to send additional supplies to sites as needed.

Outdated or remaining drug/product should be destroyed on site.

15.19 **Nursing Guidelines:**

1. Warn patients to avoid contact with the eyes as this can cause eye irritation.
2. When applied nasally, patients may experience a bad taste
3. Instruct patients to report any rash or burning with application
4. Agent should be stored at room temperature

15.2 Placebo

A matching isotonic nasal saline spray will be identical in appearance to the Rose Geranium Oil Nasal Spray. The isotonic nasal saline spray will contain 0.9% Sodium Chloride. It will also contain 0.133% of benzalkonium chloride solution 50% per 100ml of normal saline, as a preservative. The nasal spray containers with screw cap closure will be purchased from Professional Compounding Centers of America (PCCA). The contents of each container will be 30 ml. The placebo spray should be stored at controlled room temperature (20°-25 ° C or 68°-77° F), with excursions to 15-30°C (59-86°F) permitted.

15.21 **Optional crossover phase:** Patients initially enrolled on the placebo arm have the option to crossover and receive 2 weeks of the Rose Geranium Oil Nasal Spray.

16.0 Statistical Considerations and Methodology

16.1 Study Design

This is a randomized, double-blinded, controlled study to determine the ability of rose geranium in sesame oil nasal spray to alleviate nasal vestibulitis in patients undergoing systemic, antineoplastic therapy when compared with isotonic nasal saline. Patients will be randomized in a 1:1 ratio to receive either rose geranium in sesame oil nasal spray or isotonic nasal saline. Randomization will be stratified on the basis of sex (female; male), age in years (≤50; > 50), and seasonal allergies and/or asthma (yes; no). To enhance participation, patients who were

assigned isotonic nasal saline have the option to receive rose geranium in sesame oil nasal spray within two weeks after completion of isotonic nasal saline (i.e. provided that they are still receiving chemotherapy at the time of "crossover") and continue to receive rose geranium in sesame oil nasal spray for two weeks.

16.2 Description of Randomization Routine

After a patient is registered they will be assigned to one of the two arms (rose geranium in sesame oil nasal spray; isotonic nasal saline) in a 1:1 ratio utilizing a dynamic allocation algorithm based on the methods by Pocock and Simon (10). The goal of the algorithm is to maintain arm balance with respect to the aforementioned stratification factors. In order to ensure that arm assignment is not deterministic, a level of randomness has been added to the algorithm such that patients will be assigned to the arm that leads to more imbalance 10% of the time. Dynamic allocation is a common approach in cancer clinical trials where we desire arms to be balanced across several prognostic factors. The method is considered robust because it ensures excellent arm balance overall and within the stratification factor levels, even with a large number of stratification factors (11).

16.3 Sample Size, Accrual Time, and Study Duration

Based on our clinical experience, we assume that 30% of the patients on the isotonic nasal saline arm will report that the nasal symptom that was most prominent prior to starting the study will be moderately better or very much better 2 weeks after initiation of the nasal spray. We hypothesize that 65% of the patients receiving rose geranium in sesame oil nasal spray will indicate that their most prominent nasal symptom prior to starting the study will be moderately better or very much better 2 weeks after initiation of the nasal spray. This corresponds to an odds ratio of 1 under the null hypothesis and an odds ratio of 4.33 (rose geranium in sesame oil nasal spray / isotonic nasal saline). Using a Fisher's exact test and testing at a 0.05 two-sided significance level, we will have 85% power to detect this difference if we randomize 80 eligible and evaluable patients on the study. We anticipate that up to 20% of patients will not have met the eligibility criteria and/or not be evaluable for response assessment, and thus the target sample size will be inflated to 106 patients (53 per arm).

Using conservative estimates, we anticipate an accrual rate of 10 patients per month; therefore, to achieve the targeted accrual of 50 patients per arm, we anticipate that the accrual period will be approximately 10 months. Because the patients randomized to receive isotonic nasal saline may elect to receive rose geranium in sesame oil nasal spray for 2 weeks following the 2-week active monitoring phase, the corresponding total study duration will be approximately 11 months.

May, 2022 addendum: This month it became apparent that 6 patients erroneously received the opposite product to which they had been randomized to receive. This was due to a pharmacy error, by the institution that makes the rose geranium in sesame oil and the nasal saline containers. When this pharmacy had prepared a batch of product and sent such to one participating institution, they put nasal saline code numbers on 5 containers of rose geranium in sesame oil and rose geranium in sesame oil code numbers on 5 containers that had nasal saline product. Only 6 of these containers were given to patients. Given this, we plan to increase the accrual number by 6 patients, to a total of 106 patients. The 6 patients that received the wrong treatment will be retained on the study and included in an intent-to-treat analyses (analyzing patients according to the arm in which they were randomized). As sensitivity analyses, we will also perform a per-protocol analysis (analyzing patients according to the treatment they received) and a separate analysis after excluding the 6 patients that received the wrong treatment. The additional 6 accrued patients will assure that there is adequate power for each of these sensitivity analyses.

16.4 Statement for Primary Endpoint

16.4.1 Primary Endpoint

The primary endpoint is a binary variable indicating whether the patient achieves a response (yes; no) at 2 weeks after initiating the nasal spray. Response is determined from a patient global impression of change scale and is defined as a patient reporting that the nasal symptom that was most prominent prior to starting the study has been moderately better or very much better 2 weeks after initiating the nasal spray.

16.4.2 Analysis Plan for Primary Endpoint

The primary analysis will be based on a modified intention-to-treat (mITT) population, defined as all patients who signed a consent form, met the eligibility criteria, indicated their most bothersome nasal symptom at baseline, completed the patient global impression of change scale 2 weeks after initiating the nasal spray, and were randomized; furthermore, these patients will be analyzed in the arms to which they were randomized.

The number and percentage of patients experiencing a response 2 weeks after initiating the nasal spray will be estimated within each randomized arm and the corresponding two-sided 95% exact (Clopper-Pearson) confidence interval provided. A between-arm comparison of the proportion of patients experiencing a response 2 weeks after initiating the nasal spray will be made using the Fisher's exact test. Statistical significance will be assessed at the 5% level. In addition, the estimated odds ratio with the 95% confidence interval that matches the Fisher's exact test will be provided.

16.4.3 Planned Sensitivity Analyses for Primary Endpoint

To assess the robustness of the primary results, a supportive analysis is planned. A logistic regression analysis will be undertaken to estimate the treatment effect after adjusting for the three stratification factors, the corresponding baseline severity for the most prominent nasal symptom, and potential confounding variables. Additionally, the primary analysis will be repeated to include patients who did not complete the patient global impression of change scale 2 weeks after initiating the nasal spray but would otherwise be included in the mITT population. For this analysis, we will assume that the missing values for these patients represent no improvement.

16.5 Analysis Plan for Secondary Endpoints

For the most prominent nasal symptom indicated at baseline, patients will record the severity on an ordinal scale of 1=mild, 2=moderate, 3=severe, and 4=very severe. Two weeks after initiating the nasal spray the patients will record the severity of the most prominent nasal symptom as 0=none, 1=mild, 2=moderate, 3=severe, and 4=very severe. A shift table will be created to descriptively display the number of patients who record a 1, 2, 3, or 4 at baseline and the shift two-weeks after initiating the nasal spray. [12][In addition, the within-patient change in severity of the most prominent nasal symptom will be calculated 2 weeks after initiating the nasal spray and summarized descriptively within each arm. The Wilcoxon rank-sum test will be performed, and the methods of Hodges and Lehmann will be applied to compute a point estimate and confidence interval for the difference in medians between the two arms. As a supportive analysis, the van Elteren statistic, which is an extension to the Wilcoxon rank-sum test that accounts for the stratification factors, will be calculated. Furthermore, we will model the ordinal response data obtained two weeks after initiating the nasal spray with a proportional odds

cumulative logit model; explanatory variables will include arm, corresponding baseline severity for the most prominent nasal symptom, the stratification factors, and other potential confounding variables.

In addition to summarizing the most prominent nasal symptom that the patient indicated at baseline, each nasal symptom (dryness, pain, bleeding, and scabbing) will be descriptively summarized, tabulated, and plotted according to arm at baseline, and at 1 and 2 weeks post-baseline; additionally, we will group patients according to baseline severity for each symptom and summarize changes over time and according to arm. Shift tables will also be generated to descriptively display the number of patients who record a 1, 2, 3, or 4 at baseline and the shift one- and two-weeks after initiating the nasal spray. These analyses are descriptive in nature and are intended to further contextualize the main study findings that are based on analyzing the most prominent nasal symptom reported by the patient.

The constellation of adverse events (AEs) as scored using the National Cancer Institute Common Terminology Criteria for Adverse Events, v5.0 (CTCAE v5.0) will be summarized within arms by reporting the number and percentage of patients. Specifically, to evaluate the AE profiles associated with each arm, the maximum grade for each type of AE will be recorded for each patient and frequency tables will be reviewed to determine overall patterns and compared between arms using Wilcoxon tests.

16.6 Analysis Plan for Crossover Phase

The crossover option for patients assigned to receive isotonic nasal saline is intended to provide access to a potentially beneficial treatment for nasal vestibulitis. The number and proportion of patients who elect to experience therapy with the rose geranium in sesame seed oil will be reported. Data from this portion of the protocol will be descriptively summarized with no planned statistical comparisons.

16.7 Missing Data

Every attempt will be made to obtain complete data for each patient. For the primary endpoint, evaluable patients are defined as patients who indicated their most bothersome nasal symptom at baseline and completed the patient global impression of change scale 2 weeks after initiating the nasal spray. We are targeting 106 patients to obtain 80 eligible and evaluable patients for the primary endpoint. For all other analyses, no missing data will be imputed; all available data will be listed and summarized.

16.8 Study Monitoring

16.8.1 Data and Safety Monitoring Board

This study will be monitored by the Mayo Clinic Cancer Center Data Safety and Monitoring Board (DSMB) twice per year. The DSMB will review administrative information, accrual, adverse events, and interim analysis results. Early termination of accrual will be considered if there is evidence of unacceptable toxicity.

16.8.2 Adverse Event Stopping Rule

Throughout the course of the study, we will monitor AEs in both study arms, and may suspend accrual if patients are experiencing a large number of AEs. Accrual will be temporarily suspended to this study if at any time we observe 5 or more of the first 20 patients experiencing any grade 3+ AEs that the study team considers to be at least possibly related to rose geranium (i.e. an AE with attribute specified as “possible”, “probable”, or

"definite") and also, the incidence of these grade 3+ AEs must be higher in the rose geranium arm.

After the first 20 patients, if more than 25% of the patients have grade 3+ AEs that the study team considers to be at least possibly related to rose geranium (i.e. an AE with attribute specified as "possible", "probable", or "definite") and the incidence of these grade 3+ AEs is higher in the rose geranium arm, then accrual will be temporarily suspended.

The AE stopping rule may be modified if during the course of the study, new information becomes available which suggests that such a modification is necessary, or if, after temporarily stopping accrual, the above rule is found to be overly conservative. If accrual is temporarily suspended, the study AEs will be reviewed by the investigators and the Mayo Clinic DSMB. Based on this review, accrual will then be either restarted or permanently stopped.

16.8.3 Accrual Monitoring Stopping Rule

Patient accrual will be closely monitored by the investigators and study statistician on a bi-weekly basis. If the accrual rate falls below 50% of expected accrual rate, investigators will carefully review feedback from sites and consider taking measures to encourage patient enrollment.

16.9 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of gender, race, or ethnic origin.

There is no information currently available regarding differential effects of this regimen in subsets defined by gender, race, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will look for differences in treatment effect based on gender, racial, and ethnic groupings, the sample size is not increased in order to provide additional power for subset analyses.

Expected sizes of race by ethnicity and gender subsets for patients participating in this study are shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	4	0	0	0	4
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	5	0	0	0	5
White	55	38	4	0	97
More Than One Race	0	0	0	0	0
Total	64	38	4	0	106

Ethnic Categories:	**Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
	Not Hispanic or Latino
Racial Categories:	**American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
	Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
	Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
	Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
	White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens: None

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Survival Follow-up: none

18.3 CRF completion

This study will use Medidata Rave® for remote data capture (rdc) of all study data. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on the organization roster at the enrolling site.

18.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Labeling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.6 Overdue lists

A list of overdue forms and outstanding queries will be available in Rave through the Rave Task Summary. In addition to this, the Overdue Materials report is available on the Cancer Center Systems homepage.

19.0 Budget

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded: Rose Geranium in Sesame Oil Nasal Spray and Isotonic Nasal Saline will be provided free of charge.

19.3 Other budget concerns:

The Breast Cancer Research Foundation (BCRF) has provided Mayo Clinic with funding to support the costs of running this study.

20.0 References

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Appendix I. Baseline Pre-nasal Spray Questionnaire

1. How much of a problem has nose DRYNESS been, ON AVERAGE, over the past two days? *(check one)*
   __ None
   __ Mild
   __ Moderate
   __ Severe
   __ Very Severe

2. How much of a problem has nose PAIN or TENDERNESS been, ON AVERAGE, over the past two days? *(check one)*
   __ None
   __ Mild
   __ Moderate
   __ Severe
   __ Very Severe

3. How much of a problem has nose BLEEDING been, ON AVERAGE, over the past two days? *(check one)*
   __ None
   __ Mild
   __ Moderate
   __ Severe
   __ Very Severe

4. How much of a problem has nose SCABBING been, ON AVERAGE, over the past two days? *(check one)*
   __ None
   __ Mild
   __ Moderate
   __ Severe
   __ Very Severe

5. How much of a problem has nose SORES been, ON AVERAGE, over the past two days? *(check one)*
   __ None
   __ Mild
   __ Moderate
   __ Severe
   __ Very Severe

6. Have you had nose symptoms, other than dryness, pain, bleeding, scabbing, or nose sores over the past two days? *(check one)*
   ___ No
   ___ Yes
   (If yes), Please describe: _____

7. Which symptom is the most bothersome to you, which you would like treatment for? *(check one)*
   __ Dryness
   __ Discomfort
   __ Bleeding
   __ Scabbing
   __ Sores

8. Have you been taking any medications or using any topical remedies for nose symptoms? *(check one)*

   ___ No
   ___ Yes
   (If yes),
   Please describe the name of the medication: _____

9. Do you take any aspirin or blood thinners? *(check one)*

   ___ No
   ___ Yes
   (If yes), Which medication do you take? _____

10. Do you have a history of asthma? *(check one)*

    ___ No
    ___ Yes

11. Do you have a history of allergies (NOT including allergies or sensitivities to medications)? *(check one)*

    ___ No
    ___ Yes
    (If yes), please list any current medications you take for this?
    _____

12. Do you currently smoke? *(check one)*

    ___ No
    ___ Yes

    (If no), Have you ever smoked? *(check one)*

    ___ No
    ___ Yes
    (If yes), what year did you quit? *(yyyy)* __ __ __ __

Appendix II. Nasal Symptom and Patient Experience Questionnaire

Most prominent nasal symptom reported at baseline:

(Nurse/research staff will complete everything above this line)

1. How much of a problem has nose DRYNESS been, ON AVERAGE, over the past two days? *(check one)*
   __ None
   __ Mild
   __ Moderate
   __ Severe
   __ Very Severe

2. How much of a problem has nose PAIN or TENDERNESS been, ON AVERAGE, over the past two days? *(check one)*
   __ None
   __ Mild
   __ Moderate
   __ Severe
   __ Very Severe

3. How much of a problem has nose BLEEDING been, ON AVERAGE, over the past two days? *(check one)*
   __ None
   __ Mild
   __ Moderate
   __ Severe
   __ Very Severe

4. How much of a problem has nose SCABBING been, ON AVERAGE, over the past two days? *(check one)*
   __ None
   __ Mild
   __ Moderate
   __ Severe
   __ Very Severe

5. How much of a problem has nose SORES been, ON AVERAGE, over the past two days? *(check one)*
   __ None
   __ Mild
   __ Moderate
   __ Severe
   __ Very Severe

6. Have you had nose symptoms, other than dryness, pain, bleeding, scabbing or nose sores, over the past two days? *(check one)*

___ No
___ Yes
(If yes), please describe: _____

7. Since starting this study, the nasal symptom that was most prominent in the beginning (listed above Question 1) has been: (*please circle one response*)

-3	-2	-1	0	+1	+2	+3
Very much worse	Moderately worse	A little worse	About the same	A little better	Moderately better	Very much better

8. How helpful is the nose spray in relieving your nose symptoms? *(please circle one response)*

0	1	2	3	4	5	6	7	8	9	10
Not at all helpful										Completely resolves my nasal symptoms

9. Since starting this study, I think that I was on: (*please check one response*)

☐ Nasal symptom relieving nasal spray
☐ Placebo nasal spray

10. Over the past week, the spray was prescribed to be used 14 times (twice each day). How many times do you estimate that you actually used it over the last week? *(please check one)*

☐ 12-14 times
☐ 10-12 times
☐ 6-11 times
☐ 0-5 times

11. Please provide any comment on your use of the study spray, if indicated
_____
_____

12. Do you have any unpleasant effects from the nose spray? *(check one)*

☐No
☐Yes
(If yes), please describe: _____

Appendix III PATIENT INFORMATION SHEETS

Patient Completed Booklet
BASELINE

You have been given a booklet to complete for this study. The booklet contains multiple questions about your 'quality of life' as a patient receiving nasal spray.

Please answer all of the questions, even if they sound similar to a question you have already answered.

1. This booklet contains the following questionnaires that are to be completed prior to treatment (baseline):
    a. Baseline Pre-nasal Spray Questionnaire

2. You can call anytime with any concerns or questions.

3. It is very important that you return the booklet to us, whether you finish the study or not.

Reminder: If you start any other nasal spray while on this study, notify your nurse/research staff.

Thank you for taking the time to help us.

Patient Completed Booklet
TREATMENT

You have been given a booklet to complete for this study. The booklet contains multiple questions about your 'quality of life' as a patient receiving nasal spray.

Please answer all of the questions, even if they sound similar to a question you have already answered.

1. This booklet contains the following questionnaires that are to be completed during treatment:
    a. Nasal Symptom and Patient Experience Questionnaire

2. You can call anytime with any concerns or questions.

3. It is very important that you return the booklet to us, whether you finish the study or not.

Reminder: If you start any other nasal spray while on this study, notify your nurse/research staff.

Thank you for taking the time to help us.