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A PHASE I/II STUDY TO DETERMINE THE SAFETY AND EFFICACY OF CURCUMIN IN PATIENTS WITH ORAL MUCOSITIS SECONDARY TO CHEMOTHERAPY

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PRECIS

Background:
Oral mucositis is a common and often debilitating complication associated with cancer treatment. Treatment of mucositis is mainly supportive - oral hygiene is the means of treatment. Curcumin (Turmeric), a frequently-used spice in India and Southeast Asia, can reduce bacterial load and prevent inflammation in cultured epithelial cells and prevent chemotherapy- and radiotherapy-induced mucositis in animal models.

Objectives:
The primary objective of this Phase I/II study is to determine the maximum tolerated dose (MTD) of oral curcumin in patients who have chemotherapy-induced mucositis. The secondary objectives of this study are to determine whether oral curcumin:

1. Decreases an objective measurement of oral mucositis
2. Decreases the pain associated with oral mucositis
3. Decreases the duration of mucositis
4. Has an acceptable safety profile

Eligibility:
Inclusion Criteria:

- ≥ 18 years of age
- ≥ grade 2 oral mucositis related to chemotherapy for cancer

Exclusion Criteria:

- Current use of therapeutic doses of anticoagulants such as warfarin or antiplatelet agents (prophylactic doses and agents are acceptable)
- Biliary tract obstruction or cholelithiasis

Design:
This is a phase I/II study involving 2 parts. The first part is a dose escalation to determine the maximum tolerated dose of curcumin. There will be 3 subjects at each dose level of curcumin and 4 dose levels of curcumin. Each dose will be given 3 times each day for 14 days. Each dose will be given as a mouth rinse containing curcumin and water. The mouth rinse will be used for 30 seconds and then swallowed. Subjects will be evaluated for dose-limiting toxicity until the MTD is determined.

The second part of the study is an expansion at the MTD. Subjects will be randomized 1:1 to an experimental arm (curcumin) and a control arm (standard of care), with 23 subjects enrolled to each arm. Subjects on the experimental arm will use a mouth rinse containing the MTD of curcumin 3 times each day for 14 days. Subjects on the control arm will use a standard mouth rinse 3 times each day for 14 days. Both mouth rinses will be used for 30 seconds and then swallowed. Subjects will be evaluated for response and toxicity. Statistical analysis of the response data will determine whether oral exposure to curcumin reduces mucositis.

1. Background and Significance

Oral mucositis refers to erythematous and ulcerative lesions of the oral mucosa observed in patients with cancer being treated with chemotherapy, and/or with radiation therapy to fields involving the oral cavity. Oral and/or GI mucositis has been reported in 51% of patients receiving chemotherapy for solid tumors or lymphoma[1]. Clinically significant oral mucositis has been reported in an even higher percentage (approximately 75–80%) of patients who receive high-dose chemotherapy prior to hematopoietic cell transplantation[2]. Lesions of oral mucositis are often very painful and compromise nutrition and oral hygiene as well as increase risk for local and systemic infection. In addition to reducing patients' quality of life, mucositis may act as a dose-limiting adverse event in chemotherapy and/or radiation therapy and thus, it requires attention and treatment in the oncologic setting[3].

The cause of oral mucositis induced by cancer treatment is believed to be due to the over-production of free radicals induced by the chemo- or radiotherapy, which damages cell DNA and further activates pro-inflammatory transcriptional factors such as NF-κB. Activation of NF-κB up-regulates inflammatory cytokines. The major inflammatory cytokines involved are IL-6, TNF-α and IL-1β[4, 5].

Typically, patients undergoing chemotherapy for cancer begin to show symptoms of oral mucositis about four to five days after starting treatment. Symptoms are at their peak at around the tenth day, after which they slowly improve over the following few weeks. Patients undergoing radiotherapy generally develop symptoms at the end of the second week of treatment. The symptoms can last from six to eight weeks.

Although many prophylactic and supportive treatment options exist, including cryotherapy, palifermin, amifostine, intravenous glutamine, honey, topical oral antimicrobials[6] and Lactobacillus lozenges[7], there is little consensus for a stand-out treatment for breakthrough mucositis. Hundreds of institution-specific oral rinses known as "magic " or "miracle" mouthwashes, that contain some combination of anticholinergic (i.e. diphenhydramine), anesthetic (i.e. viscous lidocaine), antacid (i.e. Maalox), coating agent (Sucralfate), anti-inflammatory (glucocorticoids), antifungal (Nystatin) and/or antibiotic (tetracycline or erythromycin) ingredients, are often used as first-line treatment[8] for breakthrough mucositis. One major issue regarding "magic" mouthwash formulations is a variance of institutional and literature standardization which inhibits the ability to accurately determine its overall efficacy in the treatment of chemotherapy and radiation-induced mucositis[9]. One controlled study to evaluate the efficacy of magic mouthwash showed no difference in efficacy among the common formulation and other treatment agents such as chlorhexidine and a simple saline/baking soda solution[10]. In addition, all these "magic mouthwashes" are formulated to provide symptomatic relief of the pain or to create a protective barrier to prevent and reduce the severity of oral mucositis caused by chemotherapy and /or radiation. However, these mouthwashes are generally not designed to target the inflammatory response associated with chemotherapy and /or radiation which cause the mucositis.

Curcumin (extracted from turmeric) is an herbal supplement that has an extensive

history of use in India and Asia for its potent anti-inflammatory action and lately is being investigated for use in treatments of rheumatoid arthritis, various cancers, and Alzheimer's disease[11]. Curcumin has been shown to prevent chemotherapy- and radiotherapy-induced mucositis in animal models[12]. Two recent studies provide a basis for our current investigation. In the first study, Luer et al. demonstrated that curcumin reduced oropharyngeal bacterial load and prevented inflammation in cultured epithelial cells[13]. In a small pilot study of juvenile patients with chemotherapy-induced mucositis, topical curcumin was found to be safe and well-tolerated[14]. Curcumin's anti-inflammatory and antibacterial action make it a viable and compelling option for chemotherapy-induced mucositis.

2. Objectives/Endpoints

The primary objective of this Phase I/II study is to determine the maximum tolerated dose (MTD) of oral curcumin in patients who have chemotherapy-induced mucositis. The secondary objectives of this study are to determine whether oral curcumin:

- Decreases an objective measurement of oral mucositis
- Decreases the pain associated with oral mucositis
- Decreases the duration of mucositis
- Has an acceptable safety profile.

3. Study Design

This is a phase I/II study involving 2 parts: a dose escalation part and an expansion at the maximum tolerated dose.

In the first part, there will be 3 subjects at each dose level of curcumin (see table below). The doses will be taken 3 times each day for 14 days. Each dose will be taken as a mouth rinse containing curcumin and water, 3 times each day for 14 days. The mouth rinse will be used for 30 seconds and then swallowed. Subjects will be evaluated for dose-limiting toxicity (DLT, defined in section 6.1). The maximum tolerated dose (MTD, defined in section 2) will be determined. Subjects may participate in the study at a higher dose level, after they have completed the study at the current dose level and if they are eligible.

# Subjects	Curcumin/dose (gram)	Curcumin/day (gram)
3	0.33	1
3	1.0	3
3	2.0	6
3	3.0	9

In the second part of the study, there will be 23 subjects enrolled to an experimental (curcumin) arm and 23 subjects enrolled to a control (standard of care) arm. Subjects will be randomized to take a mouth rinse with or without the MTD of curcumin, 3 times each day for 14 days. The rinses will be swallowed. Subjects will be evaluated for response and toxicity. Subjects in the first part of the study may participate in the second part of the study, if they are eligible.

In both parts of the study, if the mucositis score ≤ Grade 2 but is unresolved after 14 days of taking the study mouth rinse (curcumin or control), then the subject will

continue to receive the study mouth rinse until the mucositis is resolved (Grade 0).

This study will involve 12 subjects in the first part, plus an additional 3 subjects if a dose-limiting toxicity occurs (see section 2) and 46 subjects in the second part for a total of 61 subjects. This study is expected to take 2 years to complete enrollment, treatment and follow-up (6 months for the first part and 18 months for the second part).

4. Subject Selection

Potential subjects will be identified and recruited from within the practice population of the investigators (including via referrals to the investigators from other physicians). Patients' medical charts may be reviewed to identify potential subjects and to help determine eligibility; a 502-A form is being submitted to allow this preparatory to research activity.

4.1 Inclusion Criteria

- ≥ grade 2 oral mucositis related to chemotherapy for cancer
- Ability to understand and the willingness to review and sign a written informed consent document.
- ≥ 18 years of age
- Willingness to use adequate contraception prior to study entry, for the duration of study participation and for 30 days after the last dose for women of child-bearing potential and men

4.2 Exclusion Criteria

- Current use of therapeutic doses of anticoagulants such as warfarin or antiplatelet agents (prophylactic doses and agents are acceptable)
- Biliary tract obstruction or cholelithiasis
- History of gastric or duodenal ulcers or hyperacidity syndromes
- AST or ALT > 2 x ULN
- Total bilirubin ≥ 2 x ULN
- INR > 1.5
- Previous stem cell transplant (allogeneic or autologous)
- Preexisting oral disease, such as active oral infection, trauma to the oral mucosa or oral ulceration prior to chemotherapy
- Known allergy/hypersensitivity to curcumin, yellow food colorings, or other members of the Zingiberaceae (ginger) family
- Pregnant or breastfeeding

Potential subjects are identified by medical record review. Eligible subjects are asked to give their written consent to participate in this study. The tests required to screen subjects for this study include a pregnancy test, INR and CMP.

5. Study Procedures and Schedule

The study mouth rinse will be initiated when subjects have > grade 2 mucositis, which could be at any point during their chemotherapy cycle. Subjects who develop > grade 2 mucositis will receive appropriate adjustments in their chemotherapy dose to reduce toxicity with subsequent cycles.

In the first part, there will be 3 subjects at each dose level of curcumin. Each dose will be given as a mouth rinse containing curcumin and water.

In the second part, subjects will be randomized to take a mouth rinse with the MTD of curcumin or a standard mouth rinse, 3 times each day for 14 days. The curcumin mouth rinse will be designated “study mouth rinse” to differentiate it from the standard mouth rinse.

All subjects will be instructed to rinse their mouths with the study or standard mouth rinse 3 times each day for 14 days. Subjects will be instructed to use the study or standard mouth rinse for 30 seconds and then swallow the rinse. Subjects will be instructed not to eat within one hour after using the study or standard mouth rinse. Subjects will be instructed to use a saline mouth rinse after eating any food to keep their mouth clean. A daily log (Appendix A) will be available for each subject and will include a checklist that will simplify the rinsing schedule as well as an area for the subject (or family member) to document mouth rinse administration. No other adjunctive topical treatment will be used during the study.

Subject adherence to the treatment schedule will be assessed through subject reports, by review of the daily log (Appendix A) and by review of returned medications collected during the site visits.

5.1 Study Visits

All procedures and assessments are conducted for research purposes.

5.1.1 Visit 1 (Screening)

Subjects will be asked to sign a consent form. An oral exam will be conducted to ensure good oral hygiene. A blood or urine sample will be collected for pregnancy testing, if applicable. A blood sample will be collected to assess liver function (CMP) and clotting function (PT and INR). A mucositis assessment (CTAE version 4.0 and WHO Oral Toxicity Scale) will be conducted and documented by a health provider (Appendix B). This visit will take approximately one hour.

5.1.2 Visit 2

5.1.3 THIS VISIT MUST OCCUR WITHIN 48 HOURS AFTER THE SCREENING VISIT. IF VISIT 2 OCCURS ON A DIFFERENT DAY THAN VISIT 1, ANOTHER MUCOSITIS ASSESSMENT (CTAE VERSION 4.0 AND WHO ORAL TOXICITY SCALE) WILL BE CONDUCTED AND DOCUMENTED BY A HEALTH PROVIDER (APPENDIX B) AND WILL BE CONSIDERED THE BASELINE ASSESSMENT. THE PROVIDER WILL ALSO ASK THE SUBJECT TO COMPLETE A SUBJECT SELF-ASSESSMENT (APPENDIX C). SUFFICIENT MOUTH RINSE WILL BE GIVEN TO THE SUBJECT FOR THE FIRST WEEK OF THE STUDY. THE DAILY LOG (APPENDIX A) AND THE PATIENT SELF-ASSESSMENT TOOL (APPENDIX C) WILL BE GIVEN TO THE SUBJECT. THE SUBJECT WILL BE ASKED TO COMPLETE THE LOG EVERY DAY UNTIL VISIT 3. THE SUBJECT WILL BE ASKED TO COMPLETE THE SELF-ASSESSMENT TOOL ON DAY 3 OR 4 AFTER THE FIRST DAY OF TAKING THE MOUTH RINSE. A BLOOD AND SALIVA SAMPLE WILL BE OBTAINED FOR RESEARCH PURPOSES (SECTION 10). THIS VISIT WILL TAKE APPROXIMATELY 30 MINUTES.Phone call 1

On day 3 or 4 after the first day of taking the mouth rinse for the study, the subject will be called by a study staff member, who will review and follow up on any side-effects that the subject is experiencing and answer any questions about the study or study mouth rinse. The staff member will remind the subject to complete a subject self-assessment tool (Appendix C) and the daily log (Appendix A) and bring them to the next visit. The phone call will take about 15 minutes.

5.1.4 Visit 3

This visit will occur 7 days (+/- 1 day) after Visit 2. A mucositis assessment (CTAE version 4.0 and WHO Oral Toxicity Scale) will be conducted and documented by a health provider (Appendix B), who will also review and follow up on any side-effects that the subject is experiencing and check the daily log (Appendix A) to ensure that the subject is complying with the study. Sufficient mouth rinse will be given to the subject for the second week of the study. A blood sample will be obtained to assess liver function (CMP) and clotting function (PT and INR). A blood and saliva sample will be obtained for research purposes (section 10). This visit will take approximately 30 minutes.

5.1.5 Phone call 2

On day 10 or 11 after the first day of taking the mouth rinse for the study, the subject will be called by a study staff member, who will review and follow up on any side-effects that the subject is experiencing and answer any questions about the study or study mouth rinse. The staff member will remind the subject to complete a subject self-assessment tool (Appendix C) and the daily log (Appendix A) and bring them to the next visit. The phone call will take about 15 minutes.

5.1.6 Visit 4

This visit will occur 7 days (+/- 1 day) after Visit 3. A mucositis assessment (CTAE version 4.0 and WHO Oral Toxicity Scale) will be conducted and documented by a health provider (Appendix B), who will review and follow up on any side-effects that the subject is experiencing and obtain the daily log (Appendix A) from the subject. A blood sample will be obtained to assess liver function (CMP) and clotting function (PT and INR). A blood and saliva sample will be obtained for research purposes (section 10). If the mucositis score ≤ Grade 2 but is unresolved, then the subject will continue to receive the study mouth rinse (curcumin or standard mouth rinse) until the mucositis is resolved (Grade 0). Sufficient mouth rinse will be given to the subject for the subsequent week of the study. This visit will take approximately 30 minutes.

5.1.7 Phone call 3

On day 17 or 18 after the first day of taking the mouth rinse for the study, the subject will be called by a study staff member, who will review and follow up on any side-effects that the subject is experiencing and answer any questions about the study or study mouth rinse. The staff member will remind the subject to complete a subject self-assessment tool (Appendix C) and the daily log (Appendix A) (only if they are still on study mouth rinse) and bring them to the next visit. The phone call will take about 15 minutes.

5.1.8 Visit 5

This visit will occur 7 days (+/- 1 day) after Visit 4. A mucositis assessment (CTAE version 4.0 and WHO Oral Toxicity Scale) will be conducted and documented by a health provider (Appendix B), who will review and follow up on any side-effects that the subject is experiencing and obtain the daily log (Appendix A) from the subject (if the subject is still on study mouth rinse). A blood sample will be obtained to assess liver function (CMP) and clotting function (PT and INR). A blood and saliva sample will be obtained for research purposes (section 10). If the mucositis score ≤ Grade 2 but is unresolved, then the subject will continue to receive the study treatment (curcumin or standard mouth rinse) until the mucositis is resolved (Grade 0). Sufficient mouth rinse will be given to the subject for the subsequent week of the study. This visit will take approximately 30 minutes.

5.1.9 Weekly phone calls to subjects receiving study mouth rinse (curcumin or standard mouth rinse)

Between each visit, each subject will be called by a study staff member, who will review and follow up on any side-effects that the subject is experiencing and answer any questions about the study or study mouth rinse. The staff member will remind the subject to complete a subject self-assessment tool (Appendix C) and the daily log (Appendix A) and bring them to the next visit. The phone call will take about 15 minutes.

5.1.10 Weekly visits for subjects receiving study mouth rinse (curcumin or standard mouth rinse)

A mucositis assessment (CTAE version 4.0 and WHO Oral Toxicity Scale) will be conducted and documented by a health provider (Appendix B), who will review and follow up on any side-effects that the subject is experiencing and obtain the daily log (Appendix A) from the subject. A blood sample will be obtained to assess liver function (CMP) and clotting function (PT and INR). A blood and saliva sample will be obtained for research purposes (section 10). If the mucositis score ≤ Grade 2 but is unresolved, then the subject will continue to receive the study mouth rinse (curcumin or standard mouth rinse) until the mucositis is resolved (Grade 0). Sufficient mouth rinse will be given to the subject for the subsequent week of the study. This visit will take approximately 30 minutes.

5.2 Study Calendar

		Week 1		Week 2		Week 3		Week 4- mucosits resolution		
Study Procedure	**Visit 1** (Screening)	**Visit 2:**	**Phone call 1:**	**Visit 3:**	**Phone call 2:**	**Visit 4:**	**Phone call 3:**	**Visit:**	**Phone calls**	**Final visit**
	day -1	**day 0**	**day 3**	**day 7**	**day 10**	**day 14**	**day 17**	**For phase II:** weekly cycle repeated until mucositis is resolved (and no AEs)		**day 21**, or 7 days after visit when mucositis was resolved
activity window		At or w/in 48hr of Visit 1	+ 1 day	+/- 1 day	+ 1 day	+/- 1 day	+ 1 day	+/- 1 day	+ 1 day	+/- 1 day
Sign Informed Consent	**X**									
Oral exam for hygiene	**X**									
Pregnancy test	**X**[1]									
Provider mucositis assessment[2]	**X**	**X**[3]		**X**		**X**		**X**[a]		**X**
Provider supplies study mouth rinse		**X**		**X**		**X**[a]		**X**[a]		**X**
Provider supplies study journal, self-assessment		**X**		**X**		**X**[a]		**X**[a]		**X**
Provider collects journal and self-assessments				**X**		**X**		**X**[a]		**X**
Remind subject to complete self-assessment		**X**	**X**		**X**		**X**		**X**[a]	
Blood collection for liver function (CMP) [4]	**X**			**X**		**X**		**X**[a]		**X**
Blood collection for clotting (PT and INR) [4]	**X**			**X**		**X**		**X**[a]		**X**
Research blood collection [5]		**X**		**X**		**X**		**X**[a]		
Research saliva collection [5]		**X**		**X**		**X**		**X**[a]		
Collect AEs			**X**	**X**	**X**	**X**	**X**	**X**[a]	**X**[a]	**X**
Review of concomitant medications	**X**	**X**		**X**		**X**		**X**[a]		**X**

[1] Blood or urine pregnancy test, if not already done as part of standard of care
[2] Includes CTAE version 4.0 and WHO oral Toxicity scale.
[3] Mucositis assessment at Visit 2, only if a different day than Visit 1 (does not need to be repeated is Visit 1 and 2 are done on the same day)
[4] Does not need to be repeated if already done for standard of care.
[5] 6 ml of peripheral blood into a non-anti-coagulated tube, 2 ml salvia into a sterile tube; processed and stored as described in the operations manual.
[a] Only if subject is still taking study mouth rinse based on improvement of mucositis at each visit, beginning at visit 4.

5.3 Preparation of Standard Mouth Rinse

The standard mouth rinse will be prepared by the pharmacy and provided in 200 mL bottles and will utilize measured dosing cup for accurate dosing. The standard mouth rinse contains 40% Benadryl, 40% Maalox, and 20% of 2% Viscous Lidocaine. Subjects will use 15 ml each of the 3 times they rinse their mouths each day.

5.4 Preparation of Study Mouth Rinse (Curcumin)

The appropriate daily dose of study drug (powder) will be dispensed by the pharmacy in a plastic amber vial. Subjects will receive 8 vials (1 week supply +1 in case of spilled/lost dose) of curcumin powder and vials of sterile water to prepare their study mouth rinse at home. The volume of water dispensed in each vial will vary based on the dose of curcumin the subject is assigned to. Regardless of dose, all prepared curcumin solutions will total 45 ml in volume. These vials will be stored at room temperature. Subjects will be instructed to add a vial of sterile water to each vial of curcumin powder on each day. Subjects will shake the vial to disperse the curcumin powder and then use a third of the volume (15 mLs) three times a day. Subjects will be provided a plastic dosing cup to help measure out 15 mLs. Subjects will store the curcumin suspended in water at room temperature until it is used up. Subjects will obtain a second one week supply of study mouth rinse, prior to preparation of day 7 (+/- 1 day) dosing in order to ensure no break in treatment.

5.5 Study Drug (Curcumin) Dose

The recommended oral dose of curcumin is 1-3 gram/day for healthy adults. Previous studies in adults with gastrointestinal disorders ranged from 72 mg/day to 2 g/day and the dose duration lasted from 1 to 6 months (IND Table 2). The dosing regimen for topical use of curcumin in a recent study in adolescents and young adults with oral mucositis[14] was 165 mg twice per day for 2 weeks (330 mg/day).

To determine MTD in this study, the first dose level will be the dose used in the aforementioned study[14], multiplied by 3 (adult dose is 3 times the pediatric dose), which is 1 gram/day. The subsequent dose levels will be 3 grams/day, 6 grams/day and 9 grams/day. The duration of patient exposure to the drug will be 3 times a day for 30 seconds of topical exposure each time before swallowing, for 14 days.

5.6 Determination of MTD

The MTD will be determined as follows: If a DLT occurs in any one of the 3 patients at a specific dose level, an additional 3 patients must be treated at that dose level to achieve statistical validity of the MTD. If 2 of the 6 patients (17%) at a dose level develop a DLT, the previous dose level will be used as the MTD. If no DLT is observed, then the MTD will be the highest dose. To ensure safety of subjects at each dose level, all assessments will be completed at Visit 5 for subjects at a dose level before another subject is given study drug at the

subsequent dose level.

6. Expected Adverse Events

Toxicities will be graded by health care providers using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 weekly after initiation of study mouth rinse until mucositis is resolved (Grade 0) (see Provider Assessment in calendar, section 5.2). Toxicities will be assessed by subject self-evaluation during study mouth rinse administration between clinic visits (see Subject Assessment in calendar, section 5.2).

Very few studies have reported any severe or serious side effects from curcumin and most studies have involved oral administration of curcumin. No major toxicity has been found in studies where curcumin is used short-term. Increased bleeding may occur due to inhibition of platelet aggregation (very rare). Possible other side effects associated with curcumin include: vomiting, nausea, rash and GI distress. In a study of subjects with colon cancer, oral curcumin at doses ranging from 0.45 to 3.6 gram/day for 1 to 4 months was associated with nausea and diarrhea and caused an increase in serum alkaline phosphatase and lactate dehydrogenase[15]. In one study of patients with advanced pancreatic cancer, 5 of the 17 patients receiving oral curcumin (8 gram/day) in combination with gemcitabine reported intractable abdominal pain after a few days to 2 weeks of curcumin intake[16]. In a recent study of topical curcumin for mucositis in juveniles and children[14], there were no oral adverse events documented and no systemic adverse events that possibly could be related to the use of the curcumin mouthwash.

Patients will receive full supportive care as appropriate. The rationale for treatment, dosage and the date of treatment will be recorded in the medical record.

6.1 Dose-limiting Toxicity

DLT resulting from any treatment component of the study will be defined in the list below. There will be no dose reductions in response to DLT.

- Any grade 2 or greater allergic response
- Any grade 3 or greater toxicity

6.2 Criteria for Subject Removal

A subject will be removed from the study for the following reasons:

- Dose limiting toxicity.
- No improvement in mucositis after 14 days of taking the study mouth rinse.
- Patient decision to withdraw consent or discontinue the study.
- Deemed by the physician to be the best medical interest of the patient.
- At the discretion of the investigator, patients who are non-compliant.

6.3 Criteria for Study Discontinuation

If 2 patients develop a DLT at dose 1, then the trial will be closed due to unacceptable toxicity. If any patient has Grade V toxicity, then, the trial will be placed on immediate hold until the protocol investigators, the sponsor of the IND, the IRB and the FDA have been notified and a determination has been made as to the re-opening of this trial.

If < 5 of the first 10 subjects in the curcumin arm of the second part of the study have Grade 0 mucositis (CTAE version 4.0 and WHO Oral Toxicity Scale) at Visit 4, then the study will be discontinued due to lack of activity.

6.4 Criteria for Dose Reduction

Subjects taking the curcumin-containing mouth rinse that experience intolerable or prolonged (>14 days) grade 2 toxicity will receive the next lowest dose from the dose escalation part of the study.

6.5 Serious Adverse Events (SAEs)

SAEs are defined as:

- Death
- Life-threatening events
- Inpatient hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly or birth defects

SAEs will be reported as described in the Regulatory/Reporting Requirements section.

7. Benefits

Turmeric has been reported to be a potent anti-inflammatory and antioxidant which may be of value in treating oral mucositis. In Ayurvedic (traditional Indian) medicine, curcumin has been used for centuries as a tonic for gastrointestinal complaints. It has also been used topically in various skin diseases. Thus its safety profile in human is well documented. The antioxidant activity of turmeric can act as free radical scavengers as well as inhibitors of leukotrienes and prostaglandin synthesis. The anti-inflammatory activity has been claimed to be comparable to NSAIDs (such as indomethacin), producing significant improvement in clinical trials involving individuals with other disease such as rheumatoid arthritis. Thus our patients who suffer from cancer-treatment associate oral mucositis may benefit from curcumin as the above indicated positive effects of curcumin. Our study may offer important data for using curcumin as a new treatment for cancer patients who develop cancer treatment induced mucositis.

8. Sample Size

This study will involve 12 subjects in the first part, plus an additional 3 subjects if a dose-limiting toxicity occurs (see section 2). This sample size is similar to other phase I dose escalation studies and will result in a determination of maximum-tolerated dose. The first objective for the second part (n=46) is to determine whether curcumin decreases an objective measurement of oral mucositis. Mucositis assessment will be conducted by the provider using the WHO scale and CTCAE scale. The scales are continuous between 0 and 4. Analysis of variance will be used to compare the two groups of subjects (standard mouth rinse versus study mouth rinse) separately for each time period (baseline and each week after study mouth rinse initiation). In a one-way ANOVA study, sample sizes of 23, and 23 are obtained from the 2 groups whose means are to be compared. The total sample of 46 subjects achieves 91% power to detect differences among the means versus the alternative of equal means using an F test with a 0.05 significance level. The size of the variation in the means is represented by their standard deviation which is 0.50. The common standard deviation within a group is assumed to be 1.00.

9. Measurement of Effect

Differences between the two mouth rinse groups will be studied with the chi-square test for categoric factors and the analysis of variance F-test for continuous variables with a 0.05 significance level.

9.1 Determination of objective measurement of oral mucositis

The objective measurements of oral mucositis will be obtained by a health provider's assessment of mucositis. Providers will be uninvolved, trained oncology clinic staff (not affiliated with the study) to reduce bias. Providers will use the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 and World Health Organization's (WHO's) Oral Toxicity Scale (OTS). They will be instructed to circle where on the scale they would assess the subject's mucositis level. A baseline evaluation will occur prior to study mouth rinse administration, and then each week after study mouth rinse initiation. The Health Care Provider Assessment Tool is attached as Appendix B.

9.2 Determination of subjective measurement of oral mucositis

The subjective measurement of oral mucositis will be obtained through patient self-assessment of mucositis using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 pain scales in person at visit 1 and between each site visit. Subjects will be instructed to say where on the scale they would assess their mucositis level and providers will complete the form. The Subject Self-Assessment Tool is attached as Appendix C.

9.3 Determination of pain associated with oral mucositis

This subjective measurement will be obtained through patient self-assessment of pain scales in person at the baseline visit and independently between each site visit. Subjects will be instructed to say where on the scale they would assess their pain level and providers will complete the form. The Subject Self-Assessment Tool is attached as Appendix C.

9.4 Determination of the duration of mucositis

The healing time will be calculated using the health provider's assessment of mucositis (CTCAE and WHO scales) by determining the number of days between study mouth rinse initiation and the day on which grade 0 is achieved.

9.5 Determination of toxicity profile

Toxicities will be graded by health care providers using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. A baseline evaluation will occur prior to study mouth rinse administration, and then weekly during study mouth rinse administration. Data will be recorded and entered into a database.

9.6 Criteria to be Evaluable for Efficacy and Safety

A subject is evaluable for efficacy (reduction in mucositis) if at least 70% of the study mouth rinse doses were taken as documented on the daily log (Appendix A). Differences between groups in terms of response rate will be evaluated by ANOVA (section 8).

A subject is evaluable for safety (toxicity) if a minimum of one dose of the study mouth rinse was taken.

10. Correlative Studies (Laboratory Studies)

10.1 Sample collection

- **Serum:** A sample (6 ml) of peripheral blood will be obtained by venipuncture into a non-anti-coagulated tube at each visit during administration of study mouth rinse. The sample will be kept at room temperature for 1 h and then centrifuged at 300 g for 10 minutes at 4°C, and the serum fraction will be divided into four aliquots that will be stored at -70°C until processed.
- **Saliva:** A sample (2 ml) of non-stimulated saliva will be collected into a sterile tube at each visit during administration of study mouth rinse and then taken into the laboratory on ice. The sample will be centrifuged at 300 g for 15 minutes at 4°C. The supernatant will be divided into 2 aliquots that will be stored at -70°C until processed.

10.2 Evaluation of Proinflammatory Cytokines

NF-κB is among the most important and thoroughly studied transcription factors with regard to the development of mucositis. It is an important regulator of proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6. These proteins are effective mediators of injury, and the increase in the levels in tissue and peripheral blood correlates well with non-haematological toxicities induced by chemotherapy[17]. Levels of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 will be evaluated in serum and/or saliva samples using a Becton

Dickinson Cytometric Bead Array (CBA) flow cytometric assay. This testing is required for participation in the study.

10.3 Future Research and Sample Disposition

Serum and saliva samples will be stored at -70°C in the Immunology Research Laboratory on the Aurora St. Luke's Medical Center campus. Samples will be coded. All patient identifiers will be removed. A key for the code will be stored in the office of the study staff. Only study staff will have access to the code. Samples that are left-over after the proinflammatory cytokine analysis will be stored at -70°C for future research on chemotherapy-induced mucositis. Subjects will be asked to complete a separate consent form for this future research. Samples will be stored until they are used up. If other researchers use the samples on an IRB-approved study, they will not be given any information that will link subject identifiers to the sample. If subjects do not consent to this future research, their leftover samples will be discarded following institutional procedures.

11. Data Collection

Data collected will include: patient demographic data, cancer treatment information (chemotherapy regimen, date started chemo), the name of the referring oncologist, dental work within the past six months and/or pre-existing mouth issues, medications within 30 days of screening, grade of oral mucositis prior to study and during the whole course of the study, pain scale, duration of mucositis, duration of neutropenia, the need and length of hospitalization, use and dosage of pain medicine, need for total potential nutrition, blood culture positive infection, other mucositis related complications and cytokine levels in blood and saliva.

If data from this study is published or otherwise shared with outside institutions, all identifying information will be removed and the data will be coded. The local study staff will have access to the code. There will be no differences in data collection between the different sites at Aurora Health Care that may eventually participate in this study.

12. Monitoring Plan

Careful evaluation to ascertain the toxicity and efficacy of topical curcumin on mucositis will be performed by the Principal Investigator and the research team. For all patients, the Principal Investigator will review all serious adverse events and will monitor the data and toxicities to identify trends weekly during the study. The Principal Investigator will be responsible for revising the protocol as needed to maintain safety. The IRB will review submitted adverse events to also evaluate trends and will require a follow up plan from the Principal Investigator whenever a trend is identified. Independent quality, compliance and safety monitoring of the study will occur at least once each year that the study is enrolling subjects and may include a review of protocol compliance, informed

consent documentation, data collection accuracy, adverse event reporting, patient safety and outcomes analysis.

13. Reporting Requirements

- Subject data accrued on this study will be reported in accordance with 21CFR 312.32.
- This study will utilize the CTCAE Version 4.0 for Adverse Event (AE) Reporting. The CTCAE v4.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov).
- The Principal Investigator will notify the IRB, and the FDA and other regulatory agencies of all serious adverse events as required by law or regulation.
- Reporting requirements to the Aurora IRB is described in IRB SOP RR:403 Ongoing Oversight of Approved Research and Reporting of Problems/Events.
- Reporting requirements to the FDA is described in the "Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies" December 2012: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf.
- All participating investigators will be notified of IND Safety Reports by email.

13.1 Reporting Requirements for SAEs (21 CFR Part 312)

NOTE: Investigators MUST immediately report to the Principal Investigator 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:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for > 24 hours
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect.
- 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).

The reporting timeframes for SAE are listed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1</th><th>Grade 2</th><th>Grade 3</th><th>Grade 4 and 5</th></tr>
<tr><td>Resulting in Hospitalization > 24 hours</td><td colspan="3">10 Calendar Days*</td><td rowspan="2">24 Hour; 5 Calendar Days**</td></tr>
<tr><td>Resulting in Hospitalization < 24 hours</td><td colspan="2">Not Required</td><td>10 Calendar Days</td></tr>
<tr><td colspan="5">SAE reporting timelines are defined as:

* “10 Calendar Days” – A complete SAE report on the SAE must be submitted within 10 calendar days of learning of the AE.

** “24 Hour; 5 Calendar Days” – The AE must initially be reported within 24 hours of learning of the AE, followed by a complete SAE report within 5 calendar days of the initial 24 hour report.</td></tr>
</table>

14. Regulatory Requirements

14.1 Informed Consent

Before a subject’s participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject’s participation in the clinical study.

The investigator is also responsible for asking the subject if the subject agrees to have their primary care physician informed of the subject’s participation in the clinical study. If the subject agrees to such notification, the investigator shall inform the subject’s primary care physician of the subject’s participation in the clinical study.

The acquisition of informed consent and the subject’s agreement or refusal of his/her notification of the primary care physician will be documented in the subject’s medical records, and the informed consent form will be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form will be retained in accordance with institutional policy, and a copy of the signed consent form will be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator will provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness will sign the informed consent form to attest that informed consent was freely given and understood.

14.2 Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material will be submitted to the IRB for written approval.

The investigator will submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator will notify the IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports in accordance with IRB SOP RR:403 Ongoing Oversight of Approved Research and Reporting of Problems/Events.

The investigator is responsible for obtaining annual IRB approval/renewal throughout the duration of the study.

14.3 Subject Confidentiality

The investigator will ensure that the subject's confidentiality is maintained:

- On case report forms and other documents that are submitted, subjects will be identified by a subject identification number only.
- On Serious Adverse Event forms submitted, subjects will be identified by their initials and a subject identification number only.
- Documents that are not for submission (eg, signed informed consent forms) will be kept in strict confidence by the investigator.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to her study-related records, including personal information, without violating the confidentiality of the subject.

15. Experience of the Investigators

Principal Investigator: (Biosketch is attached as Appendix D):

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