Clinical Study Protocol

Protocol Title:	A Phase 2, multi-center, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of topically-applied AG013 for the attenuation of oral mucositis in subjects with cancers of the head and neck receiving concomitant chemoradiation therapy
Investigational Drug:	AG013
Protocol Number:	AG013-ODOM-201
IND number/ EudraCT number:	13995/2016-004161-68
Monitor:	PSI CRO AG Baarerstrasse 113a 6300 Zug Switzerland
Sponsor:	Oragenics, Inc. 4902 Eisenhower Blvd., Suite 125 Tampa, FL 33634 United States
Sponsor Signatory:	Name and Title: _____ Signature
Protocol Date:	Original Version 1.0 – 22/DEC/2016 Amended Version 2.0 - 06/DEC/2017 Amended Version 3.0 –12/FEB/2019

GCP STATEMENT

This trial will be conducted in compliance with this protocol, Good Clinical Practices and applicable regulatory requirements.

Investigator's Agreement

Protocol Title: "A Phase 2, multi-center, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of topically-applied AG013 for the attenuation of oral mucositis in subjects with cancers of the head and neck receiving concomitant chemoradiation therapy"

Original Protocol Version and Date: version 1.0 –22/DEC/2016
Amended: 06/DEC/2017
Resulting in Protocol Version and Date: version 2.0 – 06/DEC/2017

Amended: 12/FEB/2019
Resulting in Protocol Version and Date: version 3.0 – 12/FEB/2019

I have read the attached protocol and appendices and agree to abide by all provisions set forth therein. I will provide copies of the protocol and other pertinent information to all individuals responsible to me who will assist with the study.

I agree to comply with the International Council on Harmonisation (ICH), Tripartite Guideline on Good Clinical Practice (ICH-GCP) and the provisions of the Helsinki Declaration.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Oragenics.

The Sponsor or its designee will have access to source documentation from which case report forms have been completed.

_____ _____

Signature of Principal Investigator Date (DD MONTH YYYY)

_____

Printed Name of Principal Investigator

Protocol Synopsis

Protocol Title: A Phase 2, multi-center, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of topically-applied AG013 for the attenuation of oral mucositis in subjects with cancers of the head and neck receiving concomitant chemoradiation therapy

Study Phase: 2

Indication: Oral and oropharyngeal mucositis (OM) induced by chemoradiation therapy (CRT) used for the treatment of head and neck cancers (HNC)

Product: AG013 is composed of recombinant *Lactococcus (L.) lactis* strain sAGX0085, engineered to secrete human Trefoil Factor 1 (hTFF1)

Study Objectives:

Primary Objectives

Primary Efficacy Objectives:

- To evaluate the efficacy of topically administered AG013 compared to placebo for reducing OM in patients undergoing chemoradiation for the treatment of head and neck cancer, as measured by the duration, time to development, and overall incidence of OM during the active treatment phase, beginning from the start of chemoradiation therapy (CRT) until 2 weeks following its completion.

Primary Safety Objectives:

- To determine the safety and tolerability of AG013 during the active treatment phase described above.

Secondary Objectives

Secondary Efficacy Objectives:

- To evaluate the effect of AG013 on patient-reported symptoms and analgesic use during the active treatment phase, and on the cumulative radiation dose administered before the onset of OM.

Secondary Pharmacokinetic and Pharmacodynamic Objectives:

- To assess biomarkers and, in a subset of subjects, the PK profile of AG013.

Exploratory Objectives

Exploratory Efficacy Objectives for OM

- Exploratory objective for OM Severity linked to time, duration and incidence of OM (linked to Primary Efficacy Objectives)

Other Exploratory Objectives:

- To investigate the genomic differentiation of AG013 responders and non-responders.
- To compare the efficacy of AG013 in patients with human papilloma virus (HPV) negative tumors versus HPV positive tumors.
- To evaluate the effect of AG013 on healthcare resource utilization (US sites only).
- To compare the frequency and duration of RT interruptions.

Sample Size: Approximately 200 subjects will be enrolled in the study to obtain 160 evaluable subjects (i.e., those who receive at least 4 weeks of IMP and a cumulative radiation dose of at least 50 Gy).

Study Design and methodology:
This is a Phase 2, double-blind, placebo-controlled, 2-arm, multi-center trial in which subjects will be randomized in a 1:1 ratio to receive either placebo or AG013.

AG013 has already been studied in healthy volunteers and in subjects experiencing OM during induction CT for the treatment of head and neck cancers. This is however the first time AG013 will be administered to subjects with cancers of the head and neck receiving concomitant chemoradiation (CRT) therapy. To protect subjects from unanticipated safety risks, enrollment and treatment in the double-blind study will continue until 10 subjects on AG013 have been recruited. The Data Safety Monitoring Board (DSMB) will review safety data after these 10 subjects on AG013 have completed study treatment. If there are no safety signals identified, the study will continue to recruit the planned number of subjects.

There are 4 study periods as described below: screening, active treatment, short term follow-up and long term follow-up. The screening phase will be no longer than 4 weeks. The active treatment phase will be between 7 and 9 weeks depending on the subject's prescribed CRT plan. The short term follow-up phase will be 4 weeks in duration. The long term follow-up will continue until 12 months post CRT. Oral mucositis (OM) assessments will begin at the start of CRT and continue until the subject has completed short term follow-up or until the OM resolves (as defined by a WHO score of ≤ 1), whichever comes first. Long term follow-up will continue for 12 months to assure that AG013 does not adversely impact the tumor response to anti-neoplastic therapy.

A subject's Investigational Medicinal Product (IMP) treatment assignment (AG013 or placebo) will be randomized 1:1 as follows:

- Arm A: Placebo tid
- Arm B: AG013, 2 x 10^{11} CFU/15 mL tid

Table 1: Study Periods

Screening Phase	Within 4 weeks prior to randomization (Assessment of initial eligibility for study participation)
Active Treatment Phase	Start: Day 1 of CRT Completion: Day 14 Post CRT Duration: 7 to 9 weeks depending on the duration of CRT
Short Term Follow-up	Start: Day 15 Post CRT Completion: Day 42 Post CRT (± 3 days) Duration: 4 weeks Of note: For subjects with persistent grade 2 oral mucositis at week 6 post-treatment, follow-up will continue until oral mucositis decreases to grade 1 or less.
Long Term Follow-up	3, 6 and 12 months (± 14 days) post the last dose of CRT

Screening Phase (≤ 4 weeks prior to randomization): During the screening phase, subjects will be assessed for eligibility to proceed to the Active Treatment Phase of the study. Criteria include the following:

Pathologically-confirmed squamous cell carcinoma of the oral cavity, oropharynx (or HPV positive unknown primaries presumed to be of oropharyngeal origin) or hypopharynx.

Planned continuous course of intensity-modulated radiotherapy (IMRT) given as single daily fractions of 2.0 to 2.2 Gy with a minimum cumulative dose of 50 Gy and maximum dose of 72 Gy.

Planned radiation treatment fields must include at least 2 at-risk sites for oral mucositis (maxillary or mandibular labial mucosa, right or left buccal mucosa, right or left ventral and lateral tongue, floor of oral cavity, or soft palate) with each site receiving a total dose of ≥ 50 Gy. Planned monotherapy with cisplatin administered in standard weekly (30 to 40 mg/m^2) **or** tri-weekly (80 to 100 mg/m^2) regimens.

Active Treatment Phase: The Active Treatment Phase starts the first day of chemoradiation therapy and continues until two weeks following the last day of radiation therapy. A Baseline Assessment will be conducted on the first day of chemoradiation therapy prior to the start of therapy. During the active treatment phase, subjects will rinse with the suspension for 30 seconds three times each day using the assigned IMP. The suspension should then be expectorated into a sink or toilet. The first dose will be administered after the completion of the Baseline Visit. The administration of the first dose of IMP must be witnessed by a study staff member.

Subjects will undergo study assessments twice a week during the active treatment phase. Subjects will be evaluated two times per week for adverse events (AEs) and for the presence and severity of OM throughout RT. The presence and severity of OM will be determined by trained observers using the World Health Organization (WHO) OM criteria.

Subjects will complete a study diary daily starting the first day of radiation therapy and continuing through to the end of the active treatment phase of the study. Patients with WHO persistent grade mucositis of 2 or greater at the end of the active treatment phase will continue to complete the daily diaries until mucositis decreases to grade of 0 or 1. The diary contains the Oral Mucositis Daily Questionnaire (OMDQ), a record of analgesic medication use, and questions regarding IMP dosing, tolerability and general quality of life. The diary will be reviewed by study staff at each study assessment time point in order to ensure complete and accurate data collection.

Short Term Follow-up: Short term follow-up will begin after the completion of the active treatment phase (Day 15 Post CRT) and will continue for four weeks (Day 42 Post CRT (± 3 Days)). During short term follow-up, subjects will be assessed weekly for adverse events and mucositis severity. Subjects with WHO persistent grade mucositis of 2 or greater at the end of the short term follow-up phase will continue to be followed weekly until mucositis decreases to grade of 0 or 1.

Long Term Follow-up: Tumor status will be assessed at 3, 6 and 12 months (+/- 14 days) following the last dose of CRT.

Blood samples for biomarkers studies will be collected at specific time points in all subjects. Blood and buccal smears will be collected at specific time points in a subset of subjects (15 subjects on active and 15 subjects on placebo) who consent separately. These will be used to evaluate the pharmacokinetics (PK) of AG013. Additional blood samples for genetic responder/non-responder studies will be collected at specific time points for subjects who consent separately. A detailed laboratory manual will be provided to the clinical site by the Sponsor or its designee.

Primary Efficacy Endpoint

1. Duration (in days) of severe oral mucositis (WHO grades 3 or 4)

Key Secondary Efficacy Endpoints (hierarchical)

1. Time to onset of severe oral mucositis (WHO grades 3 or 4)
2. Incidence of severe oral mucositis (WHO grades 3 and 4)
3. Duration of ulcerative oral mucositis (WHO grades 2, 3 or 4)
4. Time to onset of ulcerative oral mucositis (WHO grades 2, 3 or 4)
5. Incidence of ulcerative oral mucositis (WHO grades 2, 3 or 4)

Safety Endpoints

1. Incidence of adverse events, including serious adverse events (SAEs) and clinically significant laboratory abnormalities
2. Changes in vital signs and clinical laboratory parameters
3. Overall tumor response to chemoradiation therapy (during 12 months following the last dose of CRT).

Secondary Efficacy Endpoints

1. Cumulative radiation dose to development of severe oral mucositis (WHO grades 3 or 4) and ulcerative oral mucositis (WHO grades 2-4)
2. Patient-reported pain as measured by Question 2 (mouth and throat soreness) of the Oral Mucositis Daily Questionnaire
3. Use of analgesics to control oral pain (number and percentage of subjects using per type)

Pharmacokinetic (PK) and Pharmacodynamic (PD) Endpoints

1. Assessment of biomarkers (primarily pro- and anti-inflammatory cytokines)
2. PK profile of AG013 based on blood/serum samples and buccal smears in a subset of subjects (15 subjects on AG013 and 15 subjects on placebo in up to 10 sites)

Exploratory Efficacy Endpoints for OM (linked to primary endpoint)

1. Incidence of severe mucositis (WHO grades 3 or 4) within subgroups defined by cumulative radiation doses of 30 Gy, 40 Gy, 50 Gy and 60 Gy
2. The area under the curve (AUC) of an OM severity–time curve

3. Mucositis severity parameters (incidence, duration, time to onset of grades 3,4 and 2,3,4) based on NCI-CTCAE v4.0 and RTOG criteria

Other Exploratory Endpoints

1. Genomic differentiation of AG013 responders and non-responders
2. Frequency and duration of RT interruptions
3. Healthcare resource use including: unplanned office visits, ER visits, hospitalizations, and non-prophylactic gastrostomy tube placement (US sites only)
4. Comparison of AG013 efficacy in OM in patients with HPV negative versus HPV positive tumors

Subject Eligibility Criteria

Inclusion Criteria

1. Willing and able to understand and sign the study specific Informed Consent Form (ICF) approved by the site's Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

2. Pathologically-confirmed squamous cell carcinoma of the oral cavity, oropharynx, nasopharynx or hypopharynx or HPV-positive unknown primaries presumed to be of oropharyngeal, nasopharyngeal or hypopharyngeal origin

3. Tumor HPV status established

4. Planned to receive either primary or post-operative CRT

5. Planned IMRT as single daily fractions of 2.0 to 2.2 Gy with a cumulative radiation dose of at least 50 Gy and maximum dose of 72 Gy

6. The radiation field must provide for a minimal cumulative dose of 50 Gy to at least two sites at risk for OM (maxillary or mandibular labial mucosa, right or left buccal mucosa, right or left ventral and/or lateral tongue, floor of oral cavity, or soft palate/tonsillar pillars)
7. Planned administration of cisplatin administered at a dose of 30 to 40 mg/m^2 weekly during RT or tri-weekly 80 to 100 mg/m^2 days 1, 22 and 43
8. Males or females 21 years or older
9. Karnofsky performance score (KPS) ≥ 70% (appendix E)
10. Screening laboratory assessments:

- Hemoglobin ≥ 10g/dl
- White blood count ≥ 3500 cells/mm^3
- Absolute neutrophil counts ≥ 1500 cells/ mm^3
- Serum AST and ALT ≤ 3 x ULN
- Calculated Creatinine Clearance ≥ 50 ml/min
- Negative pregnancy test (serum or urine) for females of childbearing potential[#] performed 7 days before IMP administration

11. Females of childbearing potential[#] must confirm to use an effective method of birth control during study participation and for 30 days following the last treatment with IMP. Acceptable methods of contraception for females include the following:

    a) Double contraceptive methods including the use of either male or female condom, a diaphragm or cervical cap associated with a spermicide, on top of one of the following:
    - combined estrogen and progestogen containing hormonal contraception (oral, intravaginal or transdermal)
    - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
    - Intrauterine device
    - Intrauterine hormone-releasing system

    b) Vasectomized partner

    c) Sexual abstinence[$]

    Male subjects, when having hetero-sexual intercourse with a female of childbearing potential[#], must use a condom during study participation and for 90 days following the last treatment with IMP. For non-pregnant female partners of childbearing potential[#] the contraception recommendations as described above should also be considered for 90 days after the last treatment with IMP of their male partner.

    [#]A female is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

    [$]Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception.

Exclusion Criteria:

1. Prior radiation to the head and neck

2. Increased risk of developing infectious endocarditis:
    - Prosthetic cardiac valves, including transcatheter-implanted prostheses and homografts
    - Prosthetic material used for cardiac valve repair, such as annuloplasty rings and chords
    - Previous Infectious Endocarditis
    - Unrepaired cyanotic congenital heart disease or repaired congenital heart disease, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device
    - Cardiac transplant with valve regurgitation due to a structurally abnormal valve
3. Prior gene therapy
4. Presence of active infectious oral disease
5. Presence of any oral lesions that may confound the ability to assess oral mucositis grade
6. Current use of antibiotic rinses or troches
7. Herbal, alternative remedies, and alcohol containing over-the-counter mouthwashes are excluded during the course of the study
8. Current alcohol abuse syndrome
9. Chronic immunosuppression
10. Known seropositive for HIV
11. Use of investigational agent within 30 days of signing informed consent
12. Tooth extraction prior to radiation in which the extraction site is not epithelialized (typically within 5-10 days after extraction)
13. Signs and symptoms of active dental disease including toothache, severely mobile teeth, draining intraoral fistula(e), intraoral swelling (not associated with the primary tumor), gingival suppuration, gross caries, or fractured teeth involving the pulp
14. Female subjects who are pregnant or nursing
15. Known allergy to excipients of the IMP, such as sodium glutamate, sorbitol, dextrin (from maize starch), anhydrous glucose, phosphate buffer salts and mannitol
16. Inability to give informed consent or comply with study requirements
17. Unwilling or unable to complete subject diary

18. Any other clinical condition, psychiatric condition or prior therapy that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable or to comply with follow-up visits

Investigational Medicinal Product Dosage and Administration

The clinical formulation of AG013 is an oral, topical administration in the form of a mouth rinse (MR). This MR suspension is prepared by reconstitution of the AG013-DP/Placebo, packed in individual glass bottles, into a selected solution for reconstitution (SR) to form the MR suspension prior to administration.

This SR is an aqueous solution containing glucose (dextrose), phosphate buffer salts (pH buffer) and saccharin sodium (sweetener) and a raspberry aroma in purified water.

The final concentration of AG013 in the oral rinse is 2.0×10^{11} CFU/15 ml.

Subjects assigned to the placebo group will receive appearance- and taste-matched placebo powder.

Procedures:

Screening Phase (Within 4 weeks of Randomization)

The following screening observations and procedures will be completed after ICF signature, within 4 weeks prior to randomization (data of standard of care assessments that are not study-specific procedures obtained prior to ICF signature and within 4 weeks of Day 1 of CRT can be used):

- Obtain a signed and dated ICF (In addition to study participation ICF a separate ICF will be required for participation in genomic studies)
- Assessment against inclusion/exclusion criteria including medical history
- Demographic data
- Physical examination including KPS, vital signs (weight, temperature, blood pressure, heart rate, respiration rate), height and body weight
- Indicate tumor HPV status
- Oral assessment to exclude any lesions that may confound the ability to assess oral mucositis
- Current medications
- Review of CRT plan to ensure eligibility

- Laboratory assessments
    - CBC: WBC (differential cell count in %), hemoglobin, hematocrit, platelet count, RBC indices
    - Chemistry: sodium, glucose, potassium, BUN, creatinine, phosphorus, calcium, alkaline phosphatase, LDH, AST, ALT, albumin
- Pregnancy test in urine or serum performed 7 days before IMP administration (in females of childbearing potential)

Active Treatment Phase

Baseline (Day 1 of Chemoradiation therapy)

Prior to the first dose of CRT, the following assessments and procedures will be conducted:

- Obtain and record vital signs and body weight
- Determine KPS
- Provide and review instructions for completion of the daily diary that includes OMDQ responses; questions on IMP dosing, tolerability (taste, consistency and smell) and general quality of life, and analgesic medication use
- Have the OMDQ completed prior to the oral assessment
- Conduct OM assessment and record the WHO grade
- Record concomitant medications
- Record analgesia use for oral pain
- Record all AEs and SAEs that have occurred since ICF signature
- Record presence of prophylactic gastrostomy tube
- Provide caries prevention kit and give instructions for use
- Laboratory assessments (can be performed up to a day before IMP dosing)
    - CBC: WBC (cell count differential in %), hemoglobin, hematocrit, platelet count, RBC indices
    - Chemistry: sodium, glucose, potassium, BUN, creatinine, phosphorus, calcium, alkaline phosphatase, LDH, AST, ALT, albumin
- Draw blood for biomarkers studies
- Draw blood for genetic responder/non-responder (for subjects who consent separately)
- Administer first dose of IMP (must be witnessed) prior to CT or RT whatever comes first

Administer RT and, if scheduled, CT; record the time of RT/CT administration

Twice-Weekly During the Active Treatment Phase

The following assessments and procedures will be conducted twice a week during the active treatment phase by trained study staff. Assessments will be performed a minimum of 48 hours apart:

- Record AEs and SAEs
- Record concomitant medications
- Record analgesia use for oral pain
- Record use and/or placement of gastrostomy tube
- Review daily diary with patient
    - Review with the subject the analgesic information written in the diary and ensure complete analgesic information
    - If any diary entries are blank, the subject should be counseled regarding the importance of completing the diary
    - The OMDQ must be completed prior to the oral assessment
- Collect daily diary and dispense new forms
- Assess compliance with the caries prevention regimen
- Assess compliance with IMP dosing
- Conduct OM assessment and record the WHO grade

Weekly During the Active Treatment Phase

The following assessments and procedures will be conducted weekly during the active treatment phase. These observations or assessments can be done during one of the twice-weekly assessment visits:

- Obtain and record body weight and vital signs on the last RT day of each week
- Determine KPS
- Record unscheduled office visits, emergency room (ER) visits, or hospitalizations
- Ensure subject completes questionnaire on IMP tolerability
- Conduct IMP accountability
- Laboratory assessments
    - CBC: WBC (cell count differential in %), hemoglobin, hematocrit, platelet count, RBC indices

  - Chemistry: sodium, glucose, potassium, BUN, creatinine, phosphorus, calcium, alkaline phosphatase, LDH, AST, ALT, albumin

- Week 3 and 5 only, on the last day of RT for the specified week
  - Draw serum for biomarkers studies
- On the last day of RT
  - Draw blood for biomarkers studies
  - Draw blood for genetic responder/non-responder (for subjects who consent separately)

End of Active Treatment Phase Visit (Day 14 post CRT)

All subjects will return for an End of Active Treatment Phase visit. These observations or assessments can be done as a part of the twice-weekly assessment visits:

- Conduct physical examination including vital signs and body weight
- Determine KPS
- Review subject diary entries to ensure completeness of entries and collect the diary
  - The OMDQ must be completed prior to the oral assessment
- Ensure subject completed questionnaire on IMP tolerability
- Conduct OM assessment and record the WHO grade
- Record analgesia use for oral pain
- Record concomitant medications
- Record AEs and SAEs
- Record use and/or placement of gastrostomy tube
- Record unscheduled office or ER visits or hospitalizations
- Conduct IMP accountability
- Assess compliance with the caries prevention regimen
- Laboratory assessments
  - CBC: WBC (cell count differential in %), hemoglobin, hematocrit, platelet count, RBC indices
  - Chemistry: sodium, glucose, potassium, BUN, creatinine, phosphorus, calcium, alkaline phosphatase, LDH, AST, ALT, albumin
- Pregnancy test for females of childbearing potential
- On the last day of IMP dosing:

- Draw blood for biomarkers studies

Short Term Follow-up Phase:

Weekly Assessments

The following assessments will be conducted weekly for four weeks after completion of the active treatment phase. If after four weeks, subjects have grade 2 or greater OM weekly assessments will continue until OM is 1 or less:

- Review subject diary entries to ensure completeness of entries (for subjects that still have WHO OM score grade 2 or greater)
  - The OMDQ must be completed prior to the oral assessment
- Record analgesia use for oral pain
- Record concomitant medications
- Record AEs and SAEs
- Record use and/or placement of gastrostomy tube
- Record unscheduled office, ER visits or hospitalizations
- Assess compliance with the caries prevention regimen
- Week 2 only
  - Draw blood for biomarkers studies

PK sampling in a subset of subjects (15 subjects on active and 15 subjects on placebo) who consent separately:

- ***Baseline* (*Day 1 of Chemoradiation therapy*)**
  - Draw blood and collect buccal smears before IMP dosing
  - Draw blood 90 minutes after the first dosing with IMP and collect buccal smears 5 minutes and 90 minutes after the first dosing with IMP
- ***Weekly During the Active Treatment Phase***
  - Week 3 and 5 only, on the last day of RT for the specified week
    - Draw blood and collect buccal smears before the first dosing with IMP
    - Draw blood 90 minutes after first dosing with IMP and collect buccal smears 5 minutes and 90 minutes after the first dosing with IMP
  - On the last day of RT
    - Draw blood and collect buccal smears before the first dosing with IMP

- Draw blood 90 minutes after the first dosing with IMP and collect buccal smears 5 minutes and 90 minutes after the first dosing with IMP

- ***End of Active Treatment Phase Visit (Day 14 post CRT)***
  - On the last day of IMP dosing
    - Draw blood and collect buccal smears before the first dosing with IMP
    - Draw blood 90 minutes after first dosing with IMP and collect buccal smears 5 minutes and 90 minutes after the first dosing with IMP

- **Short Term Follow-up Phase**
  - Week 2 only: Draw blood and collect buccal smears

Long term Follow-up Period

- Assess tumor status at 3, 6, and 12 months (+/- 14 days) post the last dose of CRT
- RECIST (Response Evaluation Criteria In Solid Tumors) criteria or other standard assessments on tumor response should be used as per site standard of care practice.

Statistical Considerations

Analysis Sets:

The intent-to-treat (ITT) analysis set will consist of all randomized patients. This population will serve as the basis for the primary efficacy analysis. The modified ITT population (mITT), defined as all ITT patients who receive at least one dose of IMP and have post-baseline efficacy data, will also be used for efficacy analyses.

The per protocol (PP) population will consist of all mITT subjects who receive at least 4 weeks of IMP and CRT, and a cumulative radiation dose of 50Gy to oral and oropharyngeal sites at risk; this population will be used for supportive efficacy analyses.

The safety (SAF) analysis set will consist of all randomized patients who receive at least 1 dose of IMP. This population will be used for all summaries of patient accountability, demographic and baseline data, and safety information, including AE incidence and clinical laboratory data.

Demographics and Baseline Characteristics:

Demographic data (including age, race, ethnicity, gender, height, and weight), medical history, prior treatments, and pre-treatment clinical characteristics will be summarized by treatment group.

Safety:

Safety will be evaluated on the basis of treatment-emergent AEs (TEAEs), vital signs, weight, physical examinations and clinical laboratory assessments, as well as tumor response assessments. Changes from baseline in vital signs, physical examinations, weight, and clinical laboratory values will be summarized by treatment group using descriptive statistics. All AEs will be coded by Preferred Term using the MedDRA classification dictionary. The incidence of TEAEs will be summarized by treatment group, and by severity (grade) and relationship to IMP. Serious AEs (SAEs) and AEs leading to withdrawal from the study will be tabulated. IMP compliance and tolerability ratings will be summarized descriptively for each treatment group.

Efficacy:

All efficacy data will be summarized descriptively using number of subjects, mean, median, standard deviation, standard error of the mean, minimum, and maximum for continuous data and frequencies and percentages for categorical data.

For each subject, the duration of severe oral mucositis will be calculated as the number of days from the first WHO grade 3 or 4 until the first time WHO grade 2 or less is observed after last WHO grade 3 or 4. Subjects who do not experience severe OM will be assigned a duration of zero days. Subject who die or discontinue the study with severe OM will be assumed to have severe OM for the remainder of the observation period. In these cases, duration of severe OM will be calculated from the date of first onset (WHO grade 3 or 4) until 2 weeks after the last planned dose of radiation.

The generalized Cochran-Mantel-Haenszel (CHM) method stratified by cisplatin regimen (weekly versus tri-weekly), HPV status (positive versus negative) and region (US versus Europe) will be used to compare treatment groups. A test of the mean score difference with modified ridit scores will be used for the primary efficacy endpoint (duration of severe OM) and other continuous measures, including the duration of ulcerative OM and average pain severity scores. The general association form of the CMH test will be used for analysis of proportions. Analgesic use will be summarized per type of medication. A chi-square test will be used to compare the percentage of subjects taking opioids in each treatment group.

Kaplan-Meier methods will be used for estimation of time to onset of severe oral mucositis and other time to event endpoints, cumulative distribution curves will be compared using log-rank tests, stratified by cisplatin regimen and HPV status.

Additional sensitivity analyses will be performed to support the primary efficacy analysis. To account for multiple comparisons, significance testing of secondary efficacy endpoints will employ a hierarchical testing procedure to protect the overall type I error rate of 5%.

Pharmacokinetics and Biomarkers:

Biomarker assessments will be listed and summarized by time point using descriptive statistics (mean, median, standard deviation, standard error of the mean, coefficient of variation, minimum, and maximum) and graphical displays.

Serum levels of hTFF1 and buccal mucosa levels of AG013 (both AG013-sAGX0085 bacteria and hTFF1) will be summarized using descriptive statistics, including graphical methods.

Table of Contents

List of Figures and Tables

List of Abbreviations

AE	Adverse Event
AG013	Mouth Rinse formulation of *Lactococcus lactis* strain sAGX0085, deficient in the gene coding for thymidylate synthase and producing human TFF1
AG013-DP	AG013 Drug Product
AG013-DS	AG013 Drug Substance
AJCC	American Joint Committee on Cancer
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
bid	*bis in die* (twice a day)
BUN	Blood Urea Nitrogen
CAP	Clinical Assistance Programs, LLC
CAT	Computed Axial Tomography
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CFU	Colony Forming Unit
CHM	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRO	Contract Research Organization
CRT	Chemoradiation Therapy
CS	Clinically Significant
CT	Chemotherapy
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ELISA	Enzyme-Linked Immunosorbent Assay
ER	Emergency Room
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
Gy	Gray

hTFF1	Human Trefoil Factor 1
HIV	Human Immunodeficiency Virus
HNC	Head and Neck Cancer
HPV	Human Papilloma Virus
IBC	Institutional Biosafety Committee
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
IMP	Investigational Medicinal Product
IMRT	Intensity-Modulated Radiotherapy
IND	Investigational New Drug
IRB	Institutional Review Board
ITF	Intestinal Trefoil Factor
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive Web Response System
KPS	Karnofsky Performance Score
LDH	Lactic Dehydrogenase
L. lactis	*Lactococcus lactis*
MASCC	Multinational Association of Supportive Care in Cancer
MedDRA	Medical Dictionary of Regulatory Activities
mITT	Modified ITT population
MR	Mouth Rinse
MTS	Mouth and Throat Soreness
n	Number of Subjects
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	Non-clinically Significant
NIH	National Institutes of Health
NLT	Not Less Than
OBA	Office of Biotechnology Activities

OM	Oral Mucositis
OMDQ	Oral Mucositis Daily Questionnaire
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PO	per os (by mouth)
PP	Per Protocol
PRO	Patient Reported Outcomes
pS2	Former name of TFF1
PT	Preferred Term
qd	Quaque Die (once daily)
qPCR	quantitative Polymerase Chain Reaction
rhTFF3	Recombinant Human Trefoil Factor 3
RECIST	Response Evaluation Criteria In Solid Tumors
RBC	Red Blood Cell
RT	Radiation Therapy
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SEM	Standard Error of the Mean
SD	Standard Deviation
SOC	System Organ Class
SP	Spasmolytic Peptide
SR	Solution for Reconstitution
TEAE	Treatment-Emergent Adverse Event
TFF	Trefoil Factor
tid	*Ter In Die* (three times a day)
ULN	Upper Limit of Normal
WBC	White Blood Count
WHO	World Health Organization

1 INTRODUCTION AND STUDY RATIONALE

1.1 Introduction

Oral mucositis (OM) is a common, excruciatingly painful, and debilitating side effect of conventional chemoradiation regimens used to treat cancers of the head and neck. It adversely impacts a range of collateral health outcomes resulting in increased use of resources and cost of care (Nonzee et al., 2008).

1.1.1 Incidence of Oral Mucositis amongst patients receiving concomitant chemoradiation for cancers of the head and the neck

Virtually all patients who receive standard concomitant chemoradiation regimens for the treatment of cancers of the head and neck develop ulcerative (WHO grade ≥2) OM (Traynor 2010). Even more significant is the consistent observation that severe mucositis (WHO grade ≥3) is noted in more than two-thirds of the same patient population. When evaluated separately, the incidence of severe mucositis is higher for patients treated for cancers of the mouth or oropharynx (Fayette et al., 2015).

1.1.2 Clinical Effects of Oral Mucositis

The severity of OM varies from superficial erythema, accompanied by soreness, to full-thickness mucosal ulcerations, necessitating parenteral narcotics for pain control (Scully et al., 2006). Among patients receiving myeloablative CT regimens or RT to the head and neck, OM is the most commonly cited bothersome adverse event (AE) associated with treatment (Rose-Ped et al., 2002).

The clinical impact of OM is profound, especially when ulceration is present. Even OM described as slight to moderate is associated with increased oral pain, weight loss, the need to modify diet, dehydration, and reduced performance status (Elting et al., 2007). Oral mucositis results in loss of critical functions, such as the ability to eat and to swallow, which can lead to dehydration, weight loss, and the need for nutritional support (e.g., gastrostomy tube placement). Furthermore, the ulcerations associated with OM are a frequent site of secondary infections and, in myelosuppressed patients, may act as portals for systemic bacterial spread (Reuscher et al., 1998). Treatment breaks prompted by patients' inability to tolerate the symptoms associated with OM compromise cancer therapy. And there is a strong association between OM and diminished quality-of-life (QOL) outcomes (Elting et al., 2008).

Besides its symptomatic toll, OM is associated with a number of negative health and economic outcomes, including increased analgesic and antibiotic use, number of febrile days, need for parenteral nutrition, prolonged length of hospital stay, and

increased resource use and associated cost. In granulocytic patients, mucositis is strongly associated with an increased risk of bacteremia and sepsis (Reuscher et al., 1998). Among patients treated for HNC, even mild OM results in more frequent hospitalization and breaks in treatment (Vera-Llonch et al., 2006).

Despite its frequency and significance, there is no approved intervention for RT-induced OM in HNC. Furthermore, currently there is a single agent approved as a treatment for OM, Kepivance®, and its application is limited to OM associated with conditioning regimens prior to stem cell transplant for the treatment of hematologic malignancies.

1.2 Background and Rationale

The trefoil factor (TFF) family, which comprises TFF1 (formerly pS2), TFF2 (formerlyspasmolytic peptide, SP) and TFF3 (formerly intestinal trefoil factor, ITF) are small, non-mitogenic protease-resistant peptides that share a conserved distinct motif of 6 cysteine residues linked by three disulphide bonds, defining a so-called 3-leafed “trefoil domain” or “P domain”. TFF peptides are expressed in several tissues of the human body, but most pronouncedly by mucus-secreting cells of the gastrointestinal (GI) tract, including the mouth, esophagus, stomach and intestines. They bind to the much larger mucins and catalyze the formation of stable gel complexes of high viscosity that are resistant to mechanical forces and chemical degradation.

TFFs have been implicated in the protection of the GI tract against mucosal damage and its subsequent repair. All 3 TFF peptides have shown a therapeutic effect in experimental models. The peptides are rapidly upregulated and secreted in an autocrine fashion in response to GI injury (Poulsen et al., 2003; Rio et al., 1991; Wright et al., 1990). TFF peptides facilitate cell migration into the lesion, thus forming a protective barrier in a process known as restitution. Taupin and Podolsky (2003) reported that TFFs play an essential and necessary role in epithelial restitution and repair within the GI tract. In addition, TFFs are potent inhibitors of apoptosis and prevent anoikis (cell death induced by anchorage independence) during the cell migration process. The distinct signaling pathways that mediate the effects of TFFs have not been fully elucidated, nor has a definitive functional receptor for hTFF1 been identified. hTFF2 has recently been reported to bind on the chemokine CXCR4 receptor and interactions of hTFF3 with the chemokine CXCR4, CXCR7 and CXCR2 receptor have been postulated (Dubeykovskaya et al., 2009; Lau et al., 2015; Dieckow et al., 2016).

TFF1 and TFF3 are secreted by human salivary glands and are present in whole saliva (Devine et al., 2000). TFF1 and TFF3 bind to the salivary mucins and form a mucus layer over the epithelia of the mouth. This layer acts as a physical barrier against bacteria and noxious environmental agents. Moreover, it has been shown that these TFF peptides have wound-healing properties and are important in protecting and healing mucosal tissues

(Hoffman, 2004). Their potential for therapy of gastrointestinal diseases, including oral ulcers, has been established.

Beck et al. (2004) studied the role of TFF3 in intestinal damage induced by chemotherapy and radiation. They reported that mice deficient in intestinal trefoil factor were more susceptible to chemotherapy and radiation mediated injury and that oral recombinant human (rh)TFF3 reduced the severity of both chemotherapy-induced and chemotherapy/radiotherapy-induced intestinal mucositis.

The results of a Phase 2 study evaluating the safety and efficacy of rhTFF3 administered as an oral spray topically applied to the oral cavity of patients at high risk for developing oral mucositis were reported (Barker et al., 2008; Peterson et al., 2009). Frequency of WHO Grade > 2 oral mucositis in the placebo, low dose rhTFF3 and high dose rhTFF3 groups was 48.5% (16/33), 9.1% (3/33) and 12.1% (4/33), respectively. Assessment of area under the curve relative to OM incidence and severity revealed a statistically significant treatment effect of rhTFF3 versus placebo (WHO grades, $p<0.01$). Based on these data, it was concluded that prophylactic use of rhTFF3 at either high or low dose was associated with a significant (~80%) reduction in OM occurrence in patients at high risk for development of the lesion.

AG013 is made up of a recombinant *L. lactis* strains engineered to secrete hTFF1. In an established acute radiation hamster model it has been shown that topical application of AG013 to oral mucosa favorably affects the severity and course of radiation-induced oral mucositis (Caluwaerts et al. 2010).

Current OM-directed formulations (rinse or spray) require frequent mucosal exposure of large amounts of protein to demonstrate efficacy. Aside from the high cost associated with such an approach, the high levels of protein could present potential safety issues. In comparison to a mouth rinse (MR) or an oral spray with the therapeutic peptide (i.e., TFF), AG013 introduces TFF via a MR containing the modified *L. lactis* bacteria. Therefore, it is expected to be more efficacious through mucosal targeting and continuous release of hTFF1, even after the patient has rinsed. Based on the PK experiments performed in the hamster model (see Investigator's Brochure, section 4, Non-clinical studies) and the Phase 1 PK study in healthy volunteers (see Investigator's Brochure, section 5) it is anticipated that AG013 remains at the site of the buccal mucosa secreting TFF1 up to 4 hours (hamster study) and 6 hours (healthy volunteers) after oral rinsing.

The Phase 1b study AG013-ODOM-101 was the first clinical study of AG013 in humans. This study demonstrated that AG013 was generally safe and well tolerated by HNC patients; who were eligible for induction CT prior to undergoing RT; when applied topically; by MR once, 3 times, or 6 times daily beginning on the first day (Day 1) of CT during CT Cycle 2 and continuing through Day 14, at a dose level of 2.0×10^{11} CFU/15 ml

rinse. In addition, exploratory efficacy results showed that subjects who received AG013 had a lower percentage of days with ulcerative mucositis, and more subjects who received AG013 on any dosing schedule had 0 or 1 days of ulcerative mucositis compared to subjects who received placebo.

Taken together, these results indicate that oral application of hTFF1 may have therapeutic potential in the treatment of mucosal injury and OM.

1.2.1 Non-clinical Studies

The non-clinical studies have focused on the pharmacology (pharmacodynamics and safety pharmacology), pharmacokinetics and toxicology of different strain constructions of *L. lactis* engineered to secrete TFFs. In conclusion, the results of the non-clinical studies provided sufficient proof-of-concept and safety data to support administration of AG013 in the clinical trials proposed in the context of the AG013 development program.

More detailed information about these non-clinical studies is contained in the Investigator's Brochure, section 4, Non-clinical studies.

1.2.2 Effects in humans

AG013 has been studied in humans in 2 studies: a Phase 1b clinical trial AG013-ODOM-101 (Coulie B., 2012) and a Phase 1 PK study in healthy volunteers AG013-CSD-MU-004 (Coulie B., 2013).

Phase 1b clinical trial AG013 ODOM 101

The Phase 1b, multicenter, single-blinded, placebo-controlled, sequential dose escalation study evaluated the safety, tolerability, and PK profile of AG013 in subjects experiencing OM during induction CT for the treatment of head and neck cancers. The ability of AG013 to attenuate the course and severity of OM was also assessed.

A total of at least 21 subjects were planned to be enrolled in 3 successive groups of at least 7 subjects each. For each group, at least 5 subjects were assigned to AG013 and at least 2 subjects were assigned to placebo.

Doses were escalated in successive groups by increasing the frequency of administration from once per day (qd) to 3 times per day (tid) and to 6 times per day, resulting in daily dose levels of 2×10^{11} CFU/day, 6×10^{11} CFU/day, and 1.2×10^{12} CFU/day, respectively.

An independent Data Safety Monitoring Board (DSMB) assessed the safety data from the previous group before treatment of any subject in the subsequent group.

The study achieved its primary objective by demonstrating that AG013 was generally safe and well tolerated. The second objective of the study was to evaluate the pharmacokinetics of AG013.In general, live bacterial levels of AG013 were high immediately following dosing and decreased by 90 minutes post-dose. No differences were noted among the active treatment groups; no dose relationship was seen. In all treatment groups, AG013 levels were 0 by the End of Study (EOS) visit. AG013 could not be detected in blood. No dose frequency-related differences in hTFF1 levels could be detected in saliva or oral mucosa amongst the active treatment groups. Levels of hTFF1 in serum were not significantly different between treatment groups at all time points measured.

Several efficacy endpoints were measured as exploratory endpoints. Subjects who received AG013 had a lower percentage of days with ulcerative mucositis, and more subjects who received AG013 on any dosing schedule had no or only 1 day of ulcerative mucositis compared to subjects who received placebo. In addition, subjects who received AG013 had fewer unplanned office and emergency room visits compared to subjects who received placebo. For the remaining efficacy endpoints of mouth and throat soreness, opioid use, and gastrostomy tube placement, differences between the placebo and active treatment groups were minimal in this small Phase 1b study.

Phase 1 PK study in healthy volunteers AG013-CSD-MU-004

This was a single-center, open-label, Phase 1 study in healthy volunteers.

The study was divided into 4 periods. The purpose of the first period was to determine the PK profile (bacterial count and protein level) of a single dose of AG013. The purpose of the following 2 periods was to evaluate the influence of food and beverage on the PK profile of a single dose of AG013. The purpose of the last period was to determine the PK profile of AG013 administered three times on one day.

AG013 was generally safe when applied by mouth rinse once or three times on one day.

Overall, consistent levels of AG013 (bacterial count and protein) could be recovered from the different sample sites in the oral cavity, and this up to 6 hours (buccal mucosa) and 24 hours (saliva) after dosing. Furthermore, live AG013 bacteria levels coincided with protein levels. These data demonstrate that live AG013 bacteria adhere to the oral mucosa and actively secrete protein at the mucosal surface. This results in homogeneous exposure to the entire mucosal surface.

Exposure to AG013 was reduced by food intake while the intake of a beverage did not impact on exposure to AG013.

There was no evidence for systemic exposure neither to live AG013 bacteria (blood) nor to hTFF1 secreted (serum) and there was no recovery of live AG013 bacteria in feces.

More detailed information about the clinical studies is contained in the Investigator's Brochure, section 5, Effects in humans.

1.2.3 Rationale

A fixed dose of IMP will be administered at a dose frequency of three times daily. The study population consists of patients with high risk for OM associated with CRT. The dose level and dose frequency selected for evaluation in this study is expected to be safe and to show efficacy based on the results of the phase 1b clinical study and this new study will evaluate the dose frequency of AG013 three times daily oral rinses versus placebo. The selection of the dose frequency of AG013 three times daily is based on the positive efficacy trends noted in the Phase 1b trial AG013-ODOM-101, and on the results of the Phase 1 PK study in healthy volunteers AG013-CSD-MU-004 demonstrating that three times daily dosing result in a clinically relevant 24 hour exposure period of AG013.

More detailed information on the dose justification is contained in section 5.10, selection of doses.

2 OBJECTIVES

Primary Objectives

Primary Efficacy Objectives:

- To evaluate the efficacy of topically administered AG013 compared to placebo for reducing OM in patients undergoing chemoradiation for the treatment of head and neck cancer, as measured by the duration, time to development, and overall incidence of OM during the active treatment phase, beginning from the start of chemoradiation therapy (CRT) until 2 weeks following its completion.

Primary Safety Objectives:

- To determine the safety and tolerability of AG013 during the active treatment phase described above.

Secondary Objectives

Secondary Efficacy Objectives:

- To evaluate the effect of AG013 on patient-reported symptoms and analgesic use during the active treatment phase, and on the cumulative radiation dose administered before the onset of OM.

Secondary Pharmacokinetics and Pharmacodynamic Objectives:

- To assess biomarkers and, in a subset of subjects, the PK profile of AG013.

Exploratory Objectives

Exploratory Efficacy Objectives for OM

- Exploratory objective for OM Severity linked to time, duration and incidence of OM (linked to Primary Efficacy Objectives)

Other Exploratory Objectives:

- To investigate the genomic differentiation of AG013 responders and non-responders.
- To compare the efficacy of AG013 in patients with human papilloma virus (HPV) negative tumors versus HPV positive tumors.
- To evaluate the effect of AG013 on healthcare resource utilization (US sites only).
- To compare the frequency and duration of RT interruptions.

3 STUDY DESIGN

This is a Phase 2, double-blind, placebo-controlled, 2-arm, multi-center trial in which subjects will be randomized in a 1:1 ratio to receive either placebo or AG013.

AG013 has already been studied in healthy volunteers and in subjects experiencing OM during induction CT for the treatment of head and neck cancers. This is however the first time AG013 will be administered to subjects with cancers of the head and neck receiving concomitant CRT. To protect subjects from unanticipated safety risks, enrollment and treatment in the double-blind study will continue until 10 subjects on AG013 have been recruited. The DSMB will review safety data after these 10 subjects on AG013 have

completed study treatment. If there are no safety signals identified, the study will continue to recruit the planned number of subjects.

There are 4 study periods as described below: screening, active treatment, short term follow-up and long term follow-up. The screening phase will be no longer than 4 weeks. The active treatment phase will be between 7 and 9 weeks depending on the subject's prescribed CRT plan. The short term follow-up phase will be 4 weeks in duration. The long term follow-up will continue until 12 months post CRT. Oral mucositis (OM) assessments will begin at the start of CRT and continue until the subject has completed short term follow-up or until the OM resolves (as defined by a score of ≤ 1 based on WHO criteria), whichever comes first. Long term follow-up will continue for 12 months to assure that AG013 does not adversely impact the tumor response to anti-neoplastic therapy.

A subject's Investigational Medicinal Product (IMP) treatment assignment (AG013 or placebo) will be randomized 1:1 as follows:

- Arm A: Placebo tid
- Arm B: AG013, 2 x 10^{11} CFU/15 mL tid

Table 1 Study Periods

Screening Phase	Within 4 weeks prior to randomization (Assessment of initial eligibility for study participation)
Active Treatment Phase	Start: Day 1 of CRT Completion: Day 14 Post CRT Duration: 7 to 9 weeks depending on the duration of CRT
Short Term Follow-up	Start: Day 15 Post CRT Completion: Day 42 Post CRT (± 3 days) Duration: 4 weeks Of note: For subjects with persistent grade-2 oral mucositis at week 6 post treatment, follow-up will continue until oral mucositis decreases to grade 1 or less.
Long Term Follow-up	3, 6 and 12 months (± 14 days) post the last dose of CRT

Screening Phase (≤ 4 weeks prior to randomization): During the screening phase, subjects will be assessed for eligibility to proceed to the Active Treatment Phase of the study. Criteria include the following:

Pathologically-confirmed squamous cell carcinoma of the oral cavity, oropharynx, nasopharynx or hypopharynx.

Primary site: oral cavity, oropharynx, nasopharynx or hypopharynx or HPV positive unknown primaries presumed to be of oropharyngeal, nasopharyngeal or hypopharyngeal origin.

Planned continuous course of intensity-modulated radiotherapy (IMRT) given as single daily fractions of 2.0 to 2.2 Gy with a minimum cumulative dose of 50 Gy and maximum dose of 72 Gy.

Planned radiation treatment fields must include at least 2 at-risk sites for oral mucositis (maxillary or mandibular labial mucosa, right or left buccal mucosa, right or left ventral and lateral tongue, floor of oral cavity, or soft palate) with each site receiving a total dose of ≥ 50 Gy.

Planned monotherapy with cisplatin administered in standard weekly (30 to 40 mg/m2) or tri-weekly (80 to 100 mg/m2) regimens.

Active Treatment Phase: The Active Treatment Phase starts the first day of chemoradiation therapy and continues until two weeks following the last day of radiation therapy. A Baseline Assessment will be conducted on the first day of chemoradiation therapy prior to the start of therapy. During the active treatment phase, subjects will rinse with the suspension three times each day using the assigned IMP. The suspension should then be expectorated into a sink or toilet. The first dose will be administered after the completion of the Baseline Visit. The administration of the first dose of IMP must be witnessed by a study staff member.

Subjects will undergo study assessments twice a week during the active treatment phase. Subjects will be evaluated two times per week for adverse events (AEs) and for the presence and severity of OM throughout CRT. The presence and severity of OM will be determined by trained observers using the World Health Organization (WHO) OM toxicity scale.

Subjects will complete a study diary daily starting the first day of radiation therapy and continuing through to the end of the active treatment phase of the study. Patients with WHO persistent grade mucositis of 2 or greater at the end of the active treatment phase will continue to complete the daily diaries until mucositis decreases to grade of 0 or 1. The diary contains the Oral Mucositis Daily Questionnaire (OMDQ), a record of analgesic medication use, and questions regarding IMP dosing, tolerability general quality of life. The diary will be reviewed by study staff at each study assessment time point in order to ensure complete and accurate data collection.

Short Term Follow-up: Short term follow-up will begin after the completion of the active treatment phase (Day 15 Post CRT) and will continue for four weeks (Day 42 Post CRT (± 3 Days)). During short term follow-up, patients will be assessed weekly for adverse events and mucositis severity. Patients with WHO persistent grade mucositis of 2 or greater at the end of the short term follow-up phase will continue to be followed weekly until mucositis decreases to grade of 0 or 1.

Long Term Follow-up: Tumor status will be assessed at 3, 6 and 12 months (+/- 14 days) following the last dose of CRT.

Blood samples for biomarkers studies will be collected at specific time points in all subjects. Blood and buccal smears will be collected at specific time points in a subset of subjects who consent separately. These will be used to evaluate the pharmacokinetics (PK) of AG013. Additional blood samples for genetic responder/non-responder studies will be collected at specific time points for subjects who consent separately.

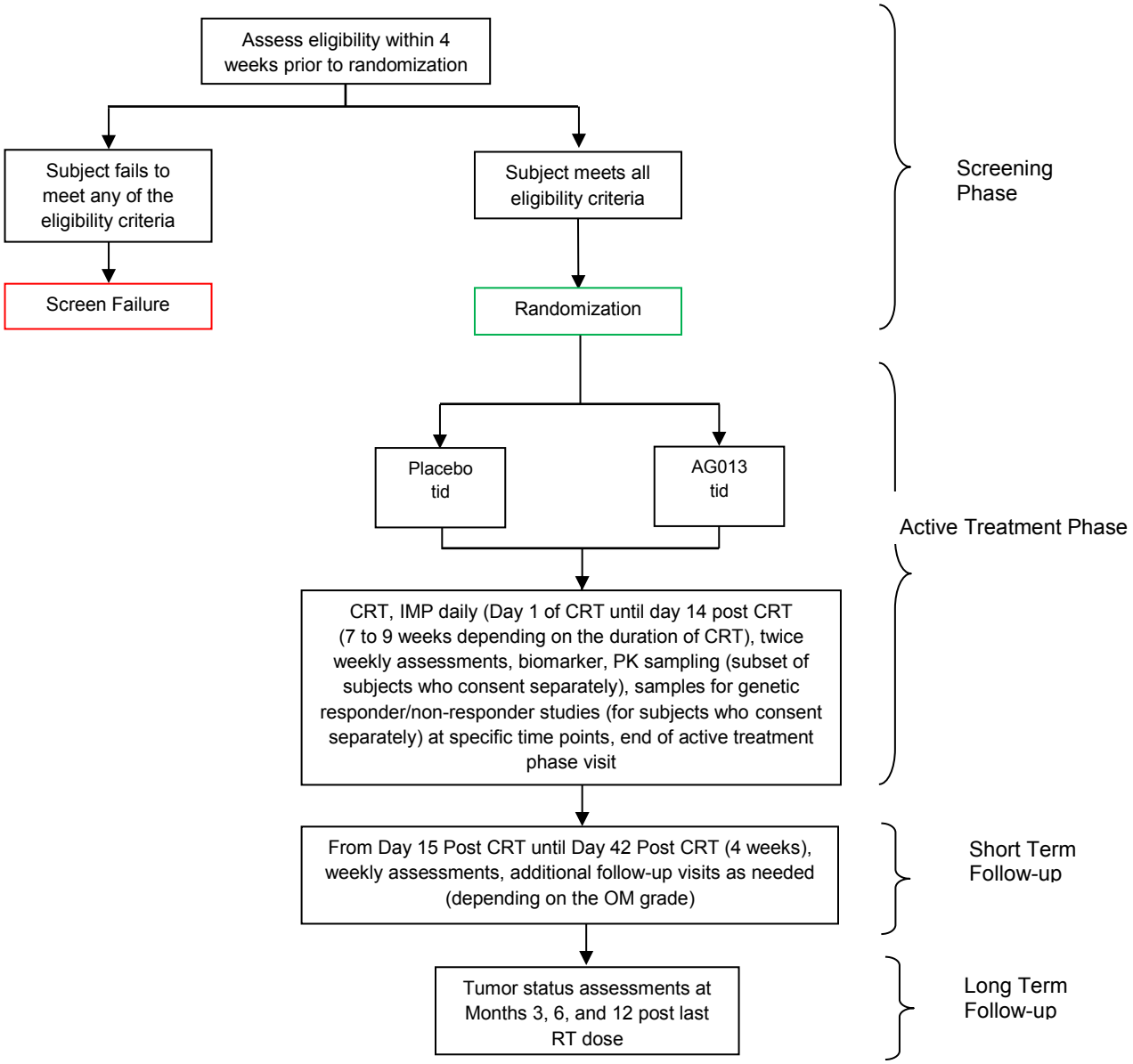
The total amount of blood taken for the whole study is maximum 300 ml. The blood sampling includes the following:

1. 11 samples of 15 ml each for routine laboratory testing
2. 6 samples of 10 m each for biomarker analysis
3. For female of childbearing potential, two samples 5 ml each might be taken for pregnancy testing
4. For patients who consent to genomic analysis, 2 samples of 2.5 ml each
5. For patients involved in PK analysis (US sites only), 11 samples of 5 ml each.

A detailed laboratory manual will be provided to the clinical site by the Sponsor or its designee.

The study design is illustrated in Figure 1.

Figure 1 Study Design



4 STUDY POPULATION

4.1 Sample Size

Approximately 200 subjects will be enrolled in the study to obtain 160 evaluable subjects (i.e., those who receive at least 4 weeks of IMP and a cumulative radiation dose of at least 50 Gy).

Approximately 60 sites in the United States and Europe will participate in the study.

4.2 Inclusion Criteria

Subjects will be included in the study if they are or have:

1. Willing and able to understand and sign the study specific Informed Consent Form (ICF) approved by the site's Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

2. Pathologically-confirmed squamous cell carcinoma of the oral cavity, oropharynx, nasopharynx or hypopharynx or unknown primary HPV-positive tumor presumed to be of oropharyngeal, nasopharyngeal or hypopharyngeal origin.

3. Tumor HPV status established

4. Planned to receive either primary or post-operative CRT

5. Planned IMRT as single daily fractions of 2.0 to 2.2 Gy with a cumulative radiation dose of at least 50 Gy and maximum dose of 72 Gy

6. The radiation field must provide for a minimal cumulative dose of 50 Gy to at least two sites at risk for OM (maxillary or mandibular labial mucosa, right or left buccal mucosa, right or left ventral and/or lateral tongue, floor of oral cavity, or soft palate/tonsillar pillars)

7. Planned administration of cisplatin administered at a dose of 30 to 40 mg/m^2 weekly during RT or tri-weekly 80 to 100 mg/m^2 days 1, 22 and 43

8. Males or females 21 years or older

9. Karnofsky performance score (KPS) ≥ 70% (appendix E)

10. Screening laboratory assessments:

    - Hemoglobin ≥ 10g/dl

- White blood count ≥ 3500 cells/mm3
- Absolute neutrophil counts ≥ 1500 cells/ mm3
- Serum AST and ALT ≤ 3 x ULN
- Calculated Creatinine Clearance ≥ 50 ml/min
- Negative pregnancy test (serum or urine)[#] performed 7 days before IMP administration

11. Females of childbearing potential[#] must confirm the use of an effective method of birth control during study participation and for 30 days following the last treatment with IMP. Acceptable methods of contraception for females include the following:

a) Double contraceptive methods including the use of either a male or female condom, a diaphragm or cervical cap associated with a spermicide, on top of one of the following:

- combined estrogen and progestogen containing hormonal contraception (oral, intravaginal or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device
- Intrauterine hormone-releasing system

b) Vasectomized partner

c) Sexual abstinence[$]

Male subjects, when having hetero-sexual intercourse with a female of childbearing potential[#], must use a condom during study participation and for 90 days following the last treatment with IMP. For non-pregnant female partner of childbearing potential[#] the contraception recommendations as described above should also be considered for 90 days after the last treatment with IMP of their male partner.

[#]A female is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

[$]Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in

relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception.

4.3 Exclusion Criteria

Subjects will be excluded from participation in the study if they are or have:

1. Prior radiation to the head and neck
2. Increased risk of developing infectious endocarditis (American Association of Endodontists, 2017):
    - Prosthetic cardiac valves, including transcatheter-implanted prostheses and homografts
    - Prosthetic material used for cardiac valve repair, such as annuloplasty rings and chords
    - Previous Infectious Endocarditis
    - Unrepaired cyanotic congenital heart disease or repaired congenital heart disease, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device
    - Cardiac transplant with valve regurgitation due to a structurally abnormal valve
3. Prior gene therapy
4. Presence of active infectious oral disease
5. Presence of any oral lesions that may confound the ability to assess oral mucositis grade
6. Current use of antibiotic rinses or troches
7. Herbal, alternative remedies, and alcohol containing over-the-counter mouthwashes are excluded during the course of the study.
8. Current alcohol abuse syndrome
9. Chronic immunosuppression
10. Known seropositive for HIV

11. Use of investigational agent within 30 days of signing informed consent

12. Tooth extraction prior to radiation in which the extraction site is not epithelialized (typically within 5-10 days after extraction)

13. Signs and symptoms of active dental disease including toothache, severely mobile teeth, draining intraoral fistula(e), intraoral swelling (not associated with the primary tumor), gingival suppuration, gross caries, or fractured teeth involving the pulp

14. Female subjects who are pregnant or nursing

15. Known allergy to excipients of the IMP, such as sodium glutamate, sorbitol, dextrin (from maize starch), anhydrous glucose, phosphate buffers salts and mannitol

16. Inability to give informed consent or comply with study requirements

17. Unwilling or unable to complete subject diary

18. Any other clinical condition, psychiatric condition or prior therapy that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable or to comply with follow-up visits

4.4 Removal of Subjects

In accordance with the Declaration of Helsinki, subjects have the right to withdraw from the study at any time for any reason. The Investigator and Sponsor also have the right to withdraw subjects from the study. Subjects may be removed from the study for the following reasons:

- Adverse experiences
- At the request of the Investigator or Sponsor, whether for administrative or other reasons
- Protocol violation or unreliable behavior
- Termination of the study by the Sponsor
- Symptoms suggesting clinically significant bacteremia that can be attributed to sAGX00085 (as determined by 3 consecutive blood cultures) (see section 6.2 Safety Assessments and 8.4 Recording of Adverse Events)

The date for a subject who discontinues and the reason for discontinuation will be recorded in the electronic case report form (eCRF). A complete listing of subject disposition (including subject discontinuation from the study and the reason for discontinuation), any concomitant medications required (including route, duration, and frequency of administration), and protocol deviations during the study will be provided in the study report.

If a subject discontinues all end of active treatment phase procedures should be conducted. If a subject expresses a desire to discontinue the study after completing a period, the investigator will make all efforts to complete the end of active treatment phase procedures.

If a subject is removed from the study, the date of the last dose of IMP and all observations collected up to the time of termination will be recorded on the eCRF along with the reason for termination. Scheduled safety evaluations and follow-up examinations will be conducted, if possible.

When a subject fails to return for scheduled assessments, the following efforts should be made to contact him/her to determine a reason for the failure to return: three phone attempts, including the date and time, should be documented in the subject's source documents. If there is no response to the phone calls, a certified letter should be sent to the subject. After these efforts have been exhausted, a subject should be identified as lost to follow-up in the eCRF.

5 STUDY TREATMENT

5.1 Radiation Therapy Treatment Plan

Subjects will receive a continuous course of intensity-modulated radiotherapy (IMRT) with a minimum cumulative dose of 50 Gy and maximum dose of 72 Gy. Planned radiation treatment fields must include at least 2 at-risk sites for oral mucositis (maxillary or mandibular labial mucosa, right or left buccal mucosa, right or left ventral and/or lateral tongue, floor of oral cavity, or soft palate/tonsillar pillars) with each site receiving a total dose of ≥ 50 Gy.

Radiation dose delivery will be clearly documented.

Changes in the radiation therapy plan will be allowed. However, the changes (example: dose delay, changes in the planned radiation dose or number of fractions) and the reason for the change should be clearly documented.

5.2 Chemotherapy Treatment Plan

Subjects will receive monotherapy with cisplatin administered at a dose of 30 to 40 mg/m^2 weekly during RT or tri-weekly 80 to 100 mg/m^2 days 1, 22 and 43.

The use of cisplatin concurrently with radiotherapy is in agreement with standard, current guidelines for the treatment of squamous cell carcinoma of the oral cavity and oropharynx (NCCN Guidelines Insights 2018; Head and Neck Cancers, Version 1.2018; Quon et al., 2017; Gregoire et al., 2010)

Chemotherapy dose and schedule will be documented.

Changes in the chemotherapy agent, dose or schedule due to treatment related toxicity will be allowed. However, the reason for the change must be clearly documented.

5.3 Investigational Medicinal Product Treatment Plan

Investigational Medicinal Product (IMP) will be applied three times daily beginning on the first day (Day 1) of CRT (CT or RT whatever comes first) and continuing for two weeks (14 days) following the last day of CRT.

5.4 Identity of Investigational Medicinal Product

AG013 is composed of a recombinant *Lactococcus (L.) lactis* strain sAGX0085, engineered to secrete hTFF1. The AG013 Drug Substance (AG013-DS) is an amorphous, slightly yellow, lyophilized powder, at a concentration of not less than (NLT) 6.4 x 10^{11} CFU/g *L. lactis* sAGX0085.

AG013-DP consists of AG013-DS, mixed with appropriate excipients and is presented as a 770 mg powder for reconstitution.

The bulk DP is formulated to reach a final strength of 2.6 x 10^{11} CFU/g of *L. lactis* sAGX0085.

Subjects assigned to the placebo group will receive appearance- and taste-matched placebo powder.

The clinical formulation of AG013 is an oral, topical administration in the form of a MR. This MR suspension is prepared by reconstitution of the AG013-DP/Placebo into a selected SR solution, packed in individual glass bottles, to form the MR suspension prior to administration.

This SR is an aqueous solution containing glucose (dextrose), phosphate buffer salts (pH buffer) and saccharin sodium (sweetener) and a raspberry aroma in purified water.

The final concentration of AG013 in the oral rinse is 2.0 x 10^{11} CFU/15 ml.

The AG013-DP/Placebo components of the mouth rinse formulation should be stored refrigerated (2°C to 8°C; 35°F to 47°F) in their original package. The SR solution can be stored at room temperature (15°C to 25°C; 59°F to 77°F) in their original package. The IMP must be kept in a secure area at the study site.

5.5 Labeling and Packaging

AG013-DP and placebo will be presented as a compressed powder in 30 ml clear glass bottles. The AG013-DP and placebo bottles will be placed in an aluminum sachet. The reconstitution solution will be delivered in a 15 ml dark glass bottle.

Labeling of the study treatment will conform to all requirements specified by governing regulations. Label directions will specify that the study drug should be stored refrigerated or at room temperature.

5.6 Investigational Medicinal Product Administration

Subjects will receive a mouth rinse package which will contain the following 2 components for the reconstitution of the mouth rinse suspension:

- AG013-DP powder or matching placebo in an aluminum sachet
- Reconstitution solution

A short summary of dose preparation is provided in Figure 2.

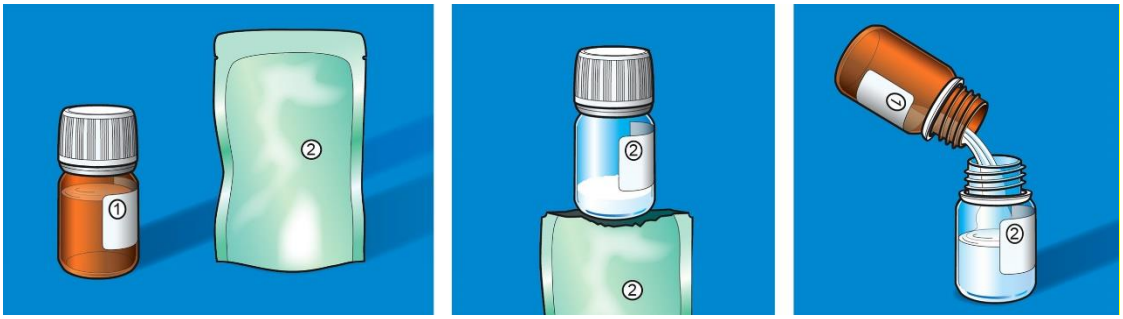


Figure 2 Summary of the different steps to reconstitute the mouth rinse suspension

Briefly, the SR needs to be added to the AG013-DP or Placebo, and shaken for at least 30 seconds to obtain a homogeneous white opaque suspension, ready for use.

Subjects will mix the study medication. Then, prior to the administration of the study medication, the patient will complete a 30 second cleansing rinse using bottled water. After

completing the cleansing rinse, subjects will shake the study medication to ensure reconstitution of the powder and then dose. Subjects will rinse with the suspension for 30 seconds three times each day using the assigned IMP. The suspension should then be expectorated into a sink or toilet. Subjects must have a witnessed dose; the first dose on Day 1 of CRT (prior to CT or RT whatever comes first). The witnessed dose should occur after the subject completes the OMDQ and prior to the subject leaving the clinic.

The IMP should be administered after meal however subjects should not eat, brush their teeth or use mouthwash for 15 minutes prior to and for 90 minutes after dosing. In addition, subjects should refrain from using processed sugars (e.g., candy, soft drinks, etc.) for 90 minutes after dosing with the study medication. Throughout participation in the study (i.e. till end of short term follow-up phase), subjects should be instructed not to drink alcohol within at least 4 hours after dosing with IMP or chew any gum other than the gum provided in the caries prevention kit (Section 5.15). Subjects should also be directed to only use the gum per the caries prevention instructions.

Detailed instructions for dose preparation and dispensing to subjects will be provided to the clinical site by the Sponsor or its designee.

5.7 IMP Accountability

The Investigator or his/her designee is responsible for ensuring adequate accountability of all used and unused IMP. This includes acknowledgement of receipt of each shipment of IMP (quantity and condition), subject dispensing records and returned or destroyed IMP. Dispensing records will document quantities received. Quantities dispensed to subjects will be documented, including lot number, date dispensed, subject identification number, subject initials and the initials of the person dispensing the IMP.

Throughout the course of the study, the Sponsor or its designee will perform IMP accountability and provide instructions for adequate IMP disposal. IMP accountability records must be readily available for audit by the Sponsor or its designee and for inspection by regulatory authorities at any time.

The Investigator will not allow IMP to be given to any subject not included in the study or any unauthorized person.

It is the responsibility of the site personnel to maintain adequate IMP dispensing records.

5.8 Compliance

IMP compliance will be reviewed by the study staff at the weekly visits during the active treatment period. Each subject will be instructed to return all used and unused bottles at each weekly dispensing visit during the active treatment period and at the End of Active

Treatment Phase Visit. A count of the used and unused bottles remaining in the mouth rinse package will be performed to assess compliance.

5.9 Method of Assigning Subjects to Treatment

Subjects who meet all inclusion and exclusion criteria will be centrally randomized 1:1 to receive placebo three times per day or AG013 three times per day. Each subject's treatment assignment will be stratified based on cisplatin schedule (weekly versus tri-weekly), and by HPV status (positive versus negative) and geographic region (US versus Europe). Dynamic randomization will be used for patient randomization in this study. A randomization number and associated treatment assignment will be made using an interactive web response system (IWRS).

5.10 Selection of Doses

In this Phase 2 study, a single dose of IMP will be administered at a dose frequency of three times daily. The selection of dose frequency is based on the intention to assess safety and tolerability of a dose frequency that is anticipated to be clinically efficacious while maximizing patient compliance. The dosing frequency selection is based on trends noted in the Phase 1b trial and PK results of the Phase 1 PK study in healthy volunteers.

The Phase 1 PK study in healthy volunteers demonstrated that live AG013 bacteria adhered to the buccal mucosa and actively secreted hTFF1 in situ. A homogeneous exposure of live AG013 bacteria to the entire mucosal surface was seen. The exposure to AG013 and hTFF1 was significantly reduced by food intake but not by beverage intake. Therefore, in order to maximize efficacy and compliance AG013 should be dosed after meal intake (3 times daily) to ensure optimal exposure and hTFF1 delivery. Three rinses of AG013 result in a clinically relevant 24 hour exposure period of AG013.

The dose per mouth rinse in the proposed Phase 2 study is $2x10^{11}$ CFU or $2.8x10^{9}$ CFU/kg BW which is similar to the dose used in the Phase 1b trial AG013-ODOM-101 and Phase 1 PK study AG013-CSD-MU-004 in healthy volunteers.

5.11 Blinding (if applicable)

Blinding will be accomplished by arranging for AG013 and placebo components to have identical packaging. IMP will be delivered in a blinded fashion, as outlined in the Pharmacy Manual. All study personnel at the site, the patient and the Sponsor will be blinded to treatment allocation for the duration of the study.

Code-breaking will be organized and logged via the central randomization system, i.e. IWRS. In case of a medical emergency, the investigator can immediately obtain the identity of IMP assigned to subject numbers or to individual boxes of IMP by access through the IWRS.

In the event that the blind is broken, the Principal Investigator should contact the medical monitor or his/her designee at the contact numbers provided to the site. A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject (i.e., medical emergency).

Where the blind is broken the patient should immediately be withdrawn from the study and IMP should immediately be discontinued.

The reason and date/time of the unblinding and the name of the individual who broke the blind must be appropriately documented in the subject's medical record or source documents and in the eCRF.

5.12 Concomitant Therapy

Any concomitant therapy used by the subject at any time following randomization through the end of the short term follow-up must be recorded on the eCRF. In addition, for any SAEs that require medication for treatment, those medications must be recorded on the concomitant medications page. The medication name, dosage, route of administration, start and stop dates, and indication for use must be recorded. The medical monitor should be notified in advance of (or as soon as possible after) any instances in which prohibited therapies are administered.

5.13 Not allowed Therapy

Investigators may prescribe any concomitant medication or supportive therapy deemed necessary to provide adequate supportive care including antiemetics, systemic antibiotics, hydration to prevent renal damage, transfusions, etc., with the following exceptions:

- Amifostine (Ethyol®)
- Antibiotic rinses and troches
- Benzydamine hydrochloride
- Caphosol®
- Glutamine (applied topically as a prophylactic agent for mucositis)
- GM-CSF (e.g., Leukine®)
- IL-11 (Neumega®)

- "Magic mouthwashes" or "Miracle mouthwashes" are allowed as long as they do not contain:
  - Chlorhexidine
  - Hydrogen peroxide
  - Diphenhydramine (Benadryl®)
  - Tetracycline
  - Any other disallowed medications
- Herbal, alternative remedies, and alcohol containing over-the-counter mouthwashes. Flouride-supplements and mouth moisturizing rinses are allowed.
- MuGard™
- GelClair®
- Episil®
- PorThelial™
- Palifermin (Kepivance®) or other keratinocyte or fibroblast growth factor
- Povidone-iodine rinses
- Prevention™ Mouth Rinse
- ReBalance^{Ca}
- Steroid rinses
- Sucralfate in suspension form (use of sucralfate tablets is not proscribed)
- Other biologic response modifiers – except hematopoietic growth factors for the management of anemia or myelosuppression
- Other investigational agents
- Other therapy: Laser therapy to treat OM symptoms

Prohibited concomitant medications are not allowed until the end of the Short Term Follow-Up Period (4 weeks post treatment with IMP) except when during this period oral mucositis resolves as indicated by a WHO score of grade 1 or less. For subjects with persistent grade-

2 oral mucositis at week 6 post treatment with IMP, this prohibition will continue until oral mucositis decreases to grade 1 or less.

Subjects who receive prohibited medications will not be removed from the study. However, use of the medications or therapies listed above will be considered a protocol deviation.

Mouthwashes or rinses containing sodium bicarbonate, viscous xylocaine, and/or viscous lidocaine are allowed. If a subject uses “Magic Mouthwash” or “Miracle Mouthwash,” all ingredients should be recorded in the subject’s medical record.

If antifungal therapy is required, by mouth (per os (PO)) or systemic (IV) formulations should be used. Antifungal mouthwashes or rinses including those containing clotrimazole (Mycelex®), nystatin or fluconazole (Diflucan®) are not allowed.

5.14 Analgesic Therapy

Since the assessment of pain is a key secondary endpoint, the amount/quantity of analgesic medications actually taken by subjects rather than merely prescribed to subjects must be recorded. Thus, subjects will record analgesic use daily in the provided diary. At the site, the study coordinator will check the diary for completeness. In addition, the study coordinator will review with the subject the analgesic information written in the diary and use analgesic information recorded in the subject’s medical record (consulting previous progress notes and prescriptions, as necessary) to ensure complete analgesic information is available. Information from the diary and medical record will be transcribed onto the concomitant medications eCRF.

The WHO's cancer pain ladder for adults should be used (Appendix G).

5.15 Standard Oral Care and Caries Prevention Regimen

The standard oral care procedures described in the MASCC (Multinational Association of Supportive Care in Cancer) and NCCN (National Comprehensive Cancer Network) guidelines should be adhered to during the course of the study.

From Day 1 of RT till the end of short term follow-up, subjects will be required to complete a daily caries prevention regimen (Appendix A). Subjects will be asked to record their daily use of the regimen in their study diary.

6 ASSESSMENTS

6.1 Pharmacokinetic Measurements

Blood and buccal smears will be collected at specific time points in a subset of subjects (15 subjects on AG013 and 15 subjects on placebo) who consent separately as described in Appendix D. These will be used to evaluate the pharmacokinetics (PK) of AG013.

The samples will be analyzed for the presence of viable AG013 bacteria (live and dead), using the viable count assay and an AG013-specific quantitative (q)PCR method, and human Trefoil Factor 1 (hTFF1), using ELISA.

Intrexon Actobiotics will analyze the samples intended to be used for PK analysis and the presence of sAGX0085 in whole blood.

6.2 Safety Assessments

Safety will be assessed by collecting and recording Adverse Events (AEs) (Section 8.4) and laboratory assessments and the presence of sAGX0085 in whole blood.

The study will utilize local laboratories for safety assessments, the samples intended for the presence of sAGX0085 in whole blood will be analyzed by Intrexon Actobiotics. The clinical laboratory will indicate laboratory values out of normal ranges. The Investigator must assess all abnormal clinical laboratory results for clinical significance in a timely fashion. Laboratory specimens will be collected at specific time points throughout the duration of the study. A notation of clinically significant (CS) or non-clinically significant (NCS) with initials and date will be documented on the respective laboratory report next to any abnormal value. An abnormal clinical laboratory value will be considered and documented as an AE, if in the opinion of the Investigator, it is clinically significant. The Investigator will follow proper adverse event reporting procedures. Should the site process for indicating CS/NCS lab values not be in accordance with the above, site will provide written procedure for assessing CS lab values and follow stated process throughout study.

Body weight, KPS, and vital signs, including temperature, systolic and diastolic blood pressures, heart rate and respiration rate, will be measured and recorded at the screening and baseline visits, once weekly during the active treatment phase and at the End of Active Treatment Phase Visit. All vital signs should be measured after two minutes of rest in the sitting position.

6.3 Efficacy Assessments

6.3.1 OM Assessments

OM assessments will be completed at the screening and baseline visit, twice weekly (no less than 48 hours apart) within each 5-day RT during the active treatment phase, at the end of active treatment visit, and weekly for four weeks during the short term follow-up phase. If OM has not decreased to less than grade 2, weekly OM assessments will continue until OM is a grade 1 or less.

OM will be assessed by a treatment-blinded, trained evaluator and scored using WHO mucositis criteria. If a subject withdraws prior to the end of the active treatment phase for any reason, a complete oral assessment must be done on that day.

Specific on-line training (6 modules) and instructions regarding oral mucositis assessment performance, grading and documentation will be provided to the clinical site by the Sponsor or its designee. Designated trained study staff (oral evaluators) will conduct all assessments using a standardized and consistent method. Completion of training for Modules 4 and 5 (Armamentarium and examination technique and Evaluation and worksheet completion) shall be performed by oral evaluators no more than 4 weeks prior to the first study subject assessment.

Oral evaluators should have one of the following qualifications: Medical Doctor (MD), Doctor of Osteopathic Medicine (DO), Doctor of Medicine in Dentistry (DMD), Doctor of Dental Surgery (DDS), Registered Nurse (RN), Nurse Practitioner (NP), Registered Dental Hygienist (RDH) (or European equivalents) or Physician Assistant (PA) To reduce inter-observer variability, as few oral evaluators as possible should be involved in the assessments of an individual subject. To the fullest extent possible the same observer should rate the same subjects OM. The oral evaluators will use a Sponsor-provided headlamp for all oral assessments conducted for this study.

The WHO grade will be the primary measure for assessing OM. The assessment of the impact of OM on a subject's ability to eat is critical for accurate scoring of the WHO scale. Therefore, standardization of the assessment is very important. In order to reduce variability in assessing food intake, definitions for solids, liquids and nothing by mouth are below:

- Solid foods are defined as foods that need to be chewed. Examples include: meat, grains and vegetables

- Liquids are defined as foods that take the shape of their container. Examples include fruit juices, soups, pureed foods, mashed potatoes, cooked cereals (oatmeal), baby food, Jell-O, pudding and ice cream

- Nothing by mouth is defined as no eating or drinking except enough liquid to allow for taking PO medications

The assessment scale is described in more detail in Appendix B.

6.3.2 Pain Assessments

Pain will be assessed with the OMDQ Question 2 (mouth and throat soreness or MTS), which will be completed daily from baseline until the end of the short term follow-up. The OMDQ is described in greater detail in Appendix C.

Detailed instructions on completion of the OMDQ by the subjects will be provided to the clinical site by the Sponsor or its designee.

6.3.3 Analgesic Consumption Assessments

Subjects often require analgesics, including opioids for pain control. Subjects will record any analgesic use, including name, dose, and frequency of dose, in a daily diary. In addition, study staff will review with the subject the analgesic information written in the diary and ensure complete analgesic information is recorded in the source documents (consulting previous progress notes and prescriptions, as necessary). Information from the source documents and the diary will be entered onto the concomitant medications eCRF. Analgesics will be converted to morphine equivalents at the time of data analysis.

6.3.4 Other Assessments

- Frequency and duration of RT interruptions will be recorded.

- Assessment of the differences in genes expression for those subjects who consent separately will be assessed by analysis of blood samples collected during the baseline visit and on the last day of RT.

- Assessment of biomarkers (primarily pro and anti-inflammatory cytokines) will be assessed by analysis of serum samples collected during the baseline visit, week 3 and 5 visit, on the last day of RT, on the last day of IMP dosing (Day 14 post CRT) and 4 weeks after the end of RT (equals week 2 of the short term follow-up phase) .

6.4 Tumor Status

The subject's tumor status will be followed for 12 months following the completion of CRT. RECIST criteria or other standard assessments of tumor response should be used as per site standard of care practice. Tumor status information will be collected and will include disease

progression, development of second primary tumors, additional malignancies (if necessary, supported by fiberoptic endoscopy and/or Computed Axial Tomography (CAT) scan or an alternative imaging technique) and survival. These assessments will take place at Months 3, 6, and 12 (each ± 14 days) following the last dose of CRT.

6.5 Health and Economic Outcomes

- Insertion of, or need for use of, gastrostomy tube feedings will be assessed and recorded (US sites only)
- Unplanned office visits, ER visits, or hospitalizations will be assessed and recorded (US sites only)

7 STUDY PROCEDURES

7.1 Schedule of Assessments

A schedule of Assessments is located in Appendix D.

7.2 Screening Phase

7.2.1 Screening Visit

The following screening observations and procedures will be completed after ICF signature, within 4 weeks prior to randomization (data of standard of care assessments that are not study-specific procedures obtained prior to ICF signature and within 4 weeks of Day 1 of CRT can be used):

- Signed and dated ICF (In addition to study participation ICF a separate ICF will be required for participation in genomic studies)
- Assessment against inclusion/exclusion criteria including medical history
- Demographic data
- Physical examination including vital signs (temperature, blood pressure, heart rate, respiration rate), KPS, height and body weight
- Indicate tumor HPV status
- Oral assessment to exclude any lesions that may confound the ability to assess oral mucositis
- Current medications
- Review of CRT plan to ensure eligibility

- Laboratory assessments
  - CBC: WBC (differential cell count in %), hemoglobin, hematocrit, platelet count, RBC indices
  - Chemistry: sodium, glucose, potassium, BUN, creatinine, phosphorus, calcium, alkaline phosphatase, LDH, AST, ALT, albumin
- Pregnancy test in urine or serum performed 7 days before IMP administration (in females of childbearing potential)

7.2.2 IWRS Randomization

Once eligibility has been confirmed, study site personnel must randomize the subject into one of the two treatment arms through IWRS. A window of 3 days prior to Day 1 of CRT (Baseline Visit) is allowed for IWRS randomization.

7.3 Active treatment Phase

7.3.1 Baseline (Day 1 of Chemoradiation therapy)

Prior to the first dose of CRT, the following observations and procedures will be completed:

- Obtain and record vital signs and body weight
- Determine KPS
- Provide and review instructions for completion of the daily diary that includes OMDQ responses; questions on IMP dosing, tolerability (taste, consistency and smell) and general quality of life, and analgesic medication use
- Have the OMDQ completed prior to the oral assessment
- Conduct OM assessment and record the WHO grade
- Record concomitant medications
- Record analgesia use for oral pain
- Record all AEs and SAEs that have occurred since ICF signature
- Record presence of prophylactic gastrostomy tube
- Provide caries prevention kit and give instructions for use
- Laboratory assessments (can be performed up to a day before IMP dosing)
  - CBC: WBC (cell count differential in %), hemoglobin, hematocrit, platelet count, RBC indices

  - Chemistry: sodium, glucose, potassium, BUN, creatinine, phosphorus, calcium, alkaline phosphatase, LDH, AST, ALT, albumin
- Draw blood for biomarkers studies
- Draw blood for genetic responder/non-responder (for subjects who consent separately)
- Administer first dose of IMP (must be witnessed) prior to CT or RT whatever comes first

Administer RT and, if scheduled, CT; record the time of RT/CT administration

7.3.2 Twice-Weekly Assessments During Active Treatment Phase

The following assessments and procedures will be conducted twice a week during the active treatment phase by trained study staff. Assessments will be performed a minimum of 48 hours apart:

- Record AEs and SAEs
- Record analgesia use for oral pain
- Record any concomitant medications
- Record use and/or placement of gastrostomy tube
- Review daily diary with patient
  - Review with the subject the analgesic information written in the diary and ensure complete analgesic information
  - If any diary entries are blank, the subject should be counseled regarding the importance of completing the diary
  - The OMDQ must be completed prior to the oral assessment
- Collect daily diary and dispense new forms
- Assess compliance with caries prevention regimen
- Assess compliance with IMP dosing
- Conduct OM assessment and record the WHO grade

7.3.3 Weekly Assessments During Active Treatment Phase

The following assessments and procedures will be conducted weekly during the active treatment phase. These observations or assessments can be done during one of the twice-weekly assessment visits:

- Obtain and record body weight and vital signs on the last RT day of each week

- Determine KPS
- Record unscheduled office visits, ER visits, or hospitalizations
- Ensure subject completes questionnaire on IMP tolerability
- Conduct IMP accountability
- Laboratory assessments
  - CBC: WBC (cell count differential in %), hemoglobin, hematocrit, platelet count, RBC indices
  - Chemistry: sodium, glucose, potassium, BUN, creatinine, phosphorus, calcium, alkaline phosphatase, LDH, AST, ALT, albumin
- Week 3 and 5 only, on the last day of RT for the specified week
  - Draw blood for biomarkers studies
- On the last day of RT
  - Draw blood for biomarkers studies
  - Draw blood for genetic responder/non-responder (for subjects who consent separately)

7.3.4 End of Active Treatment Phase Visit (Day 14 post CRT)

All subjects will return for an End of Active Treatment Phase visit. These observations or assessments can be done as a part of the twice-weekly assessment visits:

- Conduct physical examination including vital signs and body weight
- Determine KPS
- Review the subjects diary to ensure the completeness of entries and collect the diary
  - The OMDQ must be completed prior to the oral assessment
- Ensure subject completed questionnaire on IMP tolerability
- Conduct OM assessment and record the WHO grade
- Record analgesia use for oral pain
- Record concomitant medications
- Record all AEs and SAEs
- Record use and/or placement of gastrostomy tube
- Record unscheduled office visits, ER visits, or hospitalizations
- Conduct IMP accountability

- Assess compliance with the caries prevention regimen
- Laboratory assessments
  - CBC: WBC (cell count differential in %), hemoglobin, hematocrit, platelet count, RBC indices
  - Chemistry profile: glucose, sodium, potassium, BUN, creatinine, phosphorus, calcium, LDH, alkaline phosphatase, AST, ALT, albumin
- Pregnancy test for females of childbearing potential
- On the last day of IMP dosing
  - Draw blood for biomarkers studies

7.3.5 Short Term Follow-up Phase

The following assessments will be conducted weekly for four weeks after completion of the active treatment phase (Start Day 15 Post CRT, Completion Day 42 Post CRT (± 3 days)). If after four weeks, subjects have grade 2 or greater OM weekly assessments will continue until OM is 1 or less:

- Review subject diary entries to ensure completeness of entries (for subjects that still have WHO OM score grade 2 or greater)
  - The OMDQ must be completed prior to the oral assessment
- Record analgesia use for oral pain
- Record concomitant medications
- Record AEs and SAEs
- Record use and/or placement of gastrostomy tube
- Record unscheduled office, ER visits or hospitalizations
- Conduct OM assessment and record the WHO grade
- Assess compliance with the caries prevention regimen
- Week 2 only:
  - Draw blood for biomarkers studies

7.3.6 PK sampling in a subset of subjects (15 subjects on active and 15 subjects on placebo) who consent separately

- ***Baseline* (*Day 1 of Chemoradiation therapy*)**:
  - Draw blood and collect buccal smears before IMP dosing

  - Draw blood 90 minutes after the first dosing with IMP and collect buccal smears 5 minutes and 90 minutes after the first dosing with IMP
- ***Weekly During the Active Treatment Phase***
  - Week 3 and 5 only, on the last day of RT for the specified week
    - Draw blood and collect buccal smears before the first dosing with IMP
    - Draw blood 90 minutes after first dosing with IMP and collect buccal smears 5 minutes and 90 minutes after the first dosing with IMP
  - On the last day of RT
    - Draw blood and collect buccal smears before the first dosing with IMP
    - Draw blood 90 minutes after the first dosing with IMP and collect buccal smears 5 minutes and 90 minutes after the first dosing with IMP

- ***End of Active Treatment Phase Visit (Day 14 post CRT)***
  - On the last day of IMP dosing
    - Draw blood and collect buccal smears before the first dosing with IMP
    - Draw blood 90 minutes after first dosing with IMP and collect buccal smears 5 minutes and 90 minutes after the first dosing with IMP

- ***Short Term Follow-up Phase***
  - Week 2 only: Draw blood and collect buccal smears

7.4 Long Term Follow-up Phase

- Assess tumor status at 3, 6, and 12 months (+/- 14 days) post the last dose of CRT
- RECIST criteria or other standard assessments on tumor response should be used as per site standard of care practice.

8 ADVERSE EVENT REPORTING

Throughout the study, AEs will be recorded in the source documents and transcribed onto the appropriate pages of the eCRF regardless of whether the AEs are considered treatment-related. All AEs with onset dates from signature of the ICF through the end of the short term follow-up phase will be recorded as an AE on the eCRF. All SAEs with onset dates from signature of the ICF through the end of the short term follow-up phase must be recorded following the guidelines in Sections 8.6, 8.7, 8.8, 8.9 and 8.10. Any AE that occurs at any time after completion of the study, which the investigator considers to be related to

study drug, must be reported.
Conditions existing prior to screening will be recorded as part of the subject's medical history. To avoid confusion, the AE should be recorded in standard medical terminology. The Investigator is responsible for assessing the relationship of AEs to the IMP (Section 8.3).

8.1 Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a subject administered an investigational product and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to this investigational product. This includes an event that emerges during treatment having been absent pre-treatment or an event that worsens relative to the pre-treatment state. Recurrent symptoms of a chronic pre-existing condition are not considered AEs unless they occur in a worse or unexpected pattern during IMP administration.

8.2 Assessing Severity of Adverse Events

The severity of adverse events will be designated as mild, moderate, severe, life threatening, or fatal per NCI CTCAE version 4.0. If not specifically addressed in NCI CTCAE version 4.0, use the table below:

Table 2 Adverse Event Severity

Mild – Grade 1	Transient or mild discomfort; requiring no limitation of activity; no therapy
Moderate – Grade 2	Mild-moderate impact on activity; requiring some assistance and medical intervention
Severe – Grade 3	Marked impact on activity; requiring some assistance and medical intervention
Life Threatening – Grade 4	Complete disability; requiring significant assistance and medical intervention and/or hospitalization
Death – Grade 5	Adverse event with fatal outcome

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as "serious", which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.3 Assessing Relationship to Study Treatment

All AEs will be categorized by the Investigator with respect to their possible relationship to the IMP. The relationship of the AE to study treatment will be assessed by the investigator to be not related, unlikely, possible, probable or definite, as follows:

- Not related: No relationship between the AE and the administration of IMP, judged clearly and incontrovertibly due to extraneous causes (disease, environment etc.).

- Unlikely: The AE is more likely due to an alternative explanation such as concomitant medication(s), concomitant disease(s) and/or the time relationship suggests that a causal relationship is unlikely.

- Possible: The AE might be due to the administration of IMP. An alternative explanation such as concomitant medication(s), concomitant disease(s) is inconclusive. The time relationship is reasonable therefore the causal relationship cannot be excluded.

- Probable: The AE might be due to the administration of IMP. An alternative explanation such as concomitant medication(s), concomitant disease(s) is less likely. The time relationship is suggestive, i.e. it is confirmed by de-challenge.

- Definite: There is no uncertainty in relationship to the administration of IMP. The AE cannot be reasonably explained by an alternative explanation such as concomitant medication(s), concomitant disease(s). The time relationship is very suggestive, i.e. it is confirmed by de-challenge and re-challenge.

"Not related and Unlikely related" correspond to "no reasonable possibility". "Possible, probable and definite" correspond to "reasonable possibility".

8.4 Recording of Adverse Events

All AEs encountered during the clinical study will be recorded in detail in the source documents and documented in the eCRF, from signature of the ICF through the end of the short term follow-up phase. All AEs that meet the seriousness criteria (Section 8.6) should

also be recorded on the SAE Report Form. All SAEs must be reported to the sponsor or delegated organization within the timeline stated in Section 8.7.

The recording of AEs will be based on data obtained from the following sources:

- Medical and surgical history
- Physical examinations including vital signs
- Clinical laboratory test results
- Subject diary

All clinical events, including both observed (such as any reaction at sites of application) and volunteered problems, complaints, or symptoms, are to be recorded. The need to capture this information is not dependent upon whether the clinical event is associated with the use of any IMP.

Clinical symptoms or events such as mucositis or stomatitis are not to be recorded as an AE or SAE.

Clinically significant bacteremia and clinical sepsis should be recorded as AE or SAE.

The potential adverse event profile of the IMP regimen is located in Appendix H.

If at anytime during the study a subject develops symptoms suggesting clinically significant bacteremia that can be attributed to sAGX0085 (as determined by three consecutive positive blood cultures), study treatment will be discontinued.

In the event that a subject develops symptoms suggesting clinically significant bacteremia or sepsis, the subject should be treated per the site's standard of care. Prior to treatment of the event, 3 consecutive whole blood samples need to be taken from the subject and aliquots of these samples must be sent immediately to Intrexon Actobiotics for analysis. The first two samples are to be drawn together and the third sample is to be drawn 10-15 minutes after the first tube is drawn. Detailed information can be found in the laboratory manual.

A disposition plan for the management of clinical sepsis is provided in appendix I.

8.5 Adverse Event Follow-up Period

All subjects with AEs will be followed until the event resolves, stabilizes, becomes chronic, the subject completes the study or the subject is lost to follow-up.

8.6 Serious Adverse Event Definition

In addition to classifying the AE as mild, moderate, severe, life-threatening or fatal, the Investigator should determine whether or not an AE is an SAE. The Investigator shall make an accurate and adequate report on any SAE to the Sponsor or its designee and to any IRB/IEC that has reviewed and is continuing to review the study regarding any SAEs (see Section 8.10).

An SAE is defined as any AE occurring at any dose regardless of relationship to IMP that results in any of the following outcomes:

- Death
- A life-threatening adverse drug event (does not include a reaction that, had it occurred in a more severe form, might have caused death)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect in the offspring of a subject who received IMP
- Other significant medical events

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

Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, the event causing the prolongation is an SAE. Planned hospitalizations are not considered SAEs.

“Inpatient hospitalization” means the subject has been formally admitted to a hospital for medical reasons. This may or may not be overnight. It does not include presentation at an emergency department.

In instances where an SAE occurs in a subject receiving a product not licensed by the Sponsor as a control or concomitant drug, the SAE must be processed and reported as if it were a product of the Sponsor.

Unexpected AEs are further defined as any adverse experience where the specificity or severity of which is not consistent with the applicable product information (i.e., current Investigator Brochure).

Pregnancy in a female study participant, occurring after signature of the ICF is considered immediately reportable event using specific reporting forms and must be reported within 24 hours after the investigator has gained knowledge of it. The subject will discontinue IMP and must be withdrawn from the study. Details of the outcome of the pregnancy (e.g. full term delivery, stillbirth, congenital anomaly, miscarriage) will be collected and reported no longer than one month after the expected due date. Any abnormal outcome in the neonate will be followed-up.

8.7 Reporting of Serious Adverse Events

The Sponsor is required to inform worldwide regulatory authorities of SAEs that meet specific criteria. Therefore, the Sponsor must be notified immediately regarding any SAE that occurs after informed consent is obtained. All SAEs and follow-up information must be reported within 24 hours after the investigator has gained knowledge of it, as required by local regulations, by faxing a completed SAE Report Form to the fax number below or emailing a completed SAE Report Form to the PSI Safety Desk at safetydesk@psi-cro.com.

Table 3: Toll-free Safety Line Numbers for SAE Reporting*

Country	Toll-free Safety Line Numbers
Belgium	0-800-77-647 02-416-6518 (Brussels) 03-303-5457 (Antwerp)
Germany	00-800-8000-0723
US	1-800-361-9714 1-800-878-1317 1-866-600-0655
UK	0-800-471-5220

*Any fax sent to these lines will be routed to safety desk e-mail address (safetydesk@psi-cro.com)

The necessity and time requirements for reporting SAEs to the Sponsor or designee and regulatory agencies are as follows:

- All SAEs will be reported via the eCRF system within 24 hours of the investigator's first knowledge of the event, even if the event does not appear to be related to AG013. In case reporting via the eCRF is not available, the SAE may be reported via fax in order to meet the reporting requirements.

- Reports of any pregnancy in a subject, must also be reported on the Pregnancy Report Form within 24 hours of the investigator's first knowledge of the event (see section 8.6) and fax completed form to PSI Safety Desk or e-mail a scanned copy to safetydesk@psi-cro.com, even if no AE has occurred.

- For all SAEs, a detailed written description that includes anonymized copies of available relevant patient records, autopsy reports, and other documents will be sent within 24 hours of the investigator's first knowledge of the SAE.

- SAEs that are life threatening or result in death, and are unexpected and related to AG013 will be reported to regulatory authorities within 7 days of receipt of the event. Any follow up to the initial SAE report will be submitted to regulatory authorities within 8 days of the initial report (ie, within15 days of receipt of initial report).

- Any SAE that is unexpected and related to AG013, results in hospitalization or prolongs an existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect will be reported to regulatory authorities within 15 days of receipt of the report. Some regulatory authorities may have alternative timelines for submission of suspected unexpected serious adverse reactions. In those cases, specific local requirements for submission of SAE reports will be applied.

- All SAEs will be followed until resolution or stabilization. Follow-up reports for SAEs reported as 7- 15-day reports will be submitted within the same time frame as the initial report.

Additionally, the IRB and/or IEC must be notified in writing of any unexpected, related SAEs or as required by the local IRB/IEC. It is the responsibility of the investigator/contract research organization (CRO) to notify the IRB/IEC.

If applicable, SAEs will be reported to the appropriate regulatory agencies by the Sponsor or designee. In case the local regulations require notification through the investigator, the Sponsor will facilitate this process.

The information to be recorded for SAEs should include the following:

- The onset of any new AE or the worsening of an observation documented from signature of the ICF through the end of the short term follow-up phase
- The specific type of event in standard medical terminology
- The duration of the clinical event (start and stop dates)
- The severity of the clinical event
- Seriousness (SAE) criteria
- Relevant laboratory and examination results
- Dosing schedule of IMP
- Indications and dosing schedules of concomitant medications
- Relationship of the AE to the IMP as defined in Section 8.3
- Management of IMP administration and other action taken to alleviate the clinical events
- Past medical and surgical history and concurrent diseases
- De-challenge/re-challenge results, if applicable
- The outcome of the clinical event

8.8 Serious Adverse Event Recording Period

SAEs will be collected and recorded by the Investigator beginning from the signature of the ICF through the end of the short term follow-up phase.

8.9 Serious Adverse Event Follow-up Period

All subjects who experience SAEs will be followed until the events resolve, stabilize, become chronic or the subjects are lost to follow-up.

8.10 Regulatory Reporting of Adverse Events

If there are serious, unexpected adverse drug reactions (for Europe, SUSAR: Suspected Unexpected Serious Adverse Reaction) associated with the use of the IMP, the appropriate regulatory agency(ies) and all participating investigators will be notified in accordance with the following Guidance for Industry: Clinical Safety Data Management: Definitions and

Standards for Expedited Reporting (ICH-E2A), Detailed Guidance on the Collection, Verification and Presentation of Adverse Event/Reaction Reports Arising from Clinical Trials on Medicinal Products for Human Use (CT-3). Clinically significant bacteremia and clinical sepsis associated with the use of the IMP will also be reported on an expedited basis.

It is the responsibility of the investigator to promptly notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of all unexpected serious adverse drug reactions involving risk to human subjects. An unexpected event is one that is not reported in the current Investigator's Brochure.

9 DATA MANAGEMENT

A validated clinical data management system will be used for capturing and managing data from the study. Data will be entered into the eCRFs following the eCRF Completion Guidelines. The CRFs for this study will be eCRF.

The Investigator should ensure the accuracy, completeness and timeliness of the data recorded on the eCRFs. Data recorded on the eCRF will be consistent with source documents. Any discrepancies must be explained or resolved.

Completed eCRFs will be reviewed by the Sponsor's monitoring staff or the Sponsor's designee. An eCRF will be completed for each included subject.

After the last subject completes the end of the short term follow-up phase, the database will be locked and the study will be unblinded for the purpose of the statistical analysis. Evaluation of all efficacy, safety, PK and PD endpoints as described in Section 10.1 will occur, except for the overall tumor response to chemoradiation therapy (Safety endpoint 3). This safety endpoint will be evaluated following the second database lock after the last subject completes the long term follow-up phase (i.e. 12 months after the last dose of CRT).

10 STATISTICAL METHODS

Statistical considerations are briefly described below.

More details on the analysis and presentation of study results will be provided in the statistical analysis plan (SAP). The SAP will be finalized prior to the unblinding of treatment allocation codes.

Descriptive statistics will be used to summarize all data collected from this study, with inferential statistics provided for the primary and secondary endpoints. Unless stated

otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation (SD), standard error of the mean (SEM), minimum, and maximum for continuous data, and frequency tables with counts and percentages for categorical data. The term "treatment group" refers to the randomly assigned IMP, either AG013 or placebo, each topically applied three times daily.

For change from baseline calculations, "baseline" refers to the last measurement obtained prior to the first dose of IMP. Study days will be defined relative to the Baseline Visit (Day 1 of CRT).

All available assessments of oral mucositis (OM) will be used to derive efficacy endpoints (duration, incidence and onset of OM), including WHO severity grades recorded twice per week during the treatment phase (start of CRT until 14 days after the last CRT dose) and weekly during the short term follow-up period (4 weeks after the end of CRT) to capture resolution of OM, as required.

Adjustment for multiple significance testing will be performed using a hierarchical closed testing procedure to control the overall Type 1 error rate at 5%. If the primary efficacy endpoint demonstrates a statistically significant treatment effect (two-sided $p \leq 0.05$), secondary efficacy endpoints will be tested sequentially at the same level 0.05 in a pre-specified order (as listed below). The process continues until the first time the p-value exceeds 0.05, at which point testing stops and no further significance may be claimed.

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® Software (Version 9.3 or higher).

10.1 Study Endpoints

10.1.1 Primary Efficacy Endpoints

1. Duration (in days) of severe oral mucositis (WHO grades 3 or 4)

10.1.2 Key Secondary Efficacy Endpoints (hierarchical)

1. Time to onset of severe oral mucositis (WHO grades 3 or 4)
2. Incidence of severe oral mucositis (WHO grades 3 and 4)
3. Duration of ulcerative oral mucositis (WHO grades 2, 3 or 4)
4. Time to onset of ulcerative oral mucositis (WHO grades 2, 3 or 4)
5. Incidence of ulcerative oral mucositis (WHO grades 2, 3 or 4)

10.1.3 Safety Endpoints

1. Incidence of adverse events, including serious adverse events (SAEs) and clinically significant laboratory abnormalities
2. Changes in vital signs and clinical laboratory parameters
3. Overall tumor response to chemoradiation therapy (during 12 months following the last dose of CRT).

10.1.4 Secondary Efficacy Endpoints

1. Cumulative radiation dose to development of severe oral mucositis (WHO grades 3 or 4) and ulcerative oral mucositis (WHO grades 2-4)
2. Patient-reported pain as measured by Question 2 (mouth and throat soreness) of the Oral Mucositis Daily Questionnaire
3. Use of analgesics to control oral pain (number and percentage of subjects using per type)

10.1.5 Pharmacokinetic (PK) and Pharmacodynamic (PD) Endpoints

1. Assessment of biomarkers (primarily pro- and anti-inflammatory cytokines)
2. PK profile of AG013 based on blood/serum samples and buccal smears in a subset of subjects (15 subjects on AG013 and 15 subjects on placebo, in up to 10 sites).

10.1.6 Exploratory Efficacy Endpoints for OM (linked to primary endpoint)

1. Incidence of severe mucositis (WHO grades 3 or 4) within subgroups defined by cumulative radiation doses of 30 Gy, 40 Gy, 50 Gy and 60 Gy
2. The AUC of an OM severity–time curve
3. Mucositis severity parameters (incidence, duration, time to onset of grades 3,4 and 2,3,4) based on NCI-CTCAE v4.0 and RTOG criteria

10.1.7 Other Exploratory Endpoints

1. Genomic differentiation of AG013 responders and non-responders
2. Frequency and duration of RT interruptions
3. Healthcare resource use including: unplanned office visits, ER visits, hospitalizations, and non-prophylactic gastrostomy tube placement (US sites only)

4. Comparison of AG013 efficacy in OM in patients with HPV negative versus HPV positive tumors

10.2 Sample Size Consideration

A sample size of 160 evaluable subjects (80 per group) will provide approximately 80% power to detect a 5-day difference between groups in the average number of days with severe OM (WHO grade 3 or 4) at the two-sided 5% significance level; this calculation is based on Student's t-test and assumes the standard deviation for duration of severe OM is 10.8 days. To be evaluable, subjects must receive at least 4 weeks of IMP and a cumulative radiation dose of 50Gy. Additional subjects will be enrolled to account for non-evaluability. The primary analysis method (Cochran-Mantel-Haenszel test), though different from the t-test approach, will have higher power since the stratified analysis is expected to be more efficient.

Note that 160 subjects will also afford approximately 85% power to detect a 25% difference in the incidence of severe OM (WHO grades 3 or 4), assuming that the incidence is reduced from 75% in the placebo group to 50% in the AG013 group; this calculation is based on a Fisher's Exact test at the two-sided 5% significance level.

10.3 Definitions of Study Populations for Analysis

10.3.1 The Safety (SAF) Analysis Set

All subjects who are randomized to treatment and receive at least one dose of IMP will be included in the safety (SAF) analysis set.

Subjects in this population will be analyzed according to the treatment they actually receive. The SAF population will be used as the basis for all safety analyses, as well as summaries of demographic and baseline data, concomitant medications, and IMP exposure/compliance and tolerability data.

10.3.2 Intent-to-Treat (ITT) Population

The ITT population will include all randomized subjects. Subjects will be analyzed according to the treatment group to which they are randomized, regardless of treatment actually received. This population will serve as the basis for the primary efficacy analysis.

A modified ITT (mITT) population, defined as all ITT subjects who receive IMP and have post-baseline efficacy data, will be used for all primary and secondary efficacy endpoints.

10.3.3 The Per Protocol (PP) Population

The PP population will consist of all mITT subjects who receive a minimum of 4 weeks of IMP and a cumulative radiation dose of 50Gy to oral and oropharyngeal sites at risk; any other criteria for excluding subjects from this analysis set must be defined in the SAP and finalized

prior to unblinding the database. This population will be used for supportive efficacy analyses.

10.3.4 The Pharmacokinetic (PK) and Pharmacodynamic (PD) Analysis Sets

Subjects who receive the IMP as scheduled and provide sufficient samples to reliably estimate the PK parameters will be included in the PK analysis set. Subjects in this population will be analyzed according to the treatment they receive.

The PD analysis set will include all subjects with biomarkers evaluated at baseline and at least once after the start of IMP. The PD analysis will be performed only after an efficacy signal is determined.

10.4 Baseline Characteristics and Demographic Variables

Demographic data (e.g., age, gender, race, height, weight and ethnicity), medical history, prior treatments, and baseline disease characteristics, including primary tumor location, stage of disease and performance status, will be summarized by treatment group for the SAF Analysis Set.

10.5 Efficacy Analysis

Primary Efficacy Endpoint

The duration of severe OM (WHO grade 3 or 4) will be calculated as the number of days from the onset of severe OM (first time a WHO grade 3 or 4 is observed) to the day when severe OM has resolved (first time WHO grade 2 or less is observed after last WHO grade 3 or 4). Durations of 0 will be assigned to subjects who do not experience severe OM. Any subject who dies or withdraws prior to resolution of severe OM will be assumed to have severe OM for the remainder of the observation period. In these cases, duration will be calculated as the number of days from the first onset of severe OM (WHO grade 3 or 4) until 2 weeks after the last planned dose of CRT. As noted above, all available OM assessments will be used to derive efficacy endpoints, including WHO grades recorded during the treatment phase and the short term follow-up period in order to capture resolution of OM, as required.

The intent of the primary statistical analysis is to test the superiority of AG013 over placebo in reducing the duration of severe OM. The null hypothesis is that the AG013 and placebo groups have the same duration (in days) of severe OM. The alternative hypothesis is that the duration of severe OM in the two treatment groups is different.

The generalized Cochran-Mantel-Haenszel (CMH) method, stratified by cisplatin regimen (weekly versus tri-weekly), by HPV status (positive versus negative) and region (US versus Europe), will be used for the primary efficacy analysis. Standardized mid-ranks (also known

as modified ridit scores) will be used for the test statistic. This generalized CMH test follows a chi-square distribution with 1 degree of freedom. The efficacy analysis will be performed in the ITT, mITT, and PP populations, with the ITT designated as primary.

If numbers permit, the effect of treatment on the primary efficacy endpoint will be examined within patient subgroups defined by region, age, sex, ethnicity, and baseline disease characteristics. Descriptive summary statistics will be used for this purpose.

To ensure that primary efficacy results are robust, sensitivity analyses will be performed using alternative methods for the analysis of duration of severe OM in both the ITT, mITT and PP populations. These methods will include calculations based on the number of days with grade 3 or 4 mucositis throughout the active treatment phase (from start of CRT until 14 days after completing CRT), and the use of various imputation strategies for gap days (i.e., days between twice weekly assessments). In particular, imputation of last observation carried forward and worst-adjacent values will be employed for subjects with missing or incomplete data.

Secondary Efficacy Endpoints:

Statistical methods for the calculation and analysis of secondary efficacy endpoints are provided below. For each endpoint, significance testing will evaluate the superiority of AG013 compared to placebo; two-sided tests will be used to reject the null hypothesis (no difference between groups) in favor of the alternative hypothesis (there is a difference between groups). All efficacy analyses will be performed for the mITT population and stratified by randomization factors (region, cisplatin regimen and HPV status). To control the experiment-wise Type 1 error rate at 5%, significance tests will be performed in the hierarchical order listed here.

Time to onset of severe OM: Time to onset of severe OM (WHO grade 3 or 4) will be calculated as the elapsed time (in days) from the start of CRT until the date of first OM assessment grade 3 or 4. Subjects who do not experience an event by the end of the OM assessment period will be censored on the date of last OM assessment. Subjects with no post-baseline OM assessments will be censored on Day 1. Kaplan-Meier estimation methods and the stratified log-rank test will be used to compare time-to-event distributions and test whether or not AG013 delays the onset of severe OM.

Incidence of severe OM: The incidence of severe OM (WHO grade 3 or 4) will be calculated as the number of subjects with at least one OM WHO grade 3 or 4, divided by the number subjects in the treatment group. Subjects with no OM assessments will be assumed to have severe scores. Subjects who die or withdraw without experiencing OM grade 3 or 4 will also be assumed to have severe scores. A stratified CMH test (general association statistic) will

be used to compare proportions and test whether or not AG013 reduces the incidence of severe OM.

Duration of ulcerative OM: The duration of ulcerative OM (WHO grade 2, 3 or 4) will be calculated in a manner similar to duration of severe OM. That is, the duration of ulcerative OM will be calculated as the number of days from the onset of ulcerative OM (first time a WHO grade 2, 3 or 4 is observed) to the day when ulcerative OM has resolved (first time WHO grade 0 or 1 is observed after last WHO grade 2, 3 or 4). A similar imputation scheme will be used in the event that subjects die or withdraw prior to resolution of OM to grade 0 or 1. The stratified CMH test (with modified ridit scores) will be used to compare treatment groups and test whether or not AG013 reduces the duration of ulcerative OM.

Time to onset of ulcerative OM: Time to onset of ulcerative OM (WHO grade 2, 3 or 4) will be calculated and analyzed as described above for severe OM.

Incidence of ulcerative OM: Incidence of ulcerative OM (WHO grade 2, 3 or 4) will be calculated and analyzed as described above for severe OM.

Cumulative radiation dose to development of severe oral mucositis: Total cumulative dose of radiation (in Gy units) until the date of first severe OM (WHO grade 3 or 4) will be calculated for each subject and summarized by treatment group using descriptive statistics. Similarly, the cumulative radiation dose up to the first observed ulcerative oral mucositis (WHO grades 2-4) will be tabulated. The difference between treatment groups will be evaluated using the stratified CMH test, with modified ridit scores. This test will determine whether the AG013 group achieved a higher cumulative radiation dose before onset of severe OM, compared to the placebo group.

Patient-reported pain: The average of patient-reported mouth and throat soreness (MTS) scores, graded on a scale from 0 (no soreness) to 4 (extreme soreness), will be summarized by treatment group during each study week. The difference between treatment groups will be evaluated using the stratified CMH test, with modified ridit scores, to determine whether or not AG013 reduces pain.

Analgesic use: Use of analgesics to control oral pain (parenteral, per oral, or transdermal) will be examined by displaying number and percentages of subjects in each treatment group taking: 1) topicals, 2) OTC analgesics, 3) PO opioids, 4) parenteral opioids. Also, PO and parenteral opioids will be combined to form a category for all opioids. Treatment group differences in proportions will be evaluated using a Chi-square test.

Exploratory Efficacy Endpoints

The effects of AG013 will be explored further on the basis of the following:

Descriptive statistics will be presented for the incidence of severe mucositis (WHO grades 3 or 4) within subgroups receiving each of the following cumulative radiation doses: 30 Gy, 40 Gy, 50 Gy and 60 Gy.

For each subject, oral mucositis severity scores (WHO grades 0-4) at each time point will be used to calculate area-under-the-curve (AUC) using the trapezoidal rule. Average AUC severity-by-time curves will be generated and plotted for each treatment group, and compared using the Wilcoxon rank-sum test.

Genomic characteristics of responders will be summarized and compared with non-responders.

Frequency and duration of RT interruptions: The number of subjects in each treatment group with an unplanned break in radiotherapy during the 7- to 9-week regimen will be tabulated. Subjects with an interval of 5 days or more without an administration of radiotherapy, or who discontinue radiotherapy prior to completing the planned RT regimen, will be considered to have an unplanned break in RT. The duration of unplanned RT interruptions (in days) will also be summarized by treatment group using descriptive statistics. For subjects who prematurely discontinue radiotherapy, the time from the last dose of RT to the prescribed end date of the regimen will be used in the calculation. The number of unplanned office visits, ER visits, hospitalizations, and non-prophylactic gastrostomy tube placements (US sites only) in each treatment group will be tabulated.

The incidence and duration of severe oral mucositis will be summarized descriptively by treatment group within subgroups of patients defined by cisplatin regimen (weekly versus tri-weekly), HPV status (HPV negative versus HPV positive tumors) and region (US versus Europe).

10.6 Safety Analysis

Safety/tolerability analyses will be performed using data from the SAF analysis set. Safety will be evaluated on the basis of treatment-emergent AEs (TEAEs), vital signs, weight, physical examinations, and clinical laboratory assessments.

All adverse events will be coded by Preferred Term and System Organ Class using the most recent version of MedDRA. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.03) will be used to grade both clinical and laboratory AEs. By-patient listings of deaths, SAEs, and AEs leading to discontinuation will be provided. The by-patient AE data listings will include onset and resolution dates, verbatim term, Preferred Term, treatment, severity (grade), relationship to treatment, action taken for the event, and outcome.

The incidence of treatment-emergent AEs (TEAEs) will be summarized by treatment group and tabulated by System Organ Class (SOC) and Preferred Term (PT). A TEAE is defined as an AE that first occurs or worsens in severity on or after the first dose of the IMP. TEAEs will be further summarized by severity (grade) and relatedness to IMP. Each AE (based on PT) will be counted only once for a given subject. If the same AE occurs on multiple occasions, the highest severity and strongest relationship will be assumed. If 2 or more AEs are reported as a unit, the individual terms will be reported as separate events.

Vital signs (systolic and diastolic blood pressure, pulse, and temperature) and body weight will be summarized for each treatment group using descriptive statistics. Summary statistics (n, mean, median, SD, minimum, and maximum) will be calculated for both the actual value and the change from baseline value at each scheduled visit.

Clinical laboratory data will be presented for each treatment group using descriptive statistics based on the observed values and change from baseline values at each scheduled visit. Summary statistics (n, mean, median, SD, minimum, and maximum) will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. Shift tables from baseline to the worst post-baseline values during the treatment period will be provided for chemistry parameters and hematology parameters that have NCI-CTCAE v4.03 toxicity grades. Both scheduled and unscheduled post baseline values during the treatment period will be considered. Additionally, the number and percentage of subjects with Grade ≥3 will be presented for each CTCAE gradable laboratory test.

All clinical laboratory data will be listed by subject. Values outside the normal ranges will be flagged and toxicity grades will be displayed for relevant parameters.

To assess IMP tolerability, average daily ratings of IMP taste, consistency, and smell will be summarized descriptively, by week, for each treatment group.

Pre-study abnormalities and reported abnormalities at the end of active treatment will be tabulated by body system. Changes in physical examinations will be described in the text of the final study report.

Prior and concomitant medications will be coded using the WHO dictionary. These data will be tabulated for each treatment group; details regarding dose regimens and start/stop dates will be presented in by-subject data listings.

The number and percentage of subjects with presence of AG013-sAGX0085 bacteria will be summarized by treatment group.

Tumor response assessments will be summarized descriptively at each timepoint (3, 6, and 12 months following the last dose of CRT).

10.7 Pharmacokinetic and Pharmacodynamic Analysis

Blood and buccal smears will be collected at specific time points in a subset of subjects who consent separately (15 subjects on AG013 and 15 subjects on placebo). Descriptive summary statistics will be used to evaluate the pharmacokinetics of AG013 by treatment group and study visit. Serum levels of hTFF1 and buccal mucosa levels of AG013 (both AG013-sAGX0085 bacteria and hTFF1) will be summarized using descriptive statistics, including graphical methods.

Biomarker assessments will be listed and summarized for each treatment group by time point using descriptive statistics (mean, median, SD, SEM, coefficient of variation, minimum, and maximum) and graphical displays. The relationship between biomarkers and efficacy outcomes will be explored via correlation analysis, as appropriate.

10.8 Interim Analysis

No interim analysis is planned.

10.9 Handling of Missing, Unused and Spurious data

All available efficacy and safety data collected for the study will be included in data listings and/or summary tables. Every effort will be made to obtain required data at each scheduled evaluation from all subjects enrolled. Rules for deriving efficacy endpoints will utilize imputation rules as specified in the efficacy analysis section. Sensitivity analyses will be performed to ensure that results of the primary efficacy endpoint are robust and not explained by missing or incomplete data. Worst-case assumptions will be applied to subjects who do not have OM assessments during the study period. Where necessary, missing assessments of OM will be imputed using multiple imputation procedures. Select exploratory sensitivity analyses will be conducted to ascertain the effect, if any, of these methods. No other missing data will be imputed.

10.10 Criteria for the termination of the trial.

The sequence of events that will determine if a clinical trial is to be terminated are: a) evaluations of several individuals as aggregate data, b) determination of the likelihood that the AEs are drug related, c) if the severity of study related AE(s) is judged extreme, and d) emergence of unexpected SAE(s).

In addition, the DSMB will recommend stopping the study should:

- clinical sepsis defined by one positive blood culture by PCR technique occur and be attributed to sAGX0085.

All AEs will be reviewed by the medical monitor. Any repetitive SAE attributed to IMP will be further assessed by the medical monitor in unblinded fashion. If associated with AG013 a determination will be made in consultation with the DSMB as to whether accrual hold is required.

10.11 Reporting of Deviations to Original SAP

All deviations from the original SAP will be reported in the clinical study report.

11 ETHICS

11.1 Good Clinical Practice

The Investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki", ICH guidelines, in particular ICH GCP E6, and the laws and regulations of the country in which the research is conducted, whichever affords the greatest protection to the study subject.

11.2 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

This protocol and any accompanying material for this study provided to the subject (such as subject information sheets and informed consent form) as well as any advertising or compensation given to the subject must be reviewed and approved by an appropriate IRB/IEC before subjects are included into the study. It is the responsibility of the Investigator to assure that all aspects of the institutional review are conducted in accordance with the requirements of all regulatory authorities. A signed and dated letter documenting IRB/IEC approval must be obtained prior to entering subjects at the site. The IRB/IEC must be notified of all subsequent protocol amendments.

11.3 Subject Information and Informed Consent

In accordance with regulatory and local IRB/IEC requirements, before study procedures are performed, subjects will be informed about the study and required to sign and date the IRB/IEC approved ICF. This form will be signed and dated after adequate explanation of the aims, methods, objective and potential hazards of the study and prior to undertaking any study-related procedures. The method of obtaining and documenting the informed consent and the contents of the consent must comply with ICH GCP and all applicable regulatory requirement(s). No subject is to be screened or treated until an ICF, written in a language in which the subject is fluent, has been obtained. The signed ICF will be retained with the study records. Each subject will also be given a copy of his/her signed ICF.

11.4 Data Safety Monitoring Board

An independent DSMB will be constituted before the start of the study. The DSMB will supervise the ethical performance of the study and review safety data arising during the study according to the procedures described in the DSMB Charter. The Charter will describe the following activities:

- Committee membership
- Committee responsibilities
- Frequency and content of meetings
- Procedures for the review and assessment of the safety data of the first 10 subjects on AG013 having completed study treatment
- Procedures for the expedited review for clinically significant bacteremia and clinical sepsis
- Procedures for the review and assessment of the cumulative safety data
- Criteria for determining whether to recommend stopping the study for unacceptable harm.

The DSMB will be composed of 3 or more members who will have relevant experience in the treatment of subjects with OM and/or HNC and the conduct of randomized clinical trials. One member will be a biostatistician experienced in phase 2 and 3 oncology clinical trials, and none of the members will be Investigators in this study or employees of the sponsor . Any AE that leads to a subject's treatment termination, and any SAE a subject experiences during the study, will be regularly reported to the DSMB, as specified in the Charter. The DSMB will receive unblinded data for any subject in the case of these safety events.

11.5 Financial Disclosure by Principal Investigators (if study under IND)

Since this is a "covered" clinical trial, the Investigator will ensure that 21 CFR §54 is adhered to. A "covered" clinical trial is any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or the FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety. This requires that investigators and all sub investigators (inclusive of family members) provide documentation of their financial interest or arrangement with the Sponsor or proprietary interests in the drug being studied. This documentation must be provided prior to the participation of the Investigator and any Sub Investigator. The Investigator and Sub-Investigator agree to notify the Sponsor of any change in reportable interests during the study and for one year following completion of the study. Study

completion is defined as the date that the last subject has completed the protocol defined activities.

12 STUDY MANAGEMENT AND ADMINISTRATION

12.1 Curriculum vitae

An updated copy of the curriculum vitae limited to the experience, qualification and training for each investigator and sub-investigator will be provided to the sponsor prior to the beginning of the clinical trial.

12.2 Protocol Modifications

The Sponsor may modify the protocol at any time during the life of the protocol. Protocol amendments will require IRB/IEC approval prior to implementation except when changes to the protocol are required to eliminate immediate hazards to the study subjects.

12.3 Data Quality Control and Quality Assurance

The study will be monitored and managed in accordance with ICH GCP E6.

Study data will be entered in the eCRF by trained study personnel. Data validation edit checks will be defined and implemented. Inconsistent and questionable data detected during data entry or data validation process will be queried. Queries will be generated and any discrepancies will be resolved.

12.4 Monitoring

The Sponsor or its designee will perform on-site monitoring visits periodically during the study. At these visits the monitor will review study documents to ensure adherence to the study protocol and regulatory requirements, and to review eCRF entries against source documents. Findings from the visit will be discussed with the investigator.

12.5 Audit and Inspection

The Investigator will agree to receive periodic quality assurance audits conducted by the Sponsor's clinical quality assurance personnel or its designee. In addition, the Investigator will agree to inspections by regulatory agencies to the extent permitted by law. Auditors and inspectors will have direct access to all relevant study documentation.

12.6 Source Documents

The Investigator must allow regulatory agencies, individuals delegated by the IRB/IEC or the Sponsor or its designee to have access to all the original documentation of the study, including the ICFs signed by the subjects enrolled into the study and the relevant subject medical files. The individuals who are given access to the documentation must take every reasonable precaution to keep the identity of the subjects and the proprietary information of the Sponsor as confidential information in accordance with relevant applicable legislation.

12.7 Electronic Data Capture

eCase Report Forms (eCRFs) will be supplied by the Sponsor or its designee and should be handled in accordance with the provided instructions. All eCRFs should be filled out completely by authorized study personnel.

The Investigator should ensure the accuracy, completeness and timeliness of the data recorded on the eCRF. Data recorded on the eCRF will be consistent with source documents. Any discrepancies must be explained or resolved.

Completed eCRFs will be reviewed by the Sponsor's monitoring staff or its designee. An eCRF will be completed for each subject enrolled in the study.

12.8 Premature Termination of the Study

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the investigators and the regulatory authority(ies) of the reason(s) for termination or suspension. The IRB/IEC also will be promptly informed by the Sponsor or Investigator and provided with the reason(s) for the termination or suspension, as specified by the applicable regulatory requirement(s).

12.9 End of Study

End of study is defined as the date when the last subject completes the long-term follow-up phase (i.e. 12 months after the last dose of CRT).

12.10 Study Report

The Principal Investigator will submit to the Sponsor a copy of the report issued to the IRB/IEC. A full study report will be written after completion of the statistical analysis including the evaluation of the efficacy, safety, PK and PD endpoints as described in Section 10.1. The overall tumor response to chemoradiation therapy (Safety endpoint 3) and

updated safety information will be described in an addendum to the study report after the second database lock at the end of the study.

12.11 Finance, Insurance, Trial Registration and Publication

Insurance coverage will be handled to local requirements.

Finance, insurance and publication rights are addressed in the Investigator/Institution and/or CRO agreements as applicable.

Trial registration and publication will be according to the WHO rules as laid out in the latest version of The Declaration of Helsinki.

12.12 Archiving and Data Retention

The Investigator shall retain adequate records for the study including copies of each subject's CRFs, medical records, laboratory reports, ICF(s), IMP accountability records, safety reports, information regarding subjects who were withdrawn and any other pertinent data. The Investigator must retain all records for at least 15 years or longer where required per national requirements after completion or discontinuation of the trial or at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements. The sponsor will notify the investigator when the records no longer need to be kept.

If the responsible Investigator retires, relocates or for other reasons withdraws from the responsibility of keeping records, custody must be transferred to a person who will accept the responsibility. The Sponsor will be notified in writing of the name and address of the new custodian as soon as possible.

12.13 Confidentiality

The Investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The subject's identification code and the subject's initials should be recorded on any form submitted to the Sponsor, Sponsor's designee, or IRB/IEC, unless it is forbidden to identify the subject by initials. Where it is forbidden to indicate the subject's initials, only the subject's identification code and the subject's age should be recorded.

The Investigator must keep a patient identification list showing codes, names and addresses for all subjects screened and for all subjects enrolled into the trial. The site's patient

identification list always stays on site. Only the investigator, the investigator's study team and selected members of the study team, i.e the study monitor, and possibly an auditor or inspector who will review the study data to ensure correct performance of the trial, will have access to the list of names and will be able to identify the subject. The patient identification list will not be provided to the Sponsor or anyone outside the site.

The Investigator agrees that all information received from the Sponsor, including but not limited to the Investigator's Brochure, this protocol, CRFs and any other study information remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except with prior written consent from the Sponsor). The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

However, the submission of this clinical trial protocol and other necessary documentation to the IRB/IEC is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

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14 APPENDICES

Appendix A: Caries Prevention Regimen

Purpose: To minimize the risk of dental caries in subjects participating in Protocol AG013-ODOM-201.

Preventive Care:

1. Diet – Minimize foods that contain refined sugars, i.e. cookies, candy, sugar-containing soft drinks, etc. Favor vegetables and fruits.
2. Avoid alcohol and tobacco as these reduce salivary flow.
3. Practice scrupulous oral hygiene:
    a. Use a soft toothbrush (electric toothbrush is acceptable)
    b. Use a low abrasion, fluoride-containing toothpaste
    c. Clean spaces between teeth with floss or similar device
    d. Brush at least twice daily
4. Chew sugarless chewing gum after meals (Xylitol chewing gum 5 minutes, 5 times per day). Do not chew any gum other than the type provided to you in this regimen and only use as directed.
5. Brush at bedtime with a 0.4% stannous fluoride gel.
6. Rinse twice per day with FluoriGard or similar rinse after breakfast and at bedtime.

Appendix B:

WHO Grade

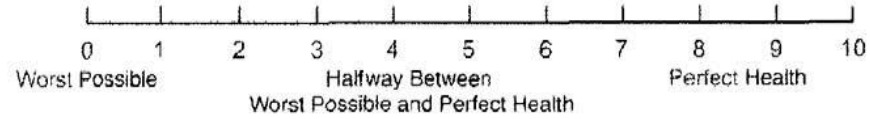
Grade 0:	None
Grade 1:	Erythema and Soreness; No ulcers
Grade 2:	Ulcers; Able to eat a solid diet
Grade 3:	Ulcers; Requires a liquid diet
Grade 4:	Ulcers; Not able to tolerate a solid or liquid diet; Requires IV or tube feeding

Appendix C: Oral Mucositis Daily Questionnaire (OMDQ)

This questionnaire (see next page) has been used as a tool to assess oral mucositis in patients undergoing hematopoietic stem cell transplantation (Stiff et al., 2006).

Subjects should be instructed to complete the OMDQ in its entirety in a comfortable area at about the same time each day. The OMDQ should be completed prior to the oral mucositis assessment on a given study day.

1. How would you rate your OVERALL HEALTH during the LAST 24 HOURS? (*circle one number*)



2. During the LAST 24 HOURS, how much MOUTH AND THROAT SORENESS did you have? (*circle one number*)

No soreness ---------- 0
A little soreness ---------- 1
Moderate soreness ---------- 2
Quite a lot of soreness ---------- 3
Extreme soreness ---------- 4

If you circled 0, please skip to question 5

3. During the LAST 24 HOURS, how much did MOUTH AND THROAT SORENESS limit you in each of the following activities? (*circle one number*)

	Not Limited	Limited A Little	Limited Some	Limited A Lot	Unable To Do
a. Swallowing	0	1	2	3	4
b. Drinking	0	1	2	3	4
c. Eating	0	1	2	3	4
d. Talking	0	1	2	3	4
e. Sleeping	0	1	2	3	4

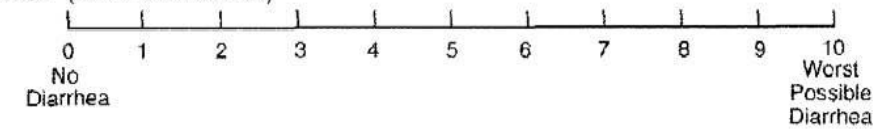
4. On a scale of 1 to 10, how would you rate your OVERALL MOUTH AND THROAT SORENESS during the LAST 24 HOURS? (*circle one number*)

5. During the LAST 24 HOURS, how much DIARRHEA did you have? (*circle one number*)

No diarrhea ---------- 0
A little diarrhea ---------- 1
Moderate diarrhea ---------- 2
Quite a lot of diarrhea ---------- 3
Severe diarrhea ---------- 4

If you circled 0, STOP here

6. On a scale of 1 to 10, how would you rate your OVERALL DIARRHEA during the LAST 24 HOURS? (*circle one number*)



Appendix D: Schedule of Events

Assessments	Screening	Active Treatment Phase (2 visits per week) All Visit must be 48 Hours apart!													Short Term Follow-up[s] (once weekly visits)		Long Term Follow-up
	Within 4 weeks of rando-mization	Week 1		Week 2 Week 4 Week 6[a]		Week 3 Week 5[a]		Week 7[a] OR last week of RT		Week 1 Post-CRT		Week 2 Post-CRT		End of Active Treatment	Week 1 Week 3 Week 4	Week 2	Month 3 Month 6 Month 12
		V1 (Baseline - prior 1st CRT)	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	= Day 14 post CRT[b]			±14days
Informed Consent	x																
Inclusion/exclusion	x																
Medical,HNC histories[c]	x																
Physical examination[d]	x													x			
Vital signs, KPS, weight	x	x	X[e]		X[e]		X[e]		X[e]		x		x	x			
Indicate tumor HPV status	x																
Pregnancy test[f]	x													x			
Current/Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Analgesia use for oral pain		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
IWRS randomization[g]		x															
AEs and SAEs(s)[h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
OMDQ dispensing (daily completion)[i,j]		x		x		x		x		x		x		x	x	x	
OM assessment[j]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Review daily diary[j]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Gastrostomy tube placement and use		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
IMP dispensing for 3 times daily administration[k]		x		x		x		x		x		x		last dosing day			
Compliance IMP dosing		x	x	x	x	x	x	x	x	x	x	x	x	x			
Compliance Caries prevention		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
RT[l] and, if scheduled, CT		x	4x	5x		5x		5x									
IMP accountability			x	x		x		x		x		x		x			
Unscheduled office visits, ER visits, hospitalizations[m]			x	x		x		x		x		x		x	x	x	
Return Questions on IMP tolerability[m]			x	x		x		x		x		x		x			
Blood draw, clinical lab measurements[n]	x	x	x	x		x		x		x		x		x			
Blood for biomarkers study[o,p]		x					X[o]		X[o]					x		x	
Blood draw, gene expression[o,q]		x							X[o]								
Blood draw, PK samples[o,r]		x					X[o]		X[o]					x		x	
Tumor status																	x

Abbreviations: AEs = adverse events; CT = hemotherapy; d = day(s); ER = emergency room; HNC = head and neck cancer; IMP = Investigational Medicinal Product; IWRS = interactive web response system; KPS = Karnofsky Performance Score; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; OM = oral mucositis; OMDQ = Oral Mucositis Daily Questionnaire; PE = physical examination; PK = Pharmacokinetic; RT = radiation therapy; SAEs = serious adverse events; Wk = Week.

[a] For patients who would only have RT treatment up to Wk5 or Wk 6 in the study, not receiving up to 72 Gy, that respective week will be the last week of RT and all assessments planned for Wk7/last Wk of RT should be performed during that respective week as per schedule of assessments. (e.g. if a patient only has 5 weeks of RT treatment, assessments for Wk5 and Wk6 become not applicable and assessments for last Wk of RT should be performed at Wk5)

[b] The end of treatment day is the day the last dosing of IMP is taken. Wk2 post-CRT visit 2 might coincide with the end of active treatment day, and if so, assessments/observations for end of active treatment can be done on Visit 2 of Wk2 post-CRT. (see section 7.3.4)

[c] The HNC history should include staging information, prior treatments, and pathology information (see Appendix F)

[d] At screening visit and at the end of active treatment phase conduct a physical examination, at screening visit, examination should include height.

[e] Obtain and record KPS, vital signs (temperature, systolic and diastolic blood pressures, heart rate, and respiration rate) and body weight at every indicated time point. During the active treatment period vital signs and body weight should be recorded weekly on the last RT day of each week. All vital signs should be measured following 2 minutes of rest in the sitting position (see section 7.3.3)

[f] Pregnancy test (serum (5 ml blood to be taken) or urine) to be completed 7 days before IMP administration, for females who are of child bearing potential (see Section 4.3)

[g] Randomization may occur when all eligibility criteria are confirmed and IMP is available for dispensing. A window of 3 days prior to Baseline Visit is allowed for IWRS randomization.

[h] AEs and SAEs with onset after the subject signed the ICF through the end of short term follow-up will be recorded on the CRF. All subjects with AEs or SAEs will be followed until the events resolve, stabilize, become chronic, the subject completes the study, or the subject is lost to follow-up.

[i] The OMDQ must be completed daily. On visit days the OMDQ must always be completed prior to the OM assessment. (see sections 7.3.1, 7.3.2, 7.3.4, and 7.3.5)

[j] Subjects with WHO persistent grade mucositis of 2 or greater at the end of the active treatment phase will continue to complete the daily diaries in the short term follow-up period until mucositis decreases to grade of 0 or 1. If OM has not decreased to less than grade 2, weekly OM assessments will continue until OM is a grade 1 or less.

[k] The first dose of IMP should be witnessed by a study staff member. IMP dosing will continue three times per day until Day 14 Post CRT visit.

[l] Planned continuous course of intensity-modulated radiotherapy (IMRT) with a minimum cumulative dose of 50 Gy and maximum dose of 72 Gy.

[m] Assessments to be carried out on weekly base during the active treatment phase, during one of both twice-weekly visits

[n] Clinical laboratory measurements (15 ml blood to be taken per sampling) will include CBC (WBC cell count differential in %, hemoglobin, hematocrit, platelet count, RBC indices) and chemistry profile (sodium, glucose, potassium, BUN, creatinine, phosphorus, calcium, alkaline phosphatase, LDH, AST, ALT, and albumin).

[o] Samples for biomarker studies, genetic samples or PK sampling, taken during active treatment period should be drawn at the last RT day of a specific week (see section 7.3.3.).

[p] Draw blood samples for biomarkers studies (10 ml blood to be taken per sampling) at baseline, week 3 and 5, on the last day of RT, on the last day of IMP and 4 weeks after the end of RT (equals week 2 of the short term follow-up).

[q] If a subject consents separately, draw blood samples (2,5 ml blood to be taken per sampling) for genetic responder/non-responder studies (baseline visit and on the last day of RT).

[r] If a subject consents separately, draw blood and collect buccal smears for AG013 pharmacokinetic (PK) measurements at baseline, Wk3 and Wk5, on the last day of RT, on the last day of IMP and 4 weeks after the end of RT (equals Wk2 of the short term follow-up). Blood samples (5 ml blood to be taken per sampling) will be collected prior to dosing and 90 minutes after 1st dosing with IMP. Buccal smears will be collected prior to, 5 minutes after and 90 minutes after the 1st dosing with IMP on the day of the visit.

[s] Completion Day 42 Post CRT (± 3 days).

Appendix E: Karnofsky Performance Score (KPS)

100%	Normal, no complaints; no evidence of disease
90	Able to carry on normal activities; minor signs or symptoms of disease
80	Normal activities with effort, some signs or symptoms of disease
70	Cares for self but unable to carry on normal activity or do active work
60	Requires occasional assistance but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated although death not imminent
20	Very ill; hospitalization and active support care necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

Appendix F: American Joint Committee on Cancer (AJCC) Tumor Staging Guidelines

TNM Classification	Histological/Clinical Features
Lip and Oral Cavity	
T1	2 cm or less
T2	> 2 but < 4 cm
T3	> 4 cm
T4(lip)	invades through cortical bone, inferior nerve, floor of mouth, or skin of face (e.g., chin or nose)
T4a (oral cavity)	invades adjacent structures (e.g., through cortical bone, into deep [extrinsic] muscle of tongue [genioglossus, hypoglossus, palataglossus, and styloglossus], maxillary sinus, skin of face)
Oropharynx	
T1	2 cm or less
T2	> 2 but < 4 cm
T3	> 4 cm
T4	invades adjacent structures
T4a	invades larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible
T4b	invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

Hypopharynx

T1	limited to one subsite of the hypopharyx and 2 cm or less
T2	involves more than one subsite of the hypopharynx or an adjacent site OR > 2 but < 4 cm without fixation hemilarynx
T3	> 4 cm or with fixation of hemilarynx
T4a	invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue including prelaryngeal strap muscles and subcutaneous fat
T4b	invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

Nasopharynx

T1	confined to nasopharynx
T2	extends to soft tissue of oropharynx and/or nasal fossa
T2a	extends to soft tissue of oropharynx and/or nasal fossa without parapharyngeal extension
T2b	extends to soft tissue of oropharynx and/or nasal fossa with parapharyngeal extension
T3	invades bony structures and/or paranasal sinuses
T4	intracranial extension, and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, or orbit

Larynx - Supraglottis

T1	limited to one subsite of supraglottis with normal vocal cord mobility
T2	invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglotic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)
T4a	invades through the thyroid cartilage and/or invades tissue beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles)
T4b	invades prevertebral space, encases carotid artery, or invades mediastinal structures

Larynx - Glottis

T1	limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	limited to one vocal cord
T1b	involves both vocal cords
T2	extends to supraglottis and/or subglottis and/or with impaired vocal cord mobility
T3	limited to larynx with vocal cord fixation and/or invades the paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)
T4a	invades through thyroid cartilage and/or extends to other tissues beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	invades prevertebral space, encases carotid artery, or invades mediastinal structures

Larynx - Subglottis

T1	limited to subglottis
T2	extends to vocal cord(s) with normal or impaired mobility
T3	limited to larynx with vocal cord fixation
T4a	invades through cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	invades prevertebral space, encases carotid artery, or invades mediastinal structures

Maxillary Sinus

T1	limited to maxillary sinus mucosa with no erosion or destruction of bone
T2	causing bone erosion or destruction including extension into hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
T3	invades any of the following: bone of the posterior wall of maxillary sinuses, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b	invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V_2), nasopharynx, or clivus

Nasal Cavity and Ethmoid Sinus

T1	restricted to any on subsite, with or without bony invasion
T2	invading two subsites in single region or extending to involve adjacent region within nasoethmoidal complex, with or without bony invasion
T3	extends to invade medial wall or floor of orbit, maxillary sinus, palate, or cribiform plate
T4a	invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b	invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than (V_2), nasopharynx, or clivus

Salivary Glands

T1	2 cm or less without extraparenchymal extension
T2	> 2 but < 4 cm without extraparenchymal extension
T3	> 4 cm and/or extraparenchymal extension
T4a	invades skin, mandible, ear canal, and/or facial nerve
T4b	invades skull base and/or pterygoid plates and/or encases carotid artery

Thyroid Gland

T1	2 cm or less without limited to thyroid
T2	> 2 but < 4 cm limited to thyroid
T3	> 4 cm limited to thyroid or any tumor with minimal extrathyroid extension
T4a	extending beyond thyroid capsule to invade subcutaneous soft tissue, larynx, trachea, esophagus or recurrent laryngeal nerve

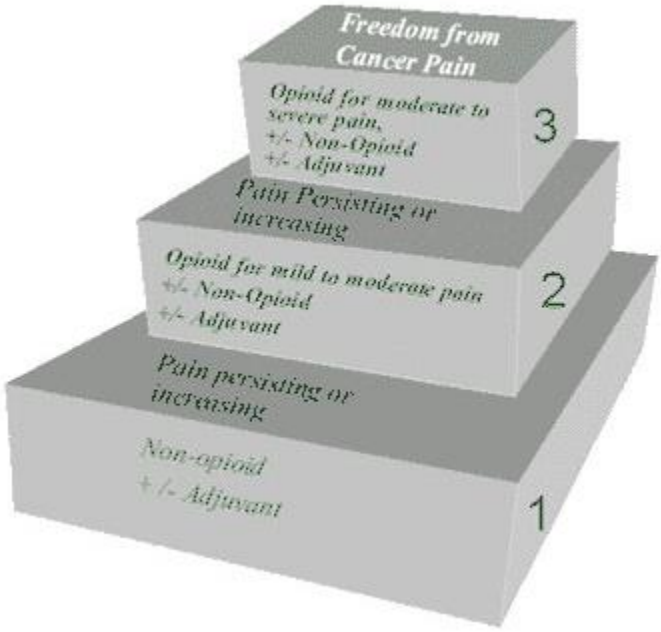
T4b	invades pervertebral fascia or encases carotid artery or mediastinal vessels

Appendix G: WHO's cancer pain ladder for adults

WHO has developed a three-step "ladder" for cancer pain relief in adults.

If pain occurs, there should be prompt oral administration of drugs in the following order: nonopioids (aspirin and paracetamol); then, as necessary, mild opioids (codeine); then strong opioids such as morphine, until the patient is free of pain. To calm fears and anxiety, additional drugs – "adjuvants" – should be used.

To maintain freedom from pain, drugs should be given "by the clock", that is every 3-6 hours, rather than "on demand" This three-step approach of administering the right drug in the right dose at the right time is inexpensive and 80-90% effective. Surgical intervention on appropriate nerves may provide further pain relief if drugs are not wholly effective.



Source: http://www.who.int/cancer/palliative/painladder/en/

Appendix H: Potential Adverse Event Profile of the IMP Regimen

Relative to the risk of clinical sepsis due to the study organism, the study organism is non-pathogenic, preclinical safety studies failed to show any evidence for clinical sepsis even after intravenous administration of the study organism in severely neutropenic animals, and subjects in other clinical trials of a similar mucosally administered non-pathogenic organism have not demonstrated bacteremia or sepsis. No patients of the phase 1b study AG013-ODOM-101 (a group that was myelosuppressed) developed sepsis from AG013 nor could AG013 be detected in the blood. No deaths or discontinuations due to AEs occurred in this study.

The chances of AG013 adversely affecting the course of oral mucositis seem equally remote. Preclinical studies have shown a clear beneficial effect on severity and duration of oral mucositis in a relevant animal model. In addition, results of a clinical study in which another form of topically administered trefoil factor was tested demonstrated its benefit in modulating the course and severity of oral mucositis. Several efficacy endpoints were measured as exploratory endpoints in the phase 1b AG013-ODOM-101 study. Subjects who received AG013 had a lower percentage of days with ulcerative mucositis, and more subjects who received AG013 on any dosing schedule had no or only 1 day of ulcerative mucositis compared to subjects who received placebo.

Within the intended study population, there is no particular population at risk, and the risks are not predictable or preventable.

Clinical sepsis due to the study organism is reversible and time-limited when antibiotic therapy is applied. Worsening of mucositis is reversible and time-limited.

Following adverse events linked to the IMP regimen can potentially occur:

- Clinically significant bacteremia
- Clinical sepsis

Appendix I: Disposition plan for the management of clinical sepsis

The rationale for the disposition plan is to describe the management of patients who have received AG013 and who develop clinical sepsis.

The exact magnitude of this AE is unknown, although the probability is likely extremely small. Relative to the risk of clinical sepsis due to the study organism, the study organism is non-pathogenic, preclinical safety studies failed to show any evidence for clinical sepsis even after intravenous administration of the study organism in severely neutropenic animals, and subjects in other clinical trials of a similar mucosally administered non-pathogenic organism have not demonstrated bacteremia or sepsis. No patients of the phase 1b study AG013-ODOM-101 (a group that was myelosuppressed) developed sepsis from AG013 nor could AG013 be detected in the blood. No deaths or discontinuations due to AEs occurred in this study. Within the intended study population, there is no particular population at risk, and the risks are not predictable or preventable. Clinical sepsis due to the study organism is reversible and time-limited when antibiotic therapy is applied.

Goals and Objectives

The goal of the disposition plan is to provide the guidelines for the management of patients who have received AG013 and who develop clinical sepsis. The objective is to reverse clinical sepsis and to ensure the safety of patients.

Strategy and Tools

The following medical measures are required when a patient develops clinical sepsis due to the study organism:

- Stop administration of study medication
- Hospital admission
- Supportive therapy aimed at maintaining organ perfusion and providing respiratory support when necessary as per standard practice and clinical judgment of the treating physician
- IV administration of antibiotics. The study organism is susceptible to following antibiotics: penicillin G, ampicillin, amoxicillin + clavulanic acid, gentamicin, chloramphenicol, tetracycline, erythromycin, bacitracin, vancomycin, levofloxacin, nitrofurantoin, cefepime, carbapenem, and linezolid.
- Reporting of clinical sepsis follows SAE reporting described in sections 8.4 and 8.7 of the clinical protocol.