Oragenics Inc.

STATISTICAL ANALYSIS PLAN

PROTOCOL AG013-ODOM-201

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

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
AG013	Mouth Rinse formulation system of Lactococcus lactis strain sAGX0085, deficient in the gene coding for thymidylate synthase and producing human TFF1
AG013-DP	AG013 Drug Product
AUC	Area Under the Curve
bid	bis in die (twice a day)
CFU	Colony Forming Unit
CHM	Cochran-Mantel-Haenszel
eCRF	Electronic Case Report Form
CRT	Chemoradiation Therapy
CT	Chemotherapy
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Board
Gy	Gray
hTFF1	Human Trefoil Factor 1
HNC	Head and Neck Cancer
HPV	Human Papilloma Virus
IMP	Investigational Medicinal Product
ITT	Intent-to-treat
IV	Intravenous
MedDRA	Medical Dictionary of Regulatory Activities
mITT	Modified ITT population
MTS	Mouth and Throat Soreness
n	Number of Subjects
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OM	Oral Mucositis
OMA	Oral Mucositis Assessment
OMDQ	Oral Mucositis Daily Questionnaire
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per Protocol
PT	Preferred Term
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFF	Trefoil Factor
TFLs	Tables, figures, listings
tid	Ter In Die (three times a day)
US	United States

WHO	World Health Organization

2. INTRODUCTION

This Statistical Analysis Plan (SAP) covers the statistical analysis and reporting for the protocol AG013-ODOM-201 Global Version 3.0 dated 12 February 2019 and German version 3.1 17 June 2019, and electronic case report form (eCRF) version 4.0037 dated 01 October 2019. A detailed list of all tables, figures, and listings (TFLs) will be supplied in a separate, version-controlled document – Mock TFL's - before the database lock.

3. STUDY OBJECTIVES

3.1 PRIMARY EFFICACY OBJECTIVES

- To evaluate the efficacy of topically administered AG013 compared to placebo for reducing oral mucositis (OM) in patients undergoing chemoradiation for the treatment of head and neck cancer (HNC), 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.

3.2 PRIMARY SAFETY OBJECTIVES

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

3.3 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.

3.4 SECONDARY PHARMACOKINETIC AND PHARMACODYNAMIC OBJECTIVES

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

3.5 EXPLORATORY EFFICACY OBJECTIVES FOR OM

- OM severity linked to time, duration and incidence of OM (linked to Primary Efficacy Objectives)

3.6 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 (United States [US] sites only).
- To compare the frequency and duration of radiotherapy (RT) interruptions.

4. STUDY DESCRIPTION

4.1 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 in conjunction with their planned course of chemoradiation therapy. Dynamic randomization will be used, with stratification by 3 factors: cisplatin schedule (weekly versus tri-weekly), HPV status (positive versus negative), and geographic region (US versus Europe).

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 completion. 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} colony forming unit (CFU)/15 mL tid

Table 1. Study Periods

Screening Phase	Randomization must occur within 4 weeks of the initiation of screening
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 patients 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

4.2 STUDY TREATMENT

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

- Arm A: placebo tid
- Arm B: AG013 $2x10^{11}$CFU/15 ml tid

Subjects will self-administer the assigned IMP while undergoing their prescribed course of radiotherapy and chemotherapy (CT).

4.2.1 RADIATION THERAPY TREATMENT PLAN

Subjects will receive a continuous course of intensity-modulated radiotherapy with a minimum cumulative dose of 50 gray (Gy) and maximum dose of 72 Gy. Planned radiation treatment fields must include at least 2 at-risk sites 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) 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.

4.2.2 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. CT dose and schedule will be documented.

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

4.2.3 INVESTIGATIONAL MEDICINAL PRODUCT TREATMENT PLAN

The 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.

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

• AG013 Drug Product (AG013-DP) powder or matching placebo

• Reconstitution solution

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 aluminium sachet. The reconstitution solution will be delivered in a 15 ml dark glass bottle.

4.3 DATA AND SAFETY MONITORING BOARD (DSMB)

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. To protect subjects from unanticipated safety risks, an initial safety analysis will be performed when enrolment and treatment in the double-blind study when 10 subjects on AG013 have been recruited. The DSMB will review safety data after these 10 subjects on AG013 have completed study treatment. The DSMB, per their Charter, will determine what, if any, changes to the study protocol or conduct are required.

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 serious adverse event (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.

In addition, the study will be stopped in case clinical sepsis should occur, defined as one positive blood culture by PCR technique occur that could be attributed to sAGX0085 (stopping rule).

5. ANALYSIS ENDPOINTS

5.1 PRIMARY EFFICACY ENDPOINT

- Duration (in days) of severe OM (WHO grades 3 or 4)

5.2 KEY SECONDARY EFFICACY ENDPOINTS (HIERARCHICAL)

- Time to onset of severe OM (WHO grades 3 or 4)
- Incidence of severe OM (WHO grades 3 and 4)
- Duration of ulcerative OM (WHO grades 2, 3 or 4)
- Time to onset of ulcerative OM (WHO grades 2, 3 or 4)
- Incidence of ulcerative OM (WHO grades 2, 3 or 4)

5.3 SAFETY ENDPOINTS

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

5.4 SECONDARY EFFICACY ENDPOINTS

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

5.5 PHARMACOKINETIC (PK) AND PHARMACODYNAMIC (PD) ENDPOINTS

- Assessment of biomarkers (primarily pro- and anti-inflammatory cytokines)

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).

Note: the PD endpoints are considered to be optional endpoints to be evaluated only in case of positive outcome of the study.

5.6 EXPLORATORY EFFICACY ENDPOINTS FOR OM (LINKED TO PRIMARY ENDPOINT)

- Incidence of severe mucositis (WHO grades 3 or 4) within subgroups defined by cumulative radiation doses of 30 Gy, 40 Gy, 50 Gy, 60 Gy, and 70 Gy
- The area under curve (AUC) of an OM severity–time curve

- Mucositis severity parameters (incidence, duration, time to onset of grades 3, 4 and 2, 3, 4) based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 and Radiation Therapy oncology Group (RTOG) criteria

5.7 OTHER EXPLORATORY ENDPOINTS

- Genomic differentiation of AG013 responders and non-responders (optional; endpoint to be evaluated only in case of positive outcome on primary endpoint)

- Frequency and duration of RT interruptions

- Healthcare resource use including: unplanned office visits, emergency room visits, hospitalizations, and non-prophylactic gastrostomy tube placement (US sites only)

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

- Other OMDQ items: overall health, limited in swallowing, drinking, eating, talking and sleeping, overall soreness and diarrhea

6. SAMPLE SIZE AND POWER CALCULATION

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 (World Health Organization [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 (SD) for duration of severe OM is 10.8 days. To be evaluable, a subject must be at least 70% compliant with IMP during the first 4 weeks of CRT (i.e., take at least 1 dose of IMP on at least 70% of the days on CRT). In addition, the subject must either (1) receive a cumulative radiation dose of at least 50 Gy, or (2) have an OMA >= 3. Additional subjects will be enrolled to account for non-evaluability.

The primary analysis method (Cochran-Mantel-Haenszel [CMH] 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 evaluable 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.

7. ANALYSIS POPULATIONS

7.1 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 SAF analysis set.

Subjects in this population will be analyzed according to the treatment they 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.

7.2 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 received. This population will serve as the basis for the primary efficacy analysis and also for baseline characteristics.

7.3 MODIFIED INTENT-TO-TREAT (MITT) POPULATION

The mITT population, defined as all ITT subjects who receive at least 1 dose of IMP and have at least 1 post baseline OM assessment, will be used for all primary and secondary efficacy endpoints. As with the ITT population, subjects will be analyzed in accordance with the treatment arm assigned at randomization.

7.4 THE PER PROTOCOL (PP) POPULATION

The PP population consists of all evaluable subjects in the mITT population with no major protocol violations. To be evaluable, a subject must be at least 70% compliant with IMP during the first 4 weeks of CRT (i.e., take at least 1 dose of IMP on at least 70% of the days on CRT). In addition, the subject must either (1) receive a cumulative radiation dose of at least 50 Gy, or (2) have an OMA >= 3. Any other criteria used to exclude subjects from the PP population will be identified prior to database lock. This population will be used for supportive efficacy analyses.

7.5 THE PHARMACOKINETIC (PK) ANALYSIS SET

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 population will be defined once the PK parameter calculation is concluded.

The PK Analysis Set will be used to report the data on PK concentrations and parameters.

7.6 THE PHARMACODYNAMIC (PD) ANALYSIS SET

The PD analysis set will be described in a separate analysis plan, since the assessment of biomarkers (primarily pro- and anti-inflammatory cytokines) is an optional analysis to be performed only in case of a positive outcome of the study.

8. ANALYTICAL PLAN AND STATISTICAL METHODS

8.1 GENERAL CONVENTIONS AND STATISTICAL CONSIDERATIONS

All statistical analyses will be performed and data appendices will be created using the SAS system version 9.4 or higher.

Summary statistics for continuous variables will include number of patients with non-missing values, number of patients with missing values, mean, standard deviation, median, Q1 (quartile 1), Q3 (quartile 3), minimum and maximum values.

Summary tables for categorical variables will include number and percentage of patients for each category. If not specified additionally, number of patients with non-missing values will be the denominator for percentage calculation. The number of patients with missing values will be presented.

All the analyses will be run displaying by treatment arm and overall.

Unless otherwise stated, all statistical tests will be performed using two-sided tests at the 5% significance level.

If necessary, the statistical analytical plan and statistical methods section may be updated before the database lock. Any changes in statistical methods that may have an impact on the primary conclusions drawn from this clinical trial will be described in an amendment to the protocol. All other changes in the statistical plan will be described in section 9.8 of the clinical study report (CSR). An explanation will be provided for deviations from the planned analysis.

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 and safety endpoints will occur. Evaluation of PK and PD endpoints will occur at a later stage, as well as the genomic analyses. Note: the PD and genomic analyses will only be performed if the study has a positive efficacy outcome. The overall tumor response to chemoradiation therapy 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).

A full study report will be written after completion of the statistical analysis including the evaluation of the efficacy and safety endpoints as described in Section 10.1. The PK data and overall tumor response to chemoradiation therapy will be described in an addendum to the study report, as well as PD endpoints and genomic analyses (in case of positive primary endpoint) after (a) later database lock(s).

8.2 DEFINITION OF BASELINE, STUDY VISITS, AND VISIT WINDOWS

Baseline will be defined as the last non-missing assessment prior to the first dose of IMP.

Summaries that show visit will be created using the visit reported in the eCRF. No visit reassignment will be done.

Study day is defined relative to the first dose of IMP. The first day of any IMP is considered Day 1. A minus (-) sign indicates days prior to the start of IMP (e.g., Day -5 represents 5 days before start of treatment. There is no Day 0. The relative study day for a specific visit is calculated as (Visit Date – Date of First Dose +1).

8.3 HANDLING OF MISSING 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.

Any imputation of missing or incomplete data will be flagged in the analysis data sets. The original value will be kept for traceability.

Incomplete dates imputation.

The following rules will be applied for AEs and concomitant medications with incomplete dates:

- If Day is missing for Start Date and Month and Year are the same as Month and Year for the First Dose of IMP Date, then Start Date equals First Dose of IMP Date.

- If Day is missing for Start Date and Month and Year are not the same as Month and Year for the First Dose of IMP Date, then impute Day 1 of the Month.

- If Day and Month are missing for Start Date and the Year is the same as the Year for the First Dose of IMP Date, then Start Date equals First Dose of IMP Date.

- If Day and Month are missing for Start Date and the Year is less than Year for the First Treatment Date, then impute July 1st of the Year.

- If Day and Month are missing for Start Date and the Year is greater than Year for the First Treatment Date, then impute January 1st of the Year.

- If the entire Start Date is missing, set it equal to First Dose of IMP Date.

No imputation for the end date of AEs will be done. However, the end date of concomitant medications will be imputed as the last day of the month if only the day is missing, and as December 31st of the year if both the day and the month are missing. The above imputation is needed to properly identify treatment-emergent adverse events (TEAEs) and prior/concomitant medications.

Other missing data imputation.

Missing OM data will be replaced using various algorithms, discussed in detail in Section 8.7.1 of this SAP.

No other missing data will be imputed.

8.4 PATIENT DISPOSITION

The number of screened subjects will be summarized. For screen failures, the reason for screen failure will be summarized using counts and percentages.

The number of randomized subjects will be summarized along with the number and percentage of randomized subjects in each of the analysis populations, completing the study, withdrawing from the study and the primary reason for withdrawal by planned treatment regimen and overall. The number of deaths will be summarized by planned treatment regimen and overall. Cisplatin schedule, HPV status and geographical region will also be summarized.

Data listings of subject disposition, screen failures, and subject assignment to analysis groups will be created.

8.5 PROTOCOL DEVIATIONS

Deviations from the protocol will be recorded in CTMS (PRIMA) and reviewed on a monthly basis by Medical Monitors. A data listing of all protocol deviations will be created. Date, description and type (major/minor) of protocol deviation will be reported. Minor/Major classification will be established by way of manual review and final determination of major protocol deviations will be done before database lock.

8.6 PATIENT CHARACTERISTICS

8.6.1 BASELINE AND DEMOGRAPHIC CHARACTERISTICS

All baseline characteristics will be summarized by actual treatment regimen and overall for the Safety Analysis Set (SAF). The following parameters will be summarized:

- Age (years)
- Race
- Ethnicity
- Gender
- Childbearing potential for women (and reason for being of not of childbearing potential)
- Pregnancy test results
- Baseline Vital Signs (including Weight [kg], Height [cm], Temperature [^{o}C], Respiratory Rate [bpm], Heart Rate [bpm], systolic blood pressure (SBP) [mmHg], diastolic Blood pressure (DBP) [mmHg], and Karnofsky performance status)
- Baseline Physical Examination

No hypothesis testing is planned for baseline characteristics, so the analysis will be purely descriptive.

Data listings of baseline characteristics and demographics will be created.

8.6.2 MEDICAL HISTORY

HNC history (primary diagnosis, tumor node metastasis (TNM) staging, presence of prior surgeries, presence of prior chemotherapy) will be summarized by treatment arm and overall for SAF and ITT populations.

Prior and concurrent medical conditions will coded using Medical Dictionary of Regulatory Activities (MedDRA) 19.0 dictionary or higher. Summaries of prior medical conditions will be prepared. The tables will be divided by system organ class (SOC) and preferred term (PT).

Prior surgical procedures and chemotherapy will be summarized by treatment arm and overall for SAF and ITT populations. Surgery summaries will be further divided by surgery name.

Listings will be prepared for HNC history, prior surgeries for HNC, for prior medical and surgical history, and for concomitant surgery and other procedures.

8.6.3 Prior and Concomitant Medication

Prior chemotherapy will be summarized by treatment arm and overall for SAF and ITT populations.

Medications will be coded with the WHO Drug Dictionary (WHO DD Mar 2017). Concomitant medications will be summarized stratifying by Anatomical Therapeutic Chemical (ATC) Classification System level 2 and 4 codes (ATC2 and ATC4). A medication will be considered to be concomitant if its end date is after the first date of IMP or its start date is on or after the first date of IMP and before the end of Short Term Follow-up. Medications with missing end date will also be considered concomitant. A medication with end date prior to the first date of IMP will be considered prior.

Separate listings for prior chemotherapy, prior medications, and concomitant medications will be generated. Any on-study surgeries or procedures will be listed.

8.7 Efficacy Endpoints and Analysis

8.7.1 Analysis of 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). This calculation allows for fluctuation in severity grades and considers separate episodes of SOM to be additive. Durations of 0 will be assigned to subjects who do not experience severe OM, even if the subject was not followed for the full planned period. Any subject who dies or withdraws prior to resolution of severe OM (i.e., with grade 3 or 4 at last assessment) 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 the end of Short Term Follow-up phase which will be taken as Week 13 (Day 91 relative to start of CRT). 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.

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 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. In case of erroneous stratification at baseline, the corrected stratification data will be used for the 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. Below is the sample code that performs this analysis:

```
proc freq
 data=test;
 tables STRATUM*TRTPN*OM_DURATION / CMH SCORE=MODRIDIT;
run;
```

The effect of treatment on the primary efficacy endpoint will be examined within subject subgroups defined by region (US vs Europe), cisplatin regimen, HPV status and baseline disease characteristics (primary cancer diagnosis for 3 subcategories: oral cavity, oropharynx and all other). Descriptive summary statistics will be used for this purpose.

The following sensitivity analyses will be performed using alternative methods for the analysis of duration of severe OM in the ITT, mITT, and PP populations:

- Repeat the primary analysis using the worst adjacent imputation strategy for gap days, replacing the days without a value with the worst value between the closest previous and following values.
- Repeat the primary analysis but using imputation for missing data. For subjects with unresolved SOM, use the median value for subjects in the same treatment group with at least that duration. For subjects without severe OM but with incomplete follow-up (i.e., discontinued before the end of the active treatment period with no short-term follow-up OM assessments), use the median duration among patients in the same treatment arm who were free of severe OM for at least that length of follow-up.
- Calculate severe OM duration as the total number of days a subject has a grade 3 or 4 mucositis from the start of CRT until the end of the short-term follow-up phase, with last observation carried forward (LOCF) imputation (so, the OM grade at a day without assessment is considered to be the same as at the closest previous valid assessment).
- Same as the above, but using the worst adjacent imputation strategy for gap days (i.e. replacing the missing value with the worst value between the closest previous and following values).
- Repeat the primary analysis but using only the period from start of CRT to the actual last day of CRT to define duration of severe OM.

Listings of individual WHO OM grades and calculated primary endpoint values will be created.

The distribution of OM severity grades at each visit will also be displayed. These summary tables will present the number and percentage of patients per OM grade at each visit, by treatment group, for the ITT, mITT, and PP populations.

8.7.2 Analysis of Key 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). The analysis of all key secondary efficacy endpoints will be performed for the ITT, mITT and PP populations.

Note: The OM assessment period includes all OM Assessments performed, including the short-term follow-up period.

To control the experiment-wise Type 1 error rate at 5%, significance tests of the key secondary efficacy endpoints will be performed in the hierarchical order listed below. As specified in the protocol, the mITT population will be the main analysis and guide the hierarchical order of testing. To support these results, the same analyses will be repeated for ITT and PP populations. Each analysis will control for stratifications factors. All the analyses described below will be performed for the purpose of displaying summary statistics, but once the first in the sequence of tests yields a p-value that exceeds 0.05, the nominal p-value for this and subsequent endpoints in the series will be declared non-significant.

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. The log-rank test will be stratified by cisplatin regimen, HPV status and region. Below is the sample SAS code that performs the intended analysis:

```
proc lifetest
 data=test;
 time Time_to_Onset*censor(1);
 strata CIS_GRP HPV REGION / group=TRTPN;
run;
```

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. 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. Incidence will be calculated for two observation periods: (1) entire follow-up period, and (2) from the first to last day of CRT. Incidence of severe OM will also be summarized descriptively for subgroups defined by 3 factors (cisplatin regimen, region, HPV status) in the mITT population only.

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). An imputation scheme similar to the primary analysis will be used in the event that subjects discontinue 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.

8.7.3 ANALYSIS OF OTHER SECONDARY EFFICACY ENDPOINTS

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 in the mITT population. Similarly, the cumulative radiation dose up to the first observed ulcerative oral mucositis (WHO grades 2-4) will be tabulated. If a subject does not experience severe OM during the study, the full cumulative radiation dose will be used. 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 MTS scores, graded on a scale from 0 (no soreness) to 4 (extreme soreness), will be summarized by treatment group during each study week as well as for the last 7 days of treatment in the mITT population.

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.

Other Diary Outcomes: For other diary items: overall health, limited in swallowing, drinking, eating, talking and sleeping, overall soreness and diarrhea descriptive statistics will be produced for each treatment and by study week as well as for the last 7 days of treatment in the mITT population. However, no significance tests will be performed.

Analgesic use: Use of analgesics (parenteral, oral, or transdermal) to control oral pain will be examined by displaying number and percentages of subjects in the mITT population taking:

- Topicals such as viscous lidocaine
- OTC analgesics such as acetaminophen or ibuprofen
- PO opioids such as Vicodin or Percocet
- Parenteral opioids such as morphine or Fentanyl

Also, PO and Parenteral opioids will be combined to form a category for all opioids. P-values for all opioids and parenteral opioids will computed using the stratified CMH test (with modified ridit scores).

All the patient-level secondary endpoints will be listed together with the primary endpoint. Listings of radiation therapy data, OMDQ, and analgesics will be created as well.

8.7.4 EXPLORATORY EFFICACY ENDPOINTS

Exploratory efficacy analyses will be conducted for the mITT population only. The effects of AG013 will be explored on the basis of the following:

Descriptive statistics will be presented for the incidence of severe OM (WHO grades 3 or 4) within subgroups receiving each of the following cumulative radiation doses: <=30 Gy, >30 and <= 40 Gy, >40 and <= 50 Gy , >50 and <= 60 Gy, and > 70 Gy. As with the secondary endpoint analysis, incidence will be defined as the proportion of subjects in each subgroup having at least one grade 3 or 4 OM assessment.

The distribution of OM severity grades at each visit will be provided for CTC and RTOG rating scales. These summary tables will display the number and percentage of patients per OM grade at each visit, by treatment group, for the mITT population.

For each subject, oral mucositis severity scores (WHO grades 0-4) at each time point will be used to calculate AUC using the trapezoidal rule. Average severity-by-time curves will

be generated and plotted for each treatment group, and compared using the Wilcoxon rank-sum test. Descriptive statistics for AUC values will be presented.

Incidence, duration and time to onset of grades 3 and 4 and grades 2, 3, and 4 OM as per NCI CTCAE and RTOG criteria will be analyzed separately, using the same methodology as described for the primary and secondary endpoints. Listings of NCI CTCAE and RTOG grades will be prepared, as well as listings of the calculated endpoints.

Frequency and duration of RT interruptions: The number of subjects in each treatment group with an unplanned break in RT during the 7- to 9-week regimen will be tabulated. Subjects with an interval of 5 days or more without an administration of RT, or who discontinue RT 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 RT, the time from the last dose of RT to the prescribed end date of the regimen will be used in the calculation.

All the RT data will be listed. Calculated values for the above listed endpoints will be listed separately.

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.

Listings of healthcare resource utilization data (US data only) will be created.

8.8 SAFETY ENDPOINTS AND ANALYSIS

All the analyses in this section will be performed on SAF population. Subjects will be analyzed according to the actual treatment they have received.

8.8.1 EXPOSURE TO STUDY TREATMENT

Extent of exposure data were obtained from weekly patient accountability data (used vs. unused vials) as well as from patient diaries in which subjects recorded each of 3 daily administrations of IMP and any missed doses on a daily base. For Extent of exposure analyses diary data will be used, containing the most detailed information, i.e. daily dosing information. Total duration of exposure to study drug will be summarized for each treatment group. Total duration of exposure to treatment will be defined as the time from first to last use of the IMP (in days). Specifically, extent of exposure = last dose date – first dose date + 1. The total number of doses planned will be calculated as the sum all doses that should have been taken according to the assigned dose regimen (i.e. total duration of exposure x 3). Total percent of doses received will be calculated as the cumulative actual doses divided by the cumulative planned doses, expressed as percentage. Number of planned doses will be calculated by taking the minimum of date

of last dose minus date of first dose plus one times three. Total number of days with at least one dose per day will also be summarized.

Summaries of the number of missed doses and percent of doses received will also be prepared per week, the last week of treatment and overall. Doses will be considered missed if either the eCRF indicates the dose was missed or there is no record for a particular administration before the end of treatment or discontinuation. Number of missed doses will be calculated as the number of doses assigned minus the number of doses taken, and percent of doses received will be calculated as the number of doses taken divided by number of doses planned. Total number of days per week with at least one dose per day will be calculated, and summary of percent of days per week with at least one dose taken will be prepared.

Separate summary tables for IMP taste, consistency, and smell will be created. Weekly averages will be calculated using daily reports. Missing assessments will be excluded from estimation.

Summaries will be displayed by treatment and by week.

A listing of exposure to the study drug will be created, including dose, taste, consistency and smell. Calculated weekly averages will be listed as well.

Details on radiation therapy plan (location of tumor, prescribed cumulative dose and treated sites) will be summarized. Cumulative actual exposure to RT will also be summarized. Dose delays and changes will be listed together with the reasons for delays/changes.

A listing of RT data and RT plan will be provided.

Cumulative exposure to chemotherapy (Cisplatin) will be summarized by timepoint. Dose delays and changes and the reasons for them will be summarized as well.

A listing of chemotherapy data will be created.

8.8.2 ADVERSE EVENTS

All AEs will be coded by PT and SOC using MedDRA version 19.0 or higher. The NCI-CTCAE (Version 4.03) will be used to grade both clinical and laboratory AEs.

The incidence of TEAEs will be summarized by treatment group and tabulated by 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 until end of short term follow-up. Summary tables will include all TEAEs. Incomplete starting dates of AEs will be imputed using the rules from section 8.3 of this SAP. 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. AE severity will not be imputed if missing.

Summaries and by-patient data listings of TEAEs, AEs leading to death, SAEs, and AEs leading to discontinuation will be provided. The by-patient AE data listings will include onset and resolution dates, verbatim term, PT, treatment, severity (grade), relationship to treatment, action taken for the event, and outcome. All the deaths, including those reported during the long-term follow-up period, will be listed with the primary causes.

8.8.3 Laboratory Data

As chemistry and hematology data are only processed by the local laboratories, summary tables for these parameters will not be created. Shift table from baseline to each visit (as well as to the worst grade) will be prepared for all parameters with NCI CTCAE grades. Separate summaries will be created for the number and proportion of subjects with Grade 3 or worse toxicity for each parameter.

All chemistry and hematology values will be listed, together with their NCI CTCAE grades. Clinically significant abnormalities will be flagged. Pregnancy test results will be listed.

8.8.4 Vital Signs and Other Safety Parameters

Vital signs (SBP and DBP, heart rate, respiratory rate, and temperature), Karnofsky Performance Score, and body weight will be summarized for each treatment group at each visit 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. A listing of vital signs will also be created.

Tumor response assessments (based on RECIST or other standard criteria used at the investigational site) at each timepoint following the last dose of CRT (3, 6, and 12 months) will be listed for individual subjects and tabulated in frequency tables, by treatment group.

Physical examination results both at baseline and at the end of the treatment will be summarized. Individual subject listings of physical examinations will be prepared as well.

8.9 Other Endpoints and Analysis

8.9.1 Pharmacokinetics, Pharmacodynamics and Genomics

The PK analysis will be performed at Precigen ActoBio (formerly Intrexon Actobiotics), and individual outcomes per patient per visit will be derived. PK parameters will be calculated by summarizing the parameters and concentrations by visit. Analysis will be descriptive, no hypothesis testing will be performed. Listings for PK data will be created as well.

Blood and buccal smears will be collected at specific time points in a subset of subjects who consent separately (targeting 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. Blood levels of AG013-sAGX0085 bacteria, 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. Note: this analysis will only be performed in case of a positive outcome on the study regarding the efficacy outcome, i.e. positive primary endpoint. .

PD (biomarker) and Genomic analyses will be described in a separate plan.

Note: PD (biomarker) and Genomic analyses will only be performed in case of a positive efficacy outcome on the study.

9. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

Per protocol, baseline characteristics and demography data should only be summarized for SAF population. We have added these summaries for ITT population as well, to support the primary analysis.

The protocol stipulates that laboratory data should be summarized using the usual set of descriptive statistics at each visit, both for actual values and changes from baseline. However, as hematology and chemistry data are only collected locally in this study, these summaries were replaced with shift tables for NCI CTCAE grades.

The Protocol states regarding Severe OM Incidence that subjects with no OM assessments will be assumed to have severe scores and subjects who die or withdraw without experiencing OM grade 3 or 4 will also be assumed to have severe scores. This will not be done in incidence analyses.

10. PROGRAMMING SPECIFICATIONS

All outputs will be produced using SAS version 9.4 or a later version.

The margins should be at least 1.50 inches for the binding edge and 1.0 inches for all others.

In the top left portion of each table/listing, the protocol number will be presented. On the next line a table/listing number followed by the title of the table/listing and population information will be displayed. Horizontal lines will appear after the column heading of the table/listing. Footnotes will be put under the main body of text at the bottom of the page. The source listing number will be displayed for all tables. The SAS program name will appear bottom left in a string and the page number will appear on the bottom right corner of each table/listing. The date and time of creation of table/listing will appear bottom left under to the SAS program name line.

Courier New 8-point bold font will be used for all tables and listings. Usually, a landscape layout is suggested for both tables and listings, but it is not mandatory. Any date information in the listing will use the date format, for example, 07MAY2002.

11. APPENDIX I. SCHEDULE OF ASSESSMENTS

Assessments	Screening	Active Treatment Phase (2 visits per week) All Visit must be 48 Hours apart!												Short Term Follow-up[b] (once weekly visits)		Long Term Follow-up
	Within 4 weeks of randomization	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[i]	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).