Galera Therapeutics, Inc
Protocol #: GT-201

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Trial of the Effects of Intravenous GC4419 on the Incidence and Duration of Severe Oral Mucositis (OM) in Patients Receiving Post-Operative or Definitive Therapy with Single-Agent Cisplatin plus IMRT for Locally Advanced, Non-Metastatic Squamous Cell Carcinoma of the Oral Cavity or Oropharynx

Statistical Analysis Plan

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Abbreviations	Description of abbreviations
AE	Adverse Event
AUC	Area Under the Curve
BMI	Body Mass Index
BSA	Body Surface Area
°C	Degrees Centigrade
CM	Concomitant Medication
CTCAE	Common Terminology Criteria for Adverse Events
CTM	Clinical Trial Material
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ER	Emergency Room
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
Gy	Gray
HIPAA	Health Insurance Portability and Accountability Act
HNC	Head and Neck Cancers
HSCT	Hematopoietic Stem Cell Transplantation
HPV	Human Papilloma Virus
IMRT	Intensity-Modulated Radiation Therapy
ITT	Intention to Treat
IV	Intravenous
IXRS	Interactive Response Technology
kg	Kilogram
lb	Pound
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger RNA
NCI	National Cancer Institute
N/V	Nausea/Vomiting
OM	Oral Mucositis
OMDQ	Oral Mucositis Daily Questionnaire
PK	Pharmacokinetic
Q3	Every 3
OS	Overall Survival
PFS	Progression Free Survival
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SOM	Severe Oral Mucositis
STD	Standard Deviation

TEAE	Treatment-Emergent Adverse Event
VAS	Visual Analog Scale
WHO	World Health Organization

CONTENTS

I. Introduction

A. Background

Oral mucositis (OM) is a common, problematic, and painful complication of cancer therapy in regimens that include radiation to the head and neck[1]. A majority of patients receiving combined chemoradiotherapy for head and neck cancer (HNC) can be expected to develop severe OM[2], and nearly all HNC patients receiving radiation therapy with concurrent cisplatin are expected to develop ulcerative OM[3].

OM is characterized by mouth sores that typically progress to an ulcerative state after two or three weeks of radiotherapy, or a cumulative dose of 20-30 Gy. These sores make eating and swallowing difficult, and can induce weight loss and dehydration. In addition to interrupting food intake, OM has a substantial number of comorbidities, including reduced performance status, secondary infections at the sites of the ulcers, diminished quality of life outcomes, xerostomia, taste change, and trismus. In addition, OM can precipitate other serious medical complications that require frequent hospitalizations and breaks in treatment, which can compromise the anti-tumor efficacy of the therapy administered to treat the cancer.

In addition to several interventions that are recommended to prevent OM, palifermin is the only FDA-approved drug intervention therapy. Its use, however, is limited to a very small cohort of patients, those who are receiving autologous hematopoietic stem cell transplantation (HSCT) for hematologic malignancies. The Investigational Product of the current study, GC4419, is a compound that can potentially be used in a larger number of eligible patients. It has been shown in an earlier Phase 1b/2a trial to reduce the incidence and severity of OM in patients receiving IMRT combined with cisplatin for the treatment of squamous cell carcinoma of the oral cavity or oropharynx. The current study will examine GC4419 efficacy further in a three-arm, randomized (1:1:1) placebo-controlled Phase 2 trial in patients with locally advanced, non-metastatic squamous cell HNC of the oral cavity or oropharynx. Two doses of GC4419, one “low” and one “high,” will be evaluated against placebo in patients receiving a backbone regimen of cisplatin plus IMRT. The primary objective is to evaluate and compare the duration of severe OM between each of the two GC4419 treatment groups and the placebo group.

The protocol for Study GT-201 describes the general approach to analysis of data from the study. This analysis plan describes additional detail needed to complete such an analysis.

B. Protocol and Amendment History

This Statistical Analysis Plan (SAP) is based on GT-201 Protocol Amendment 5. See below for a list of all protocol versions.

Version	Approval Date	Salient Changes, if any*
Original Protocol	20 April 2015	
Amendment 1	16 November 2015	Removal of Interim Analysis; Change in primary objective; Addition of exploratory endpoint; Change to reporting period for adverse events; Update to antiemetic guidelines.
Amendment 2	22 July 2016	Extension to Canada; Addition of Bezydamine to list of prohibited medications
Amendment 3	26 October 2016	Extension of tumor, xerostomia, and trismus follow-up from one to two years post-IMRT; Addition of Caphosol to list of prohibited medications
Amendment 4	21 December 2016	Addition of exclusion criterion #16; Addition of Pyridostigmine and other drugs that could create a risk of increased carotid sinus sensitivity, symptomatic bradycardia, or syncopal episodes to list of prohibited medications; Modification of dose reduction criteria
Amendment 5	08 May 2017	Increase in sample size; Demotion of secondary endpoints; Addition of exploratory endpoints
Amendment 6	20 October 2017	Change in multiplicity adjustment for Type I error from Hochberg correction to sequential testing of hypotheses Promotion of incidence of Grade 4 OM through completion of IMRT and onset of severe OM as secondary endpoints.

* Changes expected to require accommodation in analysis plan.

This SAP will govern the analysis of data from this study. The plan may be modified until the time of treatment unblinding. Any deviations from the analysis plan, including any after the time of treatment unblinding, will be documented as such in the study report.

II. Protocol Objectives

A. Primary

The protocol lists the following primary objective:

- To evaluate and compare the duration of severe OM, as assessed from the first determination of ≥ Grade 3 OM to the first instance of non-severe OM (≤ Grade 2), without a subsequent instance of ≥ Grade 3.

B. Secondary

The protocol lists the following secondary objectives:

- Efficacy
    - To evaluate and compare the effects of GC4419, administered at each of two daily doses vs. placebo, on the cumulative incidence of severe OM, defined as any occurrence of WHO Grade 3-4 OM, from the first IMRT fraction through the delivery of the 30th IMRT fraction (approximately 60 Gy delivered to tumor)
    - To evaluate and compare the cumulative incidence of severe OM from the first IMRT fraction through the last IMRT fraction
    - To evaluate and compare the cumulative incidence of Grade 4 OM from the first IMRT fraction through the last IMRT fraction
    - To evaluate and compare the time to onset of severe OM expressed as the number of IMRT fractions delivered at onset of severe OM
- Safety
    - To evaluate and compare the safety of GC4419 at the treatment assignment of each respective arm

- To evaluate and compare the effect of treatment assignment on tumor outcomes (locoregional failure, distant metastases, progression-free survival, overall survival)

C. Exploratory

The protocol lists the following exploratory objectives:

- To evaluate and compare duration of severe OM among subjects with severe OM
- To evaluate and compare the time to onset of severe OM: expressed both as cumulative IMRT dosage delivered and as time (days) at onset of severe OM
- To evaluate and compare the time to onset of severe OM among subjects with severe OM: time (days), cumulative IMRT dosage, and number of IMRT fractions delivered at onset of severe OM
- To evaluate and compare the duration of severe OM, as assessed by the number of instances of severe OM of ≥ 7 days' duration, defined as severe OM recorded at two or more consecutive OM evaluations
- To evaluate and compare severe OM incidence from the first IMRT fraction through the end of post-IMRT early follow-up; post-IMRT early follow-up will extend for up to eight weeks post the last IMRT fraction administered or until a given patient's OM is WHO Grade 0 or 1
- To evaluate and compare cumulative severe OM incidence at cumulative delivery of 20-29, 30-39, 40-49, or 50-59 Gy of IMRT
- To evaluate and compare the duration of Grade 4 OM from the first IMRT fraction through the last IMRT fraction
- To evaluate and compare the areas under the OM-severity vs. cumulative IMRT dosage curves
- To evaluate and compare the number and percentage of patients with severe OM on more than one visit prior to Week 6, Visit 2
- To evaluate and compare the total number of days (per patient) of severe OM through the end of IMRT
- To evaluate and compare the effects of GC4419 on the incidence, onset, and duration of ulcerative (≥ Grade 2) OM

- To evaluate and compare treatment delivery and delays (number and duration of delays) of IMRT and cisplatin, to include cisplatin dose reductions.

- To evaluate and compare the effects of GC4419 on other specific toxicities of interest associated with concurrent chemoradiation: xerostomia, trismus, fatigue, weight loss, radiation dermatitis, and dysgeusia (changes in taste)

- To evaluate and compare the effects of treatment on patient-reported outcomes as obtained using the Oral Mucositis Daily Questionnaire (OMDQ)

- To evaluate and compare the use of narcotic analgesics by patients according to treatment assignment

- To evaluate and compare frequency, use, and reasons for use of gastrostomy tubes

- To evaluate and compare the use and complications of indwelling venous access devices

- To evaluate and compare the frequency and reasons for unscheduled hospitalizations

- To assess the effects of treatment assignment on circulating cytokine levels and gene expression levels

III. Study Endpoints

A. Primary

The primary endpoint is the duration of severe OM, which is defined as the number of days from the first occurrence of WHO Grade 3 or 4 OM through the first occurrence of non-severe (≤ Grade 2) without a subsequent instance of ≥ Grade 3 OM. Subjects with complete study follow-up for severe OM as described in the protocol and who do not develop severe OM will be considered to have durations of 0 days.

B. Secondary

The protocol describes as secondary endpoints the following:

- Cumulative incidence of severe OM, defined as any occurrence of WHO Grade 3-4 OM, from the first IMRT fraction through the delivery of the 30th IMRT fraction

- Evaluate and compare the safety of GC4419 at the treatment assignments of each respective arm
- Cumulative incidence of severe OM from the first IMRT fraction through the last IMRT fraction
- Effect of treatment assignment on tumor outcomes (locoregional failure, distant metastases, progression-free survival, overall survival)
- Cumulative incidence of Grade 4 OM from the first IMRT fraction through the last IMRT fraction
- Onset of severe OM, expressed in number of IMRT fractions delivered at onset of severe OM

C. Exploratory

The protocol describes the following exploratory endpoints:

- Duration of severe OM, excluding those without severe OM (i.e., durations of 0 days)
- Onset of severe OM, expressed both in cumulative IMRT dosage and time (days) at onset of severe OM
- Onset of severe OM, expressed as cumulative IMRT dosage, time (days), and number of IMRT fractions delivered at onset of severe OM, when excluding those without severe OM (i.e., durations of 0 days)
- Number of instances of severe OM lasting ≥ 7 days, defined as two or more consecutive observations of severe OM
- Cumulative incidence of severe OM from the first IMRT fraction through the end of post-IMRT early follow-up; post-IMRT early follow-up will extend for up to eight weeks post the last IMRT fraction administered or until a given patient's OM is WHO Grade 0 or 1
- Cumulative severe OM incidence at cumulative delivery of 20-29, 30-39, 40-49, or 50-59 Gy of IMRT
- Duration of Grade 4 OM from the first IMRT fraction through the last IMRT fraction
- Areas under the OM-severity vs. cumulative IMRT dosage curves
- Number and percentage of patients with severe OM on more than one visit prior to Week 6, Visit 2

- Total number of days (per patient) of severe OM though the end of IMRT
- Incidence, onset, and duration of ulcerative (≥ Grade 2) OM
- Number and duration of delays of IMRT and cisplatin, or of cisplatin dose reductions
- Other specific toxicities of interest associated with concurrent chemoradiation:
    - Xerostomia (assessed using a five-point Visual Analog Scale of Leveque)
    - Trismus, based on measurement of jaw opening
    - Fatigue
    - Weight loss, from serial patient weights in scheduled study visits
    - Radiation dermatitis per NCI-CTCAE v4.03
    - Dysgeusia (changes in taste) per NCI-CTCAE v4.03
- Scores in individual questions from the Oral Mucositis Daily Questionnaire (OMDQ)
- Use of narcotic analgesics by patients according to treatment assignment
    - Percentage of patients using opioid narcotics
    - Time and cumulative IMRT delivered to first opioid narcotic use
    - Median total opioid narcotic dose (morphine equivalents) with 25th-75th percentiles
- Frequency, use, and reasons for use of gastrostomy tubes
- Frequency, use and complications of indwelling venous access devices
- Frequency and reasons for unscheduled hospitalizations
- Levels of selected circulating cytokines (cytokine selection informed by proposed GC4419 mechanism of action and Phase 1 results)
- To assess the effects of treatment assignment on circulating cytokine levels and gene expression levels.

IV. Study Design

A. Design Overview

Study GT-201 is a Phase 2, randomized, double-blind, placebo-controlled, multi-center study conducted in the US and Canada to evaluate Galera's GC4419 administered via IV for the prevention of radiation induced oral mucositis in patients receiving chemotherapy and radiation for SCCHN, limited to the oral cavity or oropharynx. Approximately 216 subjects who meet eligibility criteria and consent to participate in the study are randomly assigned equally to one of the following treatment groups. Randomization will be stratified according to HPV status at baseline (positive vs. negative) and initial chemotherapy schedule (once every 3 weeks vs. once a week cisplatin).

- Arm A: 30 mg GC4419 per day + IMRT 2.0-2.2 Gy per day + Cisplatin (80-100 mg/m^2 every 3weeks or 30-40 mg/m^2 once weekly)
- Arm B: 90 mg GC4419 per day + IMRT 2.0-2.2 Gy per day + Cisplatin (80-100 mg/m^2 every 3weeks or 30-40 mg/m^2 once weekly)
- Arm C: Placebo daily + IMRT 2.0-2.2 Gy per day + Cisplatin (80-100 mg/m^2 every 3weeks or 30-40 mg/m^2 once weekly)

After completion of screening assessments and determination of eligibility, enrolled patients will be randomized into one of the above treatment arms. Each subject will receive blinded study treatment (GC4419 or placebo) via a 60-minute IV infusion, followed within 60 minutes by a 2.0-2.2 Gy fraction of IMRT for five consecutive days, followed by two days off, for a total of approximately seven weeks. Concurrent with study treatment and IMRT, subjects will receive cisplatin at a dosage of 80-100 mg/m^2 if on a Q3 week schedule or 30-40 mg/m^2 cisplatin if on a weekly cisplatin schedule. Study treatment will continue for approximately seven weeks until IMRT completion, patient refusal, intolerance, or disease progression. At the end of IMRT, subjects with a WHO score ≥ 2 will be followed weekly for up to 8 weeks until the WHO score returns to ≤ 1. All patients will enter a post-active phase following the last day of IMRT, and will be seen at 3-month intervals for the first year and 4-month intervals for the second year. Assessments performed during this post-treatment phase will include clinical tumor assessments, complete head and neck exams, tumor imaging, and xerostomia and trismus assessments.

B. Study Population

The study population will consist of subjects ≥ 18 years of age with a pathologically-confirmed diagnosis of squamous cell carcinoma of the head and neck (SCC of the oral cavity or oropharynx) that will be treated with cisplatin plus IMRT. Patients with unknown primary tumors whose treatment plan matches the requirements of the study will be eligible for participation.

Approximately 216 patients (72 per treatment arm) will be enrolled to achieve 195 evaluable patients or roughly 65 evaluable patients per treatment arm. Refer to Section 7 of Protocol GT-201 for a complete list of the entry criteria for this study.

Patients who sign informed consent and meet all eligibility criteria for the trial will be assigned a patient number and will be considered enrolled. Patients who are issued a patient number, but who do not successfully complete the screening process and who are not randomized into a treatment arm will be considered a screen failure.

C. Sample Size

The proposed sample size of 216 assumes an early discontinuation rate of 10%, yielding approximately 65 patients per arm who will complete their IMRT course. This estimated sample size, needed to detect a median reduction in duration of 28 days for the treatment arms, relative to subject using placebo, was predicted on the basis of the following assumptions:

- Severe OM incidence of 40% in each treatment arm, compared with 65% in the control arm
- Probability of overall type I error (α) of 0.05
- A null hypothesis that the distribution of duration of severe OM in each treatment arm equals the distribution of duration of severe OM in the placebo arm. The assumed distribution of duration among all placebo subjects is (25th, 50th, 75th percentile): 0, 28, 50 days.
- An alternative hypothesis that the distribution of duration of severe OM in each treatment arm is not equal to the distribution of duration of severe OM in the placebo arm. The assumed distribution of duration among subjects in each treatment arm is (25th, 50th, 75th percentile): 0, 0, 21 days.
- Power of at least 80%

D. Treatment Randomization

A permuted fixed-block randomization scheme was created using Proc Plan in SAS to assign subjects in a 1:1:1 ratio to one of the three treatment groups (30 mg GC4419 per day, 90 mg GC4419 per day, Placebo daily). The scheme was stratified by HPV status at baseline (positive vs. negative) and initial chemotherapy schedule (q3 weeks vs. weekly cisplatin), without regard to investigative site. After obtaining informed consent and establishing study eligibility, the site pharmacist or designee will obtain the study drug assignment (one of two GC4419 treatment groups or placebo) using an IXRS system, custom designed for the study by Almac.

E. Assessment Schedule

The date at which the subject begins treatment with GC4419 (IMRT Day 1) or placebo will be referred to as the "start date" or Study Day 1. Subjects will be requested to attend a maximum of the following scheduled visits from their start date: weekly, Monday through Friday, beginning at the start date and through Study Day 47 (end of IMRT). At the end of the 7 weeks of IMRT (or early termination), subjects with a WHO score ≥ 2 will be followed weekly until their WHO score is ≤ 1, with an acceptable visit window for weekly assessments of $\pm$ 2 days. **Subjects will be considered to have completed follow-up for OM who are assessed for OM on or after the completion of IMRT with a WHO score ≤ 1**.

At the end of the Active Phase (7 weeks GC4419/IMRT/Chemo + 8 weeks OM assessments, if necessary), the subjects will enter the Post-Active Phase, consisting of visits at Months 3, 6, 9, 12, 16, 20, and 24 with an acceptable visit window of $\pm$ 30 days. Visits that subjects make to the clinic outside the visit windows are recorded as unscheduled visits.

V. Interventions

A. Clinical Trial Material

The clinical trial material (CTM) for all subjects will consist of a clear solution packaged as an 11 mL $\pm$ 0.1mL aliquot in a 10 mL amber glass vial with an S-127 4432/50 gray stopper and a 20 mm red flip-off seal. The vial contains one of the three following constituents:

- 30 mg GC4419: 3 mg/mL in 26 mM sodium bicarbonate-buffered 0.9 wt. % saline, Arm A for the entity under investigation
- 90 mg GC4419: 9 mg/mL in 26 mM sodium bicarbonate-buffered 0.9 wt. % saline, Arm B for the entity under investigation
- 26 mM sodium bicarbonate-buffered 0.9 wt. % saline, Arm C for placebo

Subjects will receive an infusion of the CTM daily, Monday-Friday, for approximately 7 weeks (up to 35 doses). The protocol provides additional information regarding the investigational product, including details on study drug supply/storage, study drug administration, and study drug handling/disposal, in Section 9.

B. Study Procedures

Refer to Section 11 of the study protocol for a complete list of study assessments and procedures. OM assessments will be scored using the WHO OM toxicity scale and will be completed at Screening, Baseline, and twice weekly within each 5-day IMRT period. Additionally, OM assessments will be made weekly for up

to 8 weeks after the last day of IMRT for subjects with ulcerative OM (WHO ≥ 2) until the WHO score returns to 0 or 1. Accompanying procedures for the examination of secondary and exploratory outcomes include assessments of trismus and xerostomia, data on placement of gastronomy tubes and indwelling venous catheters, and blood draws for cytokine levels and RNA analysis.

A Schedule of Events table is provided in Appendix 1.

VI. General Analytical Considerations

A. Data Sources

Clinical Data
Most clinical study data will be entered by the clinical site in an electronic data capture system via electronic case report forms (eCRFs). Central laboratory and PK results will be received via electronic data transfers and integrated into the clinical database for analysis. Biomarkers of mucositis will be measured from blood samples collected during the active phase of the study and integrated into the clinical database via electronic data transfers. In addition, gene expression patterns in patients who consent to the collection of RNA samples will also be received via data transfers and integrated into the clinical database. Local laboratory data, if performed during an unscheduled visit, will be entered into the eCRFs if the local labs support an applicable AE per protocol.

Patient Reported Data
Xerostomia assessments, use of narcotic medications, and answers to the OMDQ will be recorded by the patient on paper forms, which will be subsequently entered into the eCRFs by the site.

Randomization Data
The randomization data and clinical drug supply information will be managed by Almac. Since these data are unblinded, only authorized team members will be given access to these files for integration with the clinical study data for the production of the interim unblinded data summaries for the DMC. Once the study is completed, these data will be fully integrated with the clinical study data.

Section 17 of the protocol provides additional details regarding data recording and handling.

B. Definition of Baseline

Study Day 1 will be designated as the first day a patient receives GC4419 (Placebo) and will be defined as baseline. For most measurements, baseline labs will be taken pre-dose on Day 1. If pre-dose assessments on Day 1 are not available, the screening result closest to Day 1 may be substituted in some cases. Such substitutions will be noted in the clinical study report. The first dose of

Cisplatin may be administered before the first dose of GC4419 (Placebo), and will not be considered in the definition of baseline.

C. Missing Data

Every attempt will be made by the sites to enter complete dates for assessments performed during the study. In the event that an adverse event has an incomplete start date, the following rules will be used to determine treatment emergence:

- If complete date is missing, set to date of first dose of GC4419;
- If year is missing, set year to the year portion of the first dose date of GC4419.
- If the day is missing, set day to the first day of the month or the first dose date of GC4419, whichever is later.
- If the month is missing, set month to the first month of the year or the first dose date of GC4419, whichever is later.

With the exception of WHO OM scores, all other data will be reported as they are collected; no imputation methods will be used to replace missing data. The imputation of WHO OM scores for subjects who lack WHO OM scores, who discontinue from the trial without complete follow-up, or whose resolution date of severe OM is unknown will be discussed in the relevant sections below.

D. Multiple Study Centers

No adjustment for stratification by the study centers is planned.

E. Covariate Adjustment

The primary and secondary efficacy analyses will be stratified by the two stratification factors as entered at randomization, HPV status at baseline and planned chemotherapy schedule, resulting in 4 strata. Should any of the four strata have fewer than 4 subjects, the analysis will combine over HPV status for a given chemotherapy schedule. For example, should the HPV-positive/weekly cisplatin stratum have fewer than 4 subjects, the analysis will combine the HPV-positive/weekly cisplatin and HPV-negative/weekly cisplatin into a single weekly cisplatin stratum, resulting in the analysis having 3, rather than 4 strata (namely, a. weekly cisplatin, b. HPV-positive/q3 week cisplatin, and c. HPV-negative/q3 week cisplatin).

A few subjects entered the trial with unknown HPV status; subjects with oropharyngeal tumors were randomized as HPV positive, while those with oral cavity tumors were randomized as HPV negative.

F. Interim Analyses or Timing of Analyses

No formal interim analysis is planned for this study. However, as discussed in the Statistical Alignment Meeting, a review of unblinded safety data will be conducted periodically by a Data Monitoring Committee (DMC), with the first review occurring after approximately 45 subjects have completed the 7 week GC4491/IMRT/Chemotherapy active treatment phase. Subsequent DMC reviews will be held at intervals determined by the DMC. Results from this data review could result in recommendations regarding continuing enrollment, holding enrollment until further review, amending the protocol, or stopping the study.

The following blinded safety-related data displays will be produced for open discussion by the DMC. They may be shared with the project team. These displays are summary tables, with the treatment groups aggregated into one overall group for display.

- Randomization of Analysis Populations
- Subject Disposition
- Demographic and Baseline Characteristics
- Baseline Disease Characteristics and Prior Treatment
- Exposure to Study Treatment
- Exposure to IMRT
- Exposure to Chemotherapy
- Study Treatment Modifications and Interruptions
- IMRT and Chemotherapy Modifications and Interruptions
- Overall Summary of Treatment-Emergent Adverse Events
- Summary of Treatment-Emergent Adverse Events by Preferred Term
- Summary of Treatment-Emergent Adverse Events with CTCAE Grade >= 3 by Preferred Term
- Summary of Serious Treatment-Emergent Adverse Events by Preferred Term
- Summary of Study Treatment Related Treatment-Emergent Adverse Events by Preferred Term
- Summary of IMRT Related Treatment-Emergent Adverse Events by Preferred Term
- Summary of Chemotherapy Related Treatment-Emergent Adverse Events by Preferred Term
- Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment by Preferred Term
- Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of IMRT by Preferred Term
- Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Chemotherapy by Preferred Term

- Summary of Priority Treatment-Emergent Adverse Events by Preferred Term
- Summary of Treatment-Emergent Adverse Events by Preferred Term and Severity
- Hematology Shift Table for Laboratory Assessments with NCI-CTCAE (version 4.03) Toxicity Grades
- Serum Chemistry Shift Table for Laboratory Assessments with NCI-CTCAE (version 4.03) Toxicity Grades
- Summary of Tumor Status

The tables listed above will also be produced for closed discussion by the DMC, with the exception that instead of displaying the data in only one aggregated group, the data are displayed in three treatment groups, as randomized, plus a total group for all patients.

The following data listings will also be provided for the closed session only:

- Randomized Study Eligibility Criteria
- Treatment-Emergent Adverse Events with CTCAE Grade ≥ 3
- Serious Treatment-Emergent Adverse Events
- Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment, IMRT, or Chemotherapy
- Treatment-Emergent Adverse Events Leading to Death
- Priority Treatment-Emergent Adverse Events
- Vital Signs
- Hematology
- Chemistry

G. Test Sizes

Study hypotheses will be tested against two-sided alternatives using a familywise Type I error rate (α) of 0.05.

H. Multiple Comparisons

To control the overall Type 1 error at 0.05, the testing of each GC4419 dose group to placebo will be done sequentially for the primary and secondary endpoints as shown in the following table. Testing will proceed conditional on the statistical significance of the prior test(s) at the 0.05 level.

Endpoint	Comparison tested at two-sided α = 0.05
Duration of severe oral mucositis (SOM)	90 mg versus placebo ↓
	30 mg versus placebo

	↓
Incidence of SOM through the 30th IMRT fraction	90 mg versus placebo ↓
Incidence of SOM through the end of IMRT	90 mg versus placebo ↓
Incidence of SOM through the 30th IMRT fraction	30 mg versus placebo ↓
Incidence of SOM through the end of IMRT	30 mg versus placebo ↓
Incidence of Grade 4 OM through the end of IMRT	90 mg versus placebo ↓
	30 mg versus placebo ↓
Onset of SOM expressed as number of IMRT fractions at onset	90 mg versus placebo ↓
	30 mg versus placebo

Under this procedure, duration of severe OM in the 90 mg GC4419 treatment arm will be compared with placebo first. If $p \leq 0.05$ for this comparison, duration of severe OM in the 30 mg GC4419 treatment arm will be compared. Additional tests of severe OM incidence or other parameters will be performed sequentially as long as $p \leq 0.05$. If for any test $p > 0.05$, no further hypotheses will be formally tested.

I. Analysis Populations

Several analysis populations will be defined for use with various analyses. The following table illustrates the relationship between each population and the analyses for which the data from the population will be used.

	Analysis							
Analysis Population	**Baseline**	**Subject Disposition**	**Efficacy**	**Tumor Endpoints**	**Safety**	**PRO**	**Health / Economic**	**Bio-mark**
ITT	**X**	**X**	**X**	**X**				
Treated		**X**	**X**		**X**	**X**	**X**	**X**
Evaluable			**X**	**X**				
Per Protocol			**X**					

1. Intent-to-treat Population

The intent-to-treat (ITT) population will include all subjects who are randomized and will be used in the primary analysis for all efficacy endpoints. Subjects will be analyzed according to their randomized treatment assignments.

2. Treated Population

All randomized subjects who used at least one dose of the CTM will be included in the Treated population. Only subjects with clear documentation that no CTM was received may be excluded. Subjects will be analyzed according to their randomized treatment, except for analyses of safety and tumor endpoints, where analysis will be by the dose received.

3. Evaluable Population

The evaluable population will comprise anyone receiving at least 60 Gy (30 fractions) of IMRT and at least 25 infusions of CTM. Subjects who are retrospectively determined to be ineligible for participation will be excluded.

4. Per Protocol Chemotherapy Population

The per protocol chemotherapy population is defined as the subset of the Evaluable population that includes subjects whose chemotherapy consisted only of single agent cisplatin including those with dose or scheduled modifications and without any substitution of other chemotherapy or systemic agents. Subjects who are retrospectively determined to be ineligible for participation will be excluded.

PK analyses will be conducted separately and are not included in this Statistical Analysis Plan.

J. Data Display Characteristics

Data displays produced for this study will include three types—summary tables, data listings, and figures. Unless stated otherwise, data listings will be produced for all recorded data. Summary tables will be produced as specified in following sections. Additional data listings will be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes. Figures will be produced when specified in sections to follow.

Data listings will simply list the data recorded on the CRF or derived for each subject. They will be ordered by treatment, site, subject number, and time of assessment. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within subject. Data listings will not display subject initials.

Summary tables will display summary statistics calculated for each of the treatment groups, unless described otherwise in following sections. Tables may have either of two general layouts. When the greatest interest is in direct comparison of one treatment group with the other at particular times, different columns of a summary table will display the statistics for the different treatment

groups. The placebo group statistics will be displayed to the right of the treatment group statistics. When the evolution of statistics over time is of greater concern than comparison at particular moments, a group of rows may be designated for the placebo group; the table columns would be designated for different summary statistics of interest. A subsequent group of rows would then be used for the treatment group. In this layout, a group of rows that represent a treatment group would generally be ordered chronologically.

The summary statistics displayed will be a function of the type of data associated with the summarized assessment. Unless stated otherwise in relevant sections to follow, continuous data will be summarized with the number of nonmissing values, mean, standard deviation (STD), minimum, median, and maximum. Categorical data will be summarized with the number of nonmissing values and the numbers of values equal to each of the possible values. Percentages of subjects with each of the possible values will be calculated from the number of subjects in the corresponding analysis population, unless stated otherwise. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables.

K. Blinded Review of Data

After all study data have been collected but prior to examining any study outcome data by treatment group, the data may be reviewed by the study team to determine whether any clarifications of the analysis plan are needed. Any revisions made to the analysis plan as a result of the blinded review of the data will be documented. Treatment assignments will be unblinded at the time of DMC analyses as well as the final analysis.

The date of each unblinding event will be documented in the final study report.

L. Balance of Treatment Assignments

The balance of the treatment arms with respect to the randomization strata will be evaluated to assess the impact of mis-stratification errors that may occur at the time of randomization. In the event that the treatment assignments appear unbalanced across randomization strata, sensitivity analyses of the primary and/or secondary endpoints may be conducted using the actual stratification values at randomization rather than the stratification values as randomized to assess the impact of mis-stratification.

VII. Subject Accountability

A. Subject Characteristics

Demography and Baseline Characteristics. Data collected about the following subject characteristics at the screening visit will be summarized for the ITT population:

- Age. Age will be calculated as the number of years elapsed between birth date and the date of randomization, adjusted for whether the birthday has passed as of the day of randomization. (This corresponds to the typical calculation of age a person would use in conversation.)
- Race
- Ethnicity
- ECOG performance status
- Height and Weight
- Body Mass Index (BMI)
- Body Surface Area (BSA)
- Past and Current Tobacco Use
- Past and Current Alcohol Use

Baseline Disease Characteristics. SCC Cancer Histories collected at the Screening visit will be summarized for the ITT population:

- Months since Initial Histopathological Diagnosis
- Tumor Location
- Prior Surgery for SCC Cancer
- Time Since Prior Surgery
- Prior Radiation Therapy
- Prior Systemic Cancer Therapy

In addition, the following disease characteristics will be summarized for each tumor location separately:

- HPV Status (positive or negative)
- Primary Tumor Staging
- Regional Lymph Node Staging
- Distant Metastasis Staging
- Anatomic Staging/Prognostic Groups

Medical History. Medical Histories not related to cancer will be listed for the ITT population.

B. Disposition

A summary of patients in the ITT population will display the numbers and percentages of patients in each of the analysis populations, by treatment assignment and overall. The numbers and percentages of patients in the ITT population will also be presented by each of the stratification factors, HPV status and Chemotherapy schedule, both combined and separately.

A summary of patient disposition will summarize the numbers of patients in the ITT population who were treated by the length of time they were on-treatment, both during the active IMRT/Study Drug treatment period and the Active OM Follow-up period. The number and percent of patients who were seen at each of the post-active phase visits will also be presented up to the end of the 24-month follow-up period. For patients who do not receive at least 60 Gy of IMRT, the reasons for treatment discontinuation will be summarized. Reasons for early discontinuation from treatment will include the following:

- Permanent Withdrawal of Consent during the Active Phase
- Adverse Event
- Death
- Disease Progression
- Investigator Decision
- Lost to Follow-Up
- Medical Requirement for Prohibited Medication
- Patient Non-Compliance
- Sponsor Decision
- Early Termination of Study

In addition, the number and percentage of patients who are no longer on study will be summarized by reason:

- Completed Study
- Randomization Failure
- Adverse Event
- Death
- Termination of Study
- Disease Progression
- Investigator Decision
- Lost to Follow-Up
- Medical Requirement for Prohibited Medication

- Patient Non-Compliance
- Permanent Withdrawal of Consent
- Sponsor Decision

Percentages of subjects who discontinued treatment or withdrew from study for each of the above reasons will be calculated using the number of patients in the relevant treatment group as the denominator.

This summary will also be produced for the Treated population if more than 5% of subjects in the ITT population are excluded from the Treated population.

C. Protocol Deviations and Population Inclusions

A listing will identify subjects who were enrolled even though they did not meet one or more eligibility criteria, and subjects who met withdrawal criteria discernible from recorded data during the study but were not withdrawn. Criteria for the latter group of subjects will be established at the time of the blinded data review.

Protocol deviations will be tracked outside of the electronic data capture (EDC) system, and reviewed by the medical monitor. A listing of protocol deviations for all enrolled subjects will be produced, and will include the following deviations: violations of the treatment plan, eligibility and/or withdrawal violations, omitted safety and efficacy assessments, and other unanticipated problems.

VIII. Efficacy Analyses

Efficacy analyses will use data from the ITT population as the primary basis for assessing the relative effect of each dose group relative to placebo. Efficacy analyses will also be generated for the treated, evaluable and per protocol chemotherapy analysis populations.

A. Efficacy Outcomes

1. Primary Efficacy Outcome

Duration of Severe OM. Duration of severe OM is defined as the number of days from the first occurrence of WHO Grade 3 or 4 OM through the first occurrence of non-severe (≤ Grade 2) without a subsequent occurrence of ≥ Grade 3 OM. Per protocol, subjects are followed for OM post-IMRT weekly, for up to 8 weeks or until the OM score is 0 or 1. Subjects with complete follow up of OM who do not develop severe OM will be considered to have durations of 0 days. Missing OM data will be imputed based on the following rules:

- Missing OM scores with two adjacent OM assessments will be assigned the poorer of the two adjacent values.
- Subjects with unknown resolution of severe OM because of loss of follow-up for their OM status: Durations with unknown resolution will be imputed in descending order from longest duration to shortest duration to ensure a complete dataset from which to draw imputations. Subjects will have their values imputed with the median duration among all subjects in the same treatment arm with at least that observed duration. If no subject has at least that duration, the imputed duration will be 15, 30, 60, 75, or 100 days; the smallest of these values that is greater than the subject's known duration at the time of loss to follow-up will be chosen. See Appendix 2 for an example.

- Subjects with loss to follow-up for severe OM who do not develop OM while under observation: Imputation will be performed in descending order from longest length of follow-up to shortest. Duration of OM will be imputed with the median duration among subjects within the same treatment group who are free of severe OM for at least that length of follow-up. See Appendix 3 for an example. If no subject in the treatment group has at least that length of follow-up without severe OM, the imputed duration will be 0 days.

2. Secondary Efficacy Outcomes

Cumulative Incidence of Severe OM. The following measures of cumulative incidence of severe OM will be analyzed as secondary efficacy outcomes:

- Any occurrence of WHO Grade 3 or 4 OM from the first IMRT fraction through the 30th IMRT fraction. Subjects with loss to follow-up for OM before the 30th IMRT fraction will be analyzed according to their imputed durations for Grade 3 or 4 OM with onset through the 30th IMRT fraction; that is, such subjects with imputed durations greater than 0 days will be considered to have severe OM in the analysis of incidence. Imputation of duration through the 30th IMRT fraction will use a similar approach as imputation of duration for the primary analysis, except that it will only consider onset and durations of severe OM through the 30th IMRT fraction.
- Any occurrence of WHO Grade 3 or 4 OM from the first IMRT fraction through the last IMRT fraction. Subjects with loss to follow-up for OM before the last IMRT fraction will be analyzed according to their imputed durations of Grade 3 or 4 OM with onset through the last IMRT fraction; that is, subjects with imputed durations greater than 0 days will be considered to have severe OM in the analysis of incidence. Imputation of duration through the last IMRT fraction will use a similar approach as

imputation of duration for the primary analysis, except that it will only consider onset and durations of severe OM through the last IMRT fraction.

- Incidence of WHO Grade 4 OM from the first IMRT fraction through the last IMRT fraction. Subjects with loss to follow-up for OM before the planned final IMRT fraction will have duration and incidence of Grade 4 OM imputed as described above.
- Onset of Severe OM. The onset of severe OM will be measured using time-to-event methods using the cumulative IMRT fractions delivered at onset of Grade 3 or 4 OM in lieu of calendar time. Those without severe OM will be censored at their last assessment for OM.

  The onset of severe OM will also be examined using the following measures:

  - Time to onset of severe OM, defined as the number of days from the first IMRT to onset of Grade 3 or 4 OM.
  - Cumulative IMRT dose delivered at onset of Grade 3 or 4 OM.

  Those without severe OM will be censored at their last assessment for OM.

3. Exploratory Efficacy Outcomes

Duration of Severe OM in Subjects With Severe OM. Duration of severe OM is defined as the number of days from the first occurrence of WHO Grade 3 or 4 OM through the first occurrence of non-severe (≤ Grade 2) without a subsequent occurrence of ≥ Grade 3 OM. Per protocol, subjects are followed for OM post-IMRT weekly, for up to 8 weeks or until the OM score is 0 or 1. Subjects with complete follow up of OM who do not develop severe OM will be excluded. Missing OM data will be imputed based on the following rules:

- Missing OM scores with two adjacent OM assessments will be assigned the poorer of the two adjacent values.
- Subjects with unknown resolution of severe OM because of loss of follow-up for their OM status: Durations with unknown resolution will be imputed in descending order from longest duration to shortest duration to ensure a complete dataset from which to draw imputations. Subjects will have their values imputed with the median duration among all subjects in the same treatment arm with at least that observed duration. If no subject has at least that duration, the imputed duration will be 15, 30, 60, 75, or 100 days; the smallest of these values that is greater than the subject's known duration at the time of loss to follow-up will be chosen. See Appendix 2 for an example.
- Subjects with loss to follow-up for severe OM who do not develop OM while under observation will be excluded.

Onset of Severe OM in Subjects with Severe OM. The onset of severe OM will be measured using time-to-event methods using the cumulative IMRT fractions delivered in lieu of calendar time. Those without severe OM will be excluded.

The onset of severe OM will also be examined using the following measures:

- Time to onset of severe OM, defined as the number of days from the first IMRT to onset of Grade 3 or 4 OM.
- Cumulative IMRT dose delivered at onset of Grade 3 or 4 OM.

Those without severe OM will be excluded.

Instances of SOM Lasting ≥ 7 Days. The number of instances of severe OM lasting 7 days or longer is defined as the number of instances where severe OM is recorded for two or more consecutive assessments during IMRT and/or at least one post-IMRT assessment. OM scores resulting from the imputation for missing intervening values will be counted.

Cumulative Incidence of Severe OM. The following measures of cumulative incidence of severe OM will be analyzed as exploratory efficacy outcomes:

- Any occurrence of WHO Grade 3 or 4 OM from the first IMRT fraction through the end of post-IMRT early follow-up. For subjects who do not have WHO Grade 3 or 4 OM observed prior to loss of follow up, and who have incomplete follow-up for severe OM, incidence will be assigned using the the imputed duration for the primary analysis. In the event that the imputed duration for the primary analysis is 0, the subject will not be considered to have WHO Grade 3 or 4 OM through the end of post-IMRT early follow-up.
- Any occurrence of WHO Grade 3 or 4 OM from the first IMRT fraction through cumulative delivery of 20-29, 30-39, 40-49, or 50-59 Gy of IMRT. Imputation of incidence for subjects lost to OM follow-up will not be used in this analysis.

AUC. AUC is defined for each subject as the area under the OM-severity vs. cumulative IMRT dosage curve. Truncated AUCs will be imputed as described above for duration of severe OM (Section VIII.A.1).

Severe OM Prior to Week 6, Visit 2. The number and percentage of patients with severe OM on more than one visit prior to Week 6, Visit 2 will be examined.

Total Number of Severe OM Days. The total number of severe OM days is defined as the total number of days per patient of Grade 3 or 4 OM through the end of IMRT. Missing or partially missing days of severe OM will be

imputed as described above for duration of severe OM through the end of IMRT (Section VIII.A.1).

Cumulative Incidence, Onset, and Duration of Ulcerative OM. Ulcerative OM is defined as OM with WHO grade of 2 or higher. The cumulative incidence, onset and duration of ulcerative OM will be defined as above for severe OM (Section VIII.A.1 and VIII.A.2). Missing data will be imputed as described for these endpoints in Section VIII.A.1.

B. Primary Efficacy Outcome Analysis

1. Primary Analysis

The primary assessment of efficacy will use a nonparametric approach. The van Elteren test will be used to test the null hypothesis of no difference in duration of severe OM between each active arm and placebo. The analysis will be stratified by the randomization strata, HPV status and chemotherapy schedule. The non-parametric van Elteren test combines the stratum-specific Wilcoxon rank-sum statistics with weights inversely proportional to stratum sizes. The van Elteren test carried out using the ITT population will be considered the primary test of GC4419 efficacy.

The duration of severe OM will be described by presenting overall incidence of severe OM and the percentiles of duration by treatment group for all patients in the selected analysis population.

2. Sensitivity Analyses

The primary analysis of duration of severe OM for the ITT and Treated populations imputes duration for subjects with incomplete follow-up for OM with the median observed duration among subjects in the same dose group as described in Section VIII.A.1. Because missing data will be imputed only once with other observed values in the dataset, the variability of duration in the primary analysis may be less than it otherwise would have been had complete follow-up for OM occurred in all subjects.

To assess the impact of the primary analysis' single imputation of missing data the clinical study report will include the following sensitivity analysis for the ITT population:

1. For each subject with incomplete follow-up, the analysis will impute duration by substituting the duration through random selection of a subject in the imputation set, rather than selection of the median as specified for the primary analysis. If no such subject exists, the analysis will randomly select a duration from the uniform distribution between the censored duration for the subject being imputed and 75 days.
2. Using the observed and imputed durations selected in Step 1, perform the van Elteren test, stratified by HPV status and cisplatin schedule at randomization.
3. Perform Steps 1 and 2 100 times.

The reported test for the sensitivity analysis will be median of the 100 calculated p-values. The range and 25th and 75th percentiles of the van Elteren test p-values will also be reported.

C. Secondary Efficacy Outcome Analysis

Cumulative Incidence of Severe OM. Incidence endpoints will be analyzed using the Cochran-Mantel-Haenszel test stratified by the factors used in randomization.
Onset of Severe OM. Cumulative IMRT fractions to onset of severe OM will be described for each treatment group and placebo using Kaplan-Meier estimates. Subjects without severe OM will be censored at their last OM assessment. Estimates of median fractions of IMRT at onset will be summarized for each treatment group separately. Estimates of the 25th and 75th percentiles will also be included. Groups will be formally tested using a stratified log-rank test.
On an exploratory basis, analyses will also be generated for time in calendar days relative to IMRT start and for cumulative IMRT dose delivered at onset of severe OM.

D. Exploratory Efficacy Analyses

Duration of Severe OM in Subjects with Severe OM. The duration of severe OM in subjects with severe OM will be described by presenting overall incidence of severe OM and the percentiles of duration by treatment group.

Onset of Severe OM in Subjects with Severe OM. Cumulative IMRT dosage to onset of severe OM will be described using Kaplan-Meier estimates. Subjects without severe OM will be excluded. Estimates of median IMRT at onset will be summarized for each treatment group separately. Estimates of the 25th and 75th percentiles will also be included. Analyses will also be generated for time in calendar days relative to IMRT start and for number of IMRT fractions delivered at onset of severe OM.

Instances of Severe OM Lasting ≥ 7 Days. The following two analyses will be generated to compare severe OM durations that last seven or more days across treatment groups:

- The number of instances of severe OM lasting seven or more days will be described using descriptive statistics.
- The proportion of subjects with at least one episode of severe OM lasting seven or more days will be presented.

Analyses of Cumulative Incidence of Severe OM. Cumulative incidence of severe OM will be compared across treatment groups by presenting the number and percent of subjects with any occurrence of WHO Grade 3 or 4 OM through the end of post-IMRT follow-up and through cumulative delivery of 20-29, 30-39, 40-49, and 50-59 Gy of IMRT.

Analyses of Duration and Cumulative Incidence of Grade 4 OM. The duration and cumulative incidence of Grade 4 OM from the first IMRT fraction through the last IMRT fraction will be presented using descriptive statistics.

AUC Analyses. AUCs of the OM-severity vs. cumulative IMRT dose curves will be compared across treatment groups using descriptive statistics.

Severe OM Prior to Week 6, Visit 2. The number and percentage of patients with severe OM on more than one visit prior to Week 6, Visit 2 will be listed and summarized with descriptive statistics as a potential way of characterizing response to treatment.

Total Number of Severe OM Days. The total number of severe OM days through the end of IMRT will be summarized with descriptive statistics and presented in a box and whisker plot by treatment group.

Analyses of Ulcerative OM. The cumulative incidence, onset, and duration of OM analyses defined above for severe OM (Grade 3 or 4) will be repeated for ulcerative OM (Grade 2, 3, or 4).

E. Other Efficacy-Related Summaries

In support of the primary, secondary, and exploratory efficacy outcome analyses, additional figures and analyses may be generated, including the following:

- Swimmers plots -- to allow for a visual comparison of incidence and duration of severe OM across treatment groups. Each patient's OM experience during treatment and follow-up is displayed on a separate row, color-coded with yellow representing Grade 3 OM and red representing Grade 4 OM. Patients will be grouped and presented by treatment assignment.
- Subgroup analyses for hypothesis generation, based on the following subgroups:
    - Baseline HPV status

- Chemotherapy schedule
- Tumor type [oral cavity vs. oropharyngeal]
- Site for sites enrolling at least 15 subjects
- Prior SCC surgery vs. no prior surgery

IX. Analyses of Tumor Endpoints

Analyses of tumor endpoints will use data from the ITT population. Analyses will be generated for the whole population and for the sub-groups defined by tumor type (oral cavity tumors and oropharyngeal tumors) and HPV status. Tumor endpoint analyses will also be generated for the Evaluable population.

A. Tumor Outcomes

Locoregional Failure. Locoregional failure is defined as clinical or radiographic evidence of progressive disease at the primary site (local) or the neck (regional). Progression should be confirmed by biopsy, if available. If not, clinically assessed and documented progression is acceptable. The presence of a locoregional failure is captured on the eCRF TUMOR page.

Distant Metastases. Distant metastases is defined as evidence of disease outside of the primary site or neck, and should be confirmed by biopsy where possible. Distant metastases are captured on the eCRF TUMOR page.

Second Primary Neoplasm. A solitary, speculated lung mass or nodule is considered a second primary neoplasm and is captured on the eCRF TUMOR page.

New Cancer. The diagnosis of another malignancy is considered a new cancer and is captured on the eCRF TUMOR page.

B. Analysis of Tumor Outcomes

The frequencies of locoregional failure, distant metastases, second primary neoplasms, and new cancers will be summarized as the number and percent of subjects with each of the protocol-defined timepoints where tumor assessments are made. The number and percent of subjects who died are also presented.

In addition, the following time-to-event analyses will be performed using Kaplan-Meier analysis:

- Overall Survival (OS) is defined as the time from initiation of study drug until death due to any cause. Patients who remain alive will be censored at the last time that the patient is known to be alive.
- Progression Free Survival (PFS) is defined as the time from initiation of study drug until progressive disease or death, whichever comes first. Patients

will be censored at the date of their last tumor assessment visit if neither progression nor death have occurred, or if the patient has gone on to subsequent anti-cancer therapy prior to disease progression.

- Time to Locoregional Failure is defined as the time from initiation of study drug until either local or regional progressive disease has occurred. Patients will be censored at the date of their last tumor assessment visit if locoregional progression has not occurred, if the patient has gone on to subsequent anti-cancer therapy prior to locoregional progression, or if the patient dies without locoregional progression.
- Time to Distant Disease is defined as the time from initiation of study drug until distant metastasis has occurred or a second primary or new cancer has been diagnosed. Patients will be censored at the date of their last tumor assessment visit if distant metastasis or a second primary or new cancer has not occurred, or if the patient dies or goes on to subsequent anti-cancer therapy prior to distant metastasis or diagnosis of a second primary or new cancer.

Median estimates of response time and corresponding 95% Confidence Intervals will be presented in descriptive summaries for Overall Survival, Progression Free Survival, Time to Locoregional Failure, and Time to Distant Disease. Results from Kaplan-Meier analyses will also be presented in figures.

The following exploratory analyses (Uno, 2014) of the time-to-event endpoints defined above may also be performed:

- Ratio (or difference) of t-year event rates.
- Ratio (or difference) of survival function percentiles.
- Ratio (or difference) of restricted mean survival times or restricted time lost.

X. Safety Analyses

Safety analyses will use data from the Treated population.

A. Exposure

1. GC4419 or Placebo

Exposure to GC4419 or Placebo will be assessed with the following measurements:

- cumulative dose;
- the number of doses received by the patient;
- the number of weeks the patient is on treatment.

The number of doses for each subject will be determined from the dosing data entered into the eCRFs on the Study Drug Administration page. These per-subject exposure measurements will be summarized with descriptive statistics, including n, mean (standard deviation), median, and range. These measures will also be categorized into meaningful groups for the summary of the number and percentage of patients in each group. In addition, the percent of planned doses received will be calculated as the number of actual doses received divided by the number of planned doses, expressed as a percent, and summarized using descriptive statistics. The number of planned doses will be equivalent to the number of planned IMRT fractions up to a maximum of 35.

Modifications and interruptions to GC4419 or Placebo will also be summarized by presenting the number and percent of subjects with any missed or modified dose by reason. The number of modifications will be categorized and summarized.

2. IMRT

Exposure to IMRT will be summarized as the cumulative dose of IMRT received in Gy, the number of weeks the patient is on IMRT, and the total number of IMRT doses received. The IMRT dosing data will be determined from the data entered into the eCRFs on the IMRT Administration page. These per-subject exposure measurements will be summarized with descriptive statistics, including n, mean (standard deviation), median, and range. These measures will also be categorized into meaningful groups for the summary of the number and percentage of patients in each group. In addition, the Relative Dose Intensity will be calculated as the actual dose divided by the planned dose, as captured on the eCRFs, expressed as a percent, and summarized using descriptive statistics.

The number of missed doses of IMRT will be summarized with descriptive statistics (n, mean (std), median, minimum, and maximum). The number and percent of patients who missed any IMRT dose will also be presented by reason. In addition, the number and percent of patients who missed 1, 2-4 or 5+ consecutive IMRT dose fractions will be presented.

3. Chemotherapy

Exposure to Cisplatin will be summarized separately for each dosing schedule as the cumulative dose of Cisplatin received in mg/m^2, the number of weeks the patient is on Cisplatin, and the total number of Cisplatin doses received. The Cisplatin dosing data will be determined from the data entered into the eCRFs on the Chemotherapy page. These per-subject exposure measurements will be summarized with descriptive statistics, including n, mean (standard deviation), median, and range. These measures will also be

categorized into meaningful groups for the summary of the number and percentage of patients in each group. In addition, the Relative Dose Intensity will be calculated as the actual dose divided by the planned dose, expressed as a percent, and summarized using descriptive statistics. Planned cumulative chemotherapy dose will be calculated as the first dose in mg/m^2 multiplied by 3 for subjects on a Q3 schedule and by 6 for subjects on a weekly schedule.

Modifications, interruptions, and missed doses of Cisplatin will also be summarized by presenting the number and percent of subjects with any missed or modified dose by reason. The number of doses missed or replaced will be summarized with descriptive statistics. In cases where Cisplatin was substituted with another chemotherapeutic agent, the number and percent of subjects with a replacement in chemotherapeutic agent will be summarized and the new therapy will be listed.

B. Adverse Events

AE data are available to Galera from two sources, the eCRFs and the SAE forms. While reconciliation will be performed, the production of data summaries and listings will use the clinical data collected on the eCRFs.

AEs will be coded using the version 18.0 of MedDRA, associating lower-level terms with preferred terms and system organ classes by the primary hierarchy. Two sets of AE tables will be generated. The first set will display counts and percentages of subjects who reported at least one AE in each system organ class represented in the AE data. Within each system organ class, the tables will display the counts and percentages of subjects reporting at least one AE, as designated by the preferred terms. The second set of tables will display counts and percentages of subjects who reported at least one AE for each preferred term.

AE summaries will include treatment-emergent AEs (TEAEs), that is, AEs with an onset date on or after the date on which CTM was first dispensed, as recorded on the AE eCRF. Adverse events that exist before the initiation of study treatment but worsen in severity during the study will also be included as treatment-emergent.

The summary tables organized by system organ class and preferred term will be sorted by decreasing order of frequency of MedDRA system organ class code, and then, within that, by decreasing order of frequency of AE preferred term in the Total column. The summary tables organized by preferred term only will be sorted by decreasing order of frequency of MedDRA preferred term.

The following AE summaries will be produced:

- Overall summary of TEAEs

- All TEAEs
- TEAEs related to Study Drug. This table will include TEAEs with a drug relationship of "Possibly Related" or "Related." It will also include TEAEs with missing drug relationships. An AE reported by a subject more than once will be included in this table if at least one of the drug association relationship is one of the relationships listed here and will be represented in the most relatedness category.
- TEAEs related to IMRT. This table will include TEAEs with a drug relationship of "Possibly Related" or "Related." It will also include TEAEs with missing drug relationships. An AE reported by a subject more than once will be included in this table if at least one of the drug association relationship is one of the relationships listed here and will be represented in the most relatedness category.
- TEAEs related to Chemotherapy. This table will include TEAEs with a drug relationship of "Possibly Related" or "Related." It will also include TEAEs with missing drug relationships. An AE reported by a subject more than once will be included in this table if at least one of the drug association relationship is one of the relationships listed here and will be represented in the most relatedness category.
- Serious TEAEs
- Serious TEAEs related to Study Drug. This table will include serious TEAEs with the same constraints as TEAEs related to Study Drug.
- Serious TEAEs related to IMRT. This table will include serious TEAEs with the same constraints as TEAEs related to IMRT.
- Serious TEAEs related to Chemotherapy. This table will include serious TEAEs with the same constraints as TEAEs related to Chemotherapy.
- TEAEs leading to study drug withdrawal. This subset includes TEAEs with a Study Drug Action Taken of "Drug Permanently Withdrawn."
- TEAEs leading to IMRT withdrawal. This subset includes TEAEs with an IMRT Action Taken of "Radiation Permanently Withdrawn."
- TEAEs leading to withdrawal of Chemotherapy. This subset includes TEAEs with a Chemotherapy Action Taken of "Drug Permanently Withdrawn."
- TEAEs with CTCAE Grade ≥ 3.
- TEAEs by Severity. On this table, treatment groups will be subdivided into five potential grades of AE severity, based on the CTCAE, version 4.03 — Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Life threatening) or Grade 5 (Death). TEAEs missing a severity grade will not be included. An AE reported by a subject more than once will be represented in the most severe category.
- Priority TEAEs. This table will include priority TEAEs and toxicities of special interest that are listed in the protocol or identified during the DMC preparation meetings. They are considered medically relevant for treatment oversight, and include the following: Dizziness, Lightheadedness, Grade 3+

Nausea, Grade 3+ Vomiting, Paresthesia, Flushing, Hypotension, Thromboembolic events related to IV access, Infections related to IV access, Renal events, Tinnitus, Hearing loss, Weight loss, Fatigue, Radiation Dermatits, and Dysgeusia.

- TEAEs by Preferred Term

Summary tables presenting counts of TEAEs will also be generated, organized by system organ class and preferred term and by preferred term alone.

The following AE listings will be produced:

- All TEAEs, sorted chronologically within patient. This listing includes preferred term, onset and end time, and other relevant information.
- TEAEs related to Study Drug.
- TEAEs related to IMRT.
- TEAEs related to Chemotherapy.
- All serious TEAEs.
- All serious TEAEs related to Study Drug.
- All serious TEAEs related to IMRT.
- All serious TEAEs related to Chemotherapy.
- TEAEs leading to discontinuation of Study Drug. This subset includes TEAEs with an Action Taken of "Drug Permanently Withdrawn."
- TEAEs leading to discontinuation of IMRT. This subset includes TEAEs with an Action Taken of "Radiation Permanently Withdrawn."
- TEAEs leading to discontinuation of Chemotherapy. This subset includes TEAEs with an Action Taken of "Drug Permanently Withdrawn."
- TEAEs with CTCAE Grade ≥ 3.
- TEAEs resulting in Death.
- Priority TEAEs. This listing will include priority TEAEs and toxicities of special interest that are listed in the protocol or identified during the DMC preparation meetings. They are considered medically relevant for treatment oversight, and include the following: Dizziness, Lightheadedness, Grade 3+ Nausea, Grade 3+ Vomiting, Paresthesia, Flushing, Hypotension, Thromboembolic events related to IV access, Infections related to IV access, Renal events, Tinnitus, Hearing loss, Weight loss, Fatigue, Radiation Dermatits, and Dysgeusia.

C. Nausea and Vomiting Adverse Events

The following AE summaries and listings, outlined in a separate data display document developed for this study[4], will be generated for nausea and vomiting (N/V) AEs:

- Summary of N/V TEAEs by severity (Grade 1-2, 3, 4, 5), overall and by timing of onset (within 24 hours of Cisplatin or on Days 2-5 after Cisplatin).
-
- Listing of N/V TEAEs.
- Listing of antiemetic Concomitant Medications.

D. Xerostomia and Trismus

Xerostomia and trismus data will be summarized at Baseline and at the 3, 6, 9, 12, 16, 20, and 24 Month Post-IMRT Follow-up visits. Descriptive statistics and change from baseline will be presented for the measurement of the maximum opening of the mouth and the self-reported xerostomia ratings of difficulty speaking, difficulty swallowing, mouth dryness, throat dryness, and mouth/tongue discomfort. Data listings of xerostomia ratings and trismus measurements will also be generated.

E. Clinical Laboratory Results

Laboratory test results (including hematology and serum chemistry,) and abnormal laboratory values will be presented in data listings. Summaries of actual values and changes from baseline will be presented by treatment group for each assessment time point, beginning with the Screening visit. Shift tables summarizing the counts and percentages of subjects who were normal at baseline, but who became abnormal subsequently, will also be displayed for those per-protocol lab parameters that are graded according to the Common Toxicity Criteria (CTCAE v. 4.03).

F. Vital Signs

Vital signs (including supine systolic and diastolic blood pressure, heart rate, respiratory rate, temperature, weight, and body mass index) will be presented in a data listing. Body temperature will be collected in °F or °C, but reported in °C. Weight will be collected in pounds (lb) or kilograms (kg), but reported in kg.

G. Concomitant Medications

Concomitant medications (CMs) will be coded using the latest version of the WHO Drug dictionary. A summary table will be organized to display the anatomical main class of each coded CM and, within that, the pharmacological subgroup (3rd level) of the coded CM. The summary table will display counts and percentages of subjects who reported using at least 1 CM in each represented pharmacological subgroup.

A listing of CMs will be generated, ordered within subject by the "Start Date." The listing will display the recorded term from the CRF and, adjacent to that, the WHO Drug pharmacological subgroup that appears in the tables.

A separate listing of antiemetic CMs, as specified in Appendix 7 of the protocol, will also be generated to assess prophylactic use in the treatment of nausea and vomiting induced by chemotherapy

H. Electrocardiogram (ECG)

ECG results (VR, PR, QRS, QT, machine-read QTc, manually calculated QTcF QTcB, and the overall ECG result) will be presented in data listings.

I. ECOG Performance Status

ECOG Performance Status will be presented in data summaries and listings for all time points at which it is collected.

XI. Analysis of Patient Reported Outcomes

The Oral Mucositis Daily Questionnaire (OMDQ) is used to capture daily quality of life assessments during the IMRT treatment period, and is recorded daily by the patient. These assessments will be summarized using data from the Treated population, and are considered exploratory endpoints.

OMDQ Question 2 will be summarized using descriptive statistics (n, mean (std), median, range) for the ratings of overall mouth and throat soreness. All OMDQ items will be presented in a data listing.

XII. Analysis of Health and Economic Outcomes

The assessment of health and economic outcomes includes the incidence and duration of opioid use and the insertion of and need for use of gastrostomy tube feeding, complications of indwelling venous access catheters, and unplanned hospitalizations, ER visits, or office visits. These assessments will be summarized using data from the Treated population, and are considered exploratory endpoints. The analysis of these endpoints is described in a separate document outlining the data outputs and displays for this study[4].

The use of gastrostomy tubes and venous access catheters and unscheduled hospital, ER or office visits will be summarized according to treatment assignment by presenting the number and percent of subjects using each device or medical service. Complications of indwelling venous access devices and reasons for unscheduled hospital or office visits will be summarized.

Patient-reported narcotic use will be summarized by treatment assignment by presenting the number and percent of patients using opioid narcotics. In addition, descriptive statistics (n, mean (std), median, 25^{th}-75^{th} percentiles) will be presented for total opioid narcotic dose in morphine equivalents, time to first opioid narcotic use, and cumulative IMRT at first opioid narcotic use.

XIII. Biomarker Analyses

Biomarker analyses will use data from the Treated population, and will be presented by treatment assignment.

A listing of each patient's circulating cytokine and protein levels will be presented by time point. The analysis of cytokines and mRNA with respect to clinical endpoints is beyond the scope of this SAP and will be specified at a later date.

XIV. References

1. Sonis ST. The impact, biology and therapeutic opportunities of oral mucositis. Oral Oncol 2009; 45:1015-20.

2. Sonis ST, Elting LS, Keefe D. et al. Perspectives on cancer therapy-induced mucosal injuty: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer 2004; 100 (9 Suppl): 1995-2025.

3. Traynor AM, Richards GM, Hartig GK, et al. Comprehensive IMRT plus weekly cisplatin for advanced head and neck cancer: The University of Wisconsin experience. Head and Neck 2010: 32:599-606.

4. Holmlund, J. Planning for Galera Phase 2 data displays sept 2015. Unpublished, 2015.

5. Spielberger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. New Engl J Med 2004; 351: 2590-8.

APPENDIX 1: SCHEDULE OF ASSESSMENTS

Assessments	Screening Phase	Active Phase										Post-Active Phase	
	Within 28 days of IMRT start	Baseline IMRT Day 1	Wk 1 Days 2 – 7	Wk 2 Days 8 - 14	Wk 3 Days 15 - 21	Wk 4 Days 22 - 28	Wk 5 Days 29 - 35	Wk 6 Days 36 - 42	Wk 7 Days 43 - 49	Last Day of IMRT or Early Term[1]	Post-IMRT Wks 1 through 8 (±2 D)[2]	Months 3, 12, & 24 Post-IMRT (±30 D)	Months 6, 9, 16 & 20 Post-IMRT (±30 D)
Informed consent/HIPAA	X												
Inclusion/exclusion criteria[3]	X	X											
Medical and HNC histories[4]	X												
Complete PE[5]	X									X			
Height	X												
Symptom-directed PE						X							
Dental exam/IMRT clearance	X												
Vital signs, ECOG, weight[6]	X	X				X			X	X			
Record BSA[7]		X		X	X	X	X	X	X				
Serum pregnancy test[8]	X												
Tumor Imaging[9]	X											X	
Clinical Tumor Assessment[10]										X		X	X
Concomitant medications[11]	X	X	Weekdays							X	X		
Adverse Events[12]		X	Weekdays							X	X		
ECG (12-lead)[13]	X	X				X				X			
OM assessment[14]	X	X	X	Twice-weekly					X	X	X		
Trismus assessment[15]		X										X	
Xerostomia assessment[16]		X										X	
OMDQ, analgesic recording[17]		X	Daily including weekends							X	X		
Gastrostomy tube placement/use		X	X	Twice-weekly					X	X			
Unscheduled office visits, ER visits, or hospitalizations				Twice-weekly					X	X			
Placement of indwelling venous catheters	X												
Blood draw: Lab safety tests[18]	X	X	X	X	X	X	X	X	X	X[19]			
Blood draw: PK samples[20]		X	X			X							
Blood draw: Cytokines[21]	X	X		OM Visit 2		OM Visit 2		OM Visit 2		X			
Blood draw: RNA[22]	X									X			
Dosing GC4419[23]		X	Days 2-5	Days 8-12	Days 15-19	Days 22-26	Days 29-33	Days 36-40	Days 43-47				

[1] If a patient ends study participation early and withdraws consent, all last day of IMRT procedures should be completed.
[2] The Post-IMRT Weeks 1 through 8 Follow-up Visits will be scheduled based on the last day of IMRT. Patients will be seen weekly (every 7 ± 2 calendar days) until WHO < 2.
[3] See protocol Sections 7.1 and 7.2.
[4] The HNC history should include tumor HPV status (if known), staging (AJCC) information, prior treatments, and confirmation of histopathological diagnosis of SCC. Medical conditions and illnesses that have occurred since the patient signed the ICF up until the date of randomization should be recorded as medical history. Medical history also includes tobacco and alcohol use history.
[5] At the Screening and Last Day of IMRT Visits, a complete physical examination will be conducted.
[6] Vital signs (temperature, systolic and diastolic blood pressures, heart rate, and respiration rate), body weight, and ECOG will be obtained and recorded at the Screening and Baseline Visits, once during Weeks 4 and 7, and at the Last Day of IMRT Visit. All vital signs should be measured following 2 minutes of rest in the sitting position.
[7] For patients receiving tri-weekly cisplatin, body surface area (BSA) will be recorded to confirm cisplatin dosing at the Baseline Visit and once during Weeks 4 and 7. For patients receiving weekly cisplatin, body surface area (BSA) will be recorded to confirm cisplatin dosing at the Baseline Visit and once per week until chemotherapy is completed.
[8] For a woman of childbearing potential, serum pregnancy test must be performed at the Screening Visit.
[9] Radiographic imaging must be performed within 60 days prior to the first day of IMRT and at Months 12 and 24 Post-IMRT for all patients. Patients treated definitively (as opposed to post-operatively) will also undergo imaging at Month 3 Post-IMRT to assess tumor response/clearance to the degree possible. Radiographic imaging is highly recommended at any Post-IMRT follow up visit at which disease progression is suspected by the treating physician. If radiographic imaging is performed, both local/regional recurrence and distant metastases should be evaluated.
[10] At the Last Day of IMRT Visit, a clinical tumor assessment will be conducted. A neck and oral exam is sufficient at the Last Day of IMRT Visit if disease progression is not suspected. If disease progression is suspected, a laryngopharyngoscopy should be conducted. At Months 3, 6, 9, 12, 16, 20, and 24, a laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) is required if disease progression is suspected to evaluate local/regional or distant progression.
[11] All concomitant therapies (e.g., prescription and over-the-counter medications) taken by patients on or after the date of randomization through 30 days following the last GC4419/placebo, IMRT or cisplatin (i.e. whichever occurs last) dose will be collected in the CRF except for narcotics (narcotics will only be captured from the Baseline Visit through the Last Day of IMRT Visit). Additionally, any concomitant therapies used to treat any serious or related adverse event will be recorded in the CRF.
[12] AEs and SAEs with onset dates on or after the date of randomization through 30 days following the last GC4419/placebo, IMRT or cisplatin (i.e. whichever occurs last) dose will be recorded on the CRF. All patients with SAEs will be followed until the events resolve, stabilize, become chronic, the patient completes the study, or the patient is lost to follow-up.
[13] Ventricular rate and P-R, QRS, QT, and QTc intervals will be assessed and recorded. An ECG will be conducted at the Screening and Baseline Visits, during Week 4, and at the Last Day of IMRT Visit.
[14] All OM assessments must be performed by trained evaluators. The extent of the patient's OM will be scored using the WHO OM toxicity scale. OM assessments will be completed at the Screening Visit, at the Baseline Visit, and twice weekly (no less than 48 hours apart) within each 5-day IMRT period. For Week 1, the first OM assessment will occur at the Baseline Visit; one additional OM assessment must occur at least 48 hours later during the week. The extent of the patient's OM will be scored using the WHO OM toxicity scale. If a patient has ulcerative OM (WHO ≥ 2) at the Last Day of IMRT Visit, visits for OM will be repeated weekly (every 7 days ± 2 days) until the WHO score is 0 or 1 or the patient is 8 weeks post-IMRT, whichever occurs first.
[15] Using a Sponsor-provided ruler, the distance in millimeters between the incisal edges of the mandibular and maxillary incisors at midline will be measured to determine the maximum opening of the mouth that the patient can achieve at the Baseline Visit and Months 3, 6, 9, 12, 16, 20, and 24 Post-IMRT Visits.
[16] To assess xerostomia, patients will complete a VAS instrument at the Baseline Visit and 3, 6, 9, 12, 16, 20, and 24 Month Post-IMRT Visits.

[17] Beginning at the Baseline Visit (IMRT Day 1) and through the Last Day of IMRT Visit, patients will complete a daily diary (including weekends) containing the OMDQ and questions regarding narcotic use. If a patient returns for weekly visits following the last day of IMRT because WHO ≥ 2, the OMDQ only will be completed at the time of the weekly clinic visit.

[18] Clinical laboratory measurements will be conducted at the Screening Visit, twice during Week 1 (once at the Baseline Visit and again on Day 3, 4 or 5), and once weekly from Week 2 through the last day of IMRT. Clinical laboratory measurements at these visits will include the hematology profile (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count. Differential to include total neutrophils, lymphocytes, monocytes, eosinophils, and basophils) and chemistry profile (glucose, BUN, creatinine, sodium, potassium, calcium, albumin, total protein, total bilirubin, direct bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), chloride, phosphate, bicarbonate).

[19] If safety labs have already been drawn during the study week in which the last day of IMRT or early termination visit falls, then lab safety tests (chemistry and hematology profiles) do not need to be conducted on the last day of IMRT or at the early termination visit. If safety labs have not been drawn during the current study week at the time of the early termination visit or on the last day of IMRT, then safety labs should be drawn on that day. Safety labs only need to be drawn once per study week after Week 1.

[20] Blood samples will be collected for GC4419 pharmacokinetic (PK) measurements at Baseline, Day 2, Day 22 and Day 23. See Table 10 in the protocol for additional information.

[21] For cytokine analysis, blood samples will be collected at the Screening Visit (within 28 days of IMRT start but at least 72 hours prior to Baseline), at the Baseline Visit, Week 2 OM Visit 2, Week 4 OM Visit 2, Week 6 OM Visit 2, and at the Last Day of IMRT Visit. Whenever possible, blood draws for cytokine analysis should be conducted at OM Visit 2 for each protocol-specified week; however, if blood draws must be taken on another day within a given week, it will not be considered a protocol deviation.

[22] If the patient consents separately, blood samples will be collected at the Screening Visit (within 28 days of IMRT start but at least 72 hours prior to Baseline) and at the Last Day of IMRT Visit for the assessment of gene expression patterns prior to receiving the first dose of GC4419 and upon completion of GC4419 doses.

[23] GC4419 will be administered up to 35 times: weekly, Monday through Friday, beginning at Baseline (IMRT Day 1) and through Study Day 47 (end of IMRT). IMRT must begin no longer than 60 min following the end of the GC4419 infusion. If IMRT is not received on any given day due to a treatment break or unforeseen circumstances, GC4419 should not be administered on that day. Patients should resume GC4419 administration when IMRT resumes.

APPENDIX 2: HYPOTHETICAL EXAMPLES FOR IMPUTING MEDIAN DURATION AMONG SUBJECTS WITH UNKNOWN SEVERE OM RESOLUTION

Consider the following dataset, where the first four subjects have known duration of severe OM, while the fifth subject's severe OM, indicated by an asterisk, is known to have continued for at least seven days before the subject was lost to follow-up:

Ex. 1. Imputing severe OM duration for subjects without OM resolution (part 1)

Subject	OM duration
1	3 days
2	4
3	9
4	0
5	7*

The analysis plan states that the duration should be imputed using the median duration of severe OM amongst subjects who experienced severe OM for at least the same duration. In this example, it is straightforward, then, to calculate the imputed severe OM duration for Subject 5 as 9, the median duration of the only subject (Subject 3) with a duration of at least 7 days.

If, instead, Subject 5's duration had been 17 days instead of 7, no subject in the dataset would have had OM at least as long as Subject 5. In this case, the analysis plan states to use 15, 30, 60, 75, or 100 days, whichever is smallest yet still greater than the known duration at the point of loss to follow up. In this case, then, we would assign Subject 5's duration as 30 days.

Suppose we modify the example above such that Subject 3's duration is censored at 9 days:

Ex. 2. Imputing severe OM duration for subjects without OM resolution (part 2)

Subject	OM duration
1	3 days
2	4
3	9*
4	0
5	7*

Now, both Subject 3's and Subject 5's duration require imputation. For Subject 5's imputation, we could either use a value of 9 (*i.e.*, Subject 3's duration at censoring) or 15 (*i.e.*, Subject 3's imputed duration using the analysis plan's conventions).

The analysis plan states that the longest censored durations should be imputed first and to use these imputed values for any subsequent subjects who may require imputation. That is, for the situation described above, we would use Subject 3's imputed value of 15 days to impute Subject 5's duration. Accordingly, in this small example dataset, Subject 5's duration would also be 15.

APPENDIX 3: HYPOTHETICAL EXAMPLES FOR IMPUTING MEDIAN DURATION AMONG SUBJECTS WITHOUT SEVERE OM BEFORE LOSS TO FOLLOW

Consider a subject lost to follow-up for severe OM at Day 30 who did not develop severe OM during this time. Following imputation of any censored durations as outlined in Appendix 2, the dataset in Example 3 includes the 5 subjects in the same treatment group who were followed for severe OM for at least 30 days without developing severe OM through Day 30.

Ex. 3. Imputing severe OM duration for subjects without OM before loss to follow-up

Subject	Onset day of OM	OM duration
1	NA	0 days
2	43	20
3	NA	0
4	32	15
5	57	30

The analysis plan states that the duration is imputed with the median duration among subjects within the same treatment group who are free of severe OM for at least that length of follow-up. In this example, the median duration among these subjects is 15 days.