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| **Study Title:** | 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 |
| **Sponsor:** | Galera Therapeutics, Inc. |
| **IND Number:** | 111,539 |
| **Protocol ID:** | GT-201 |
| **Medical Monitor:** | Jon T. Holmlund, MD |
| **Protocol Version/Date:** | Amendment 6: 19 October 2017 |

# STUDY ACKNOWLEDGEMENT

Study Title: 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

Final Protocol: 19 October 2017

This protocol has been approved by Galera Therapeutics, Inc. The following signature documents this approval.

Jon T. Holmlund, MD
Chief Medical Officer
Galera Therapeutics, Inc.

## Investigator Statement

I have read the attached protocol and appendices dated 19 October 2017 and agree to abide by all provisions set forth therein. I will provide copies of the protocol and other pertinent information to all individuals responsible to me who will assist with the study.

I agree to comply with the International Conference on Harmonisation, Tripartite Guideline on Good Clinical Practice (ICH, GCP) and applicable FDA regulations/guidelines set forth in 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312.

I agree to ensure that Financial Disclosure Statements will be completed before study initiation, during the studies if there are changes that affect my financial disclosure status, and one year after study completion by:

- myself (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub-investigators (including, if applicable, their spouses [or legal partners] and dependent children)

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

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

_____ _____

Signature of Principal Investigator Date (DD MMM YYYY)

_____

Printed Name of Principal Investigator

# 1. SYNOPSIS

**Name of Sponsor/Company:**
Galera Therapeutics, Inc.

**Name of Investigational Product:**
GC4419

**Name of Active Ingredient:**
GC4419 (Manganese, dichloro[(4aS,13aS,17aS,21aS)-1,2,3,4,4a,5,6,12,13,13a,14,15,16,17,17a,18,19,20,21,21a-eicosahydro-11,7- nitrilo-7H-dibenzo[b,h][1,4,7,10] tetraazacycloheptadecine-κN5, κN13, κN18, κN21, κN22]-) is a water soluble, highly stable, low molecular weight manganese-containing macrocyclic ligand complex whose activity mimics that of naturally occurring SOD enzymes.

**Title of Study:**
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

**Number of Study Center(s):** Approximately 60 sites in the United States and approximately 5 sites in Canada.

**Estimated Enrollment Period:** 22 months

| **Studied period (years):** | **Phase of development:** 2 |
|---|---|
| Estimated date first patient enrolled: October 2015<br>Estimated date last patient completed Active Phase: July 2017 | |

**Objectives:**

Primary:

- 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

Secondary:

- To evaluate and compare the safety of GC4419 at the treatment assignment of each respective arm
- 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 30$^{th}$ 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 onset of severe OM expressed as the number of IMRT fractions delivered at onset of severe OM
- To evaluate and compare the effect of treatment assignment on tumor outcomes (locoregional failure, distant metastases, progression-free survival, overall survival)

Exploratory:

- 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 8 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 assessments (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 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

**Methodology:**

GT-201 is a randomized, double-blind, placebo-controlled, multi-center study conducted in the U.S. to evaluate GC4419 administered IV to reduce the duration, incidence, and severity of radiation induced oral mucositis in patients receiving chemoradiation for SCCHN, limited to the oral cavity or oropharynx. Patients will be randomized equally to 1 of 3 treatment arms:

- Arm A: 30 mg GC4419 per day (60 min IV infusion to complete within 60 minutes prior to IMRT), concurrent with daily fractions of IMRT (2.0-2.2 Gy) to a total of 60-72 Gy over approximately 7 weeks, plus cisplatin administered 80-100 mg/m$^2$ once every three weeks for 3 doses or 30-40 mg/m$^2$ once weekly for 6-7 doses (investigator's choice)
- Arm B: 90 mg GC4419 per day (60 min IV infusion to complete within 60 minutes prior to IMRT), concurrent with daily fractions of IMRT (2.0-2.2 Gy) to a total of 60-72 Gy over approximately 7 weeks, plus cisplatin administered 80-100 mg/m$^2$ once every three weeks for 3 doses or 30-40 mg/m$^2$ once weekly for 6-7 doses (investigator's choice)
- Arm C: Placebo daily (60 min IV infusion to complete within 60 minutes prior to IMRT), concurrent with daily fractions of IMRT (2.0-2.2 Gy) to a total of 60-72 Gy over approximately 7 weeks, plus cisplatin administered 80-100 mg/m$^2$ once every three weeks for 3 doses or 30-40 mg/m$^2$ once weekly for 6-7 doses (investigator's choice)

Note: Planned radiation fields in all 3 arms must include at least 2 oral sites (buccal mucosa, floor of mouth, tongue, soft palate) with each site receiving a dose of at least 50 Gy.

All patients will be assessed twice weekly for oral mucositis per WHO grading criteria until the completion of IMRT, and once weekly thereafter (if necessary) for 8 weeks, or until oral mucositis resolves to ≤ Grade 1. Sparse PK sampling will be sought from all patients.

**Number of patients (planned):**

Approximately 216 total to ensure that roughly 65 patients per arm receive study drug and complete their IMRT course, with an assumed proportion of early discontinuations of 10%.

**Diagnosis and main criteria for inclusion:**

Inclusion Criteria:

1. Pathologically-confirmed diagnosis of squamous cell carcinoma of the head and neck, defined as SCC of the oral cavity or oropharynx that will be treated with cisplatin plus concurrent IMRT

Note: Patients with unknown primary tumors whose treatment plan matches the requirements specified in Inclusion Criteria #2 and #3 below are eligible for the trial.

2. Treatment plan to receive a continuous course of IMRT delivered as single daily fractions of 2.0 to 2.2 Gy with a cumulative radiation dose between 60 Gy and 72 Gy. Planned radiation treatment fields must include at least two oral sites (buccal mucosa, floor of mouth, tongue, soft palate) that are each planned to receive a total of ≥ 50 Gy. Patients who have had prior surgery are eligible, provided they have fully recovered from surgery, and patients who may have surgery in the future are eligible.

   Note: Unavoidable doses of at least 50 Gy, to include entrance, exit, and scatter doses, still constitutes planned radiation.

3. Treatment plan to receive standard cisplatin monotherapy administered either every three weeks (80-100 mg/m$^2$ for 3 doses) or weekly (30-40 mg/m$^2$ for 6-7 doses). The decision on which cisplatin regimen to use in combination with IMRT and GC4419 will be at the discretion of the investigator.
4. Age 18 years or older
5. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
6. Adequate hematologic function as indicated by:
   - Absolute neutrophil counts (ANC) ≥ 1,500/mm$^3$
   - Hemoglobin (Hgb) ≥ 9.0 g/dL
   - Platelet count ≥ 100,000/mm$^3$
7. Adequate renal and liver function as indicated by:
   - Serum creatinine acceptable for treatment with cisplatin per institutional guidelines
   - Total bilirubin ≤ 1.5 x upper-normal limit (ULN)
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN
   - Alkaline phosphatase ≤ 2.5 x ULN
8. Human papilloma virus (HPV) status in tumor has been documented using tumor immunohistochemistry for HPV-p16 or other accepted test
9. Serum pregnancy test negative for females of childbearing potential
10. Males and females must agree to use effective contraception starting prior to the first day of treatment and continuing for 30 days after the last dose of GC4419
11. Properly obtained written informed consent

Exclusion Criteria:

1. Tumor of the lips, larynx, hypopharynx, nasopharynx, sinuses, or salivary glands
2. Metastatic disease (Stage IV C)
3. Prior radiotherapy to the region of the study cancer or adjacent anatomical sites or more than 25% of total body marrow-bearing area (potentially interfering with chemo-tolerance)

4. Prior induction chemotherapy
5. Receiving any approved or investigational anti-cancer agent other than those provided for in this study
6. Concurrent participation in another interventional clinical trial or use of another investigational agent within 30 days of study entry

   Note: Patients who are participating in non-interventional clinical trials (e.g., QOL, imaging, observational, follow-up studies, etc.) are eligible, regardless of the timing of participation.
7. Requirement for significantly modified diet (liquids and/or nothing by mouth) due to compromised oral/pharyngeal function at baseline
8. Complete reliance on parenteral or gastrointestinal tube-delivered nutrition at baseline

   Note: Patients who have gastrostomy tubes prophylactically placed <u>are</u> eligible. Patients receiving supplemental nutrition through a gastrostomy tube at baseline <u>may be</u> eligible depending on diet.
9. Malignant tumors other than HNC within the last 5 years, unless treated definitively and with low risk of recurrence in the judgment of the treating investigator
10. Active infectious disease excluding oral candidiasis
11. Presence of oral mucositis (WHO Score ≥ Grade 1) at study entry
12. Known history of HIV or active hepatitis B/C (patients who have been vaccinated for hepatitis B and do not have a history of infection are eligible)
13. Female patients who are pregnant or breastfeeding
14. Known allergies or intolerance to cisplatin and similar platinum-containing compounds
15. Requirement for concurrent treatment with nitrates or other drugs that may, in the judgment of the treating investigator, create a risk for a precipitous decrease in blood pressure.
16. Medical history that includes any condition, or requires the use of concomitant medications which, in the investigator's judgment, are associated with or create a risk of increased carotid sinus sensitivity, symptomatic bradycardia, or syncopal episodes.

**Investigational product, dosage and mode of administration:**

GC4419 is formulated as a clear solution at a concentration of 3 mg/mL or 9 mg/mL (Arm A [30mg] and B [90mg], respectively) in 26 mM sodium bicarbonate-buffered 0.9 wt. % saline for parenteral administration (drug product). GC4419 will be presented in 35 single use amber vials, one vial per day. Vials will be filled with 11 mL of GC4419, of which 10 mL be added into a 250 mL bag of normal saline, for daily IV administration over 60 minutes. GC4419 will be administered concurrent with daily fractions of IMRT (2.0-2.2 Gy) to a total of 60-72 Gy over 7 weeks, plus cisplatin administered 80-100 mg/m$^2$ once every three weeks for 3 doses or 30-40 mg/m$^2$ once weekly for 6-7 doses (investigator's choice).

**Duration of treatment:**

Approximately 35 doses, on days in which IMRT is administered, Monday-Friday, for approximately 7 weeks. GC4419 will be administered within 1 hour prior to each IMRT treatment.

**Reference therapy, dosage and mode of administration:**

Placebo will consist of 26 mM sodium bicarbonate-buffered 0.9 wt. % saline for parenteral administration only (Arm C). Placebo will be presented in 35 single use amber vials, one vial per day. Vials will be filled with 11 mL of placebo, of which 10 mL be added into a 250 mL bag of normal saline, for daily IV administration over 60 minutes. Placebo will be administered concurrent with daily fractions of IMRT (2.0-2.2 Gy) to a total of 60-72 Gy over 7 weeks, plus cisplatin administered 80-100 mg/m$^2$ once every three weeks for 3 doses or 30-40 mg/m$^2$ once weekly for 6-7 doses (investigator's choice).

**Clinical Laboratory Assessment:** A central laboratory vendor will be utilized.

**Criteria for evaluation:**

Efficacy:

- World Health Organization (WHO) Criteria for Oral Mucositis

Safety:

- National Cancer Institute - Common Terminology Criteria for Adverse Events, version 4.03

Patient-Reported Outcomes:

- Oral Mucositis Daily Questionnaire
- Visual Analogue Scale of Xerostomia

**Safety Monitoring and Toxicity Management:**

1. Adverse/Serious Adverse Event assessments per CTCAE version 4.03 and GCP standards
2. Safety will be monitored by a Data Monitoring Committee.
3. Toxicity requiring 25% GC4419 or PBO dose reduction:
   - Grade 3 flushing
   - Grade 2 or greater hypotension within 2 hours after the start of GC4419/placebo infusion
   - Grade 3 or 4 infusion reaction with GC4419/placebo
   - Grade 4 vomiting despite optimal antiemetic therapy per current ASCO and MASCC guidelines

Two dose reductions for toxicity will be permitted per patient. Patients unable to tolerate GC4419/placebo after two dose reductions must discontinue treatment with the study drug GC4419 but may continue with cisplatin/IMRT at the discretion of the treating investigator.

For other toxicities (including those attributable to cisplatin and IMRT): management per institutional and ASCO guidelines and investigator judgment. Cisplatin toxicities should be managed by modification of the cisplatin dose and schedule, not by substitution of another systemic agent.

OM and xerostomia will NOT be considered adverse events requiring dose modification for the purposes of this study.

**Concomitant Medications/Treatments:**

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

- Low-level laser treatment for OM
- Amifostine (Ethyol®)
- Benzydamine (Difflam®)
- Cetuximab (Erbitux®)
- Glutamine applied topically
- GM-CSF applied topically
- 'Magic mouthwashes' or 'Miracle mouthwashes' are permitted, provided they do not contain:
  - Chlorhexidine
  - Hydrogen peroxide
  - Diphenhydramine (Benadryl®)
  - Tetracycline
  - Any other listed disallowed medications
  - Notes:
    - Topical lidocaine preparations are permitted
    - Diphenhydramine (Benadryl®) administered as tablets for by injection is permitted; only diphenhydramine liquid formulation is prohibited
- MuGard™, Gelclair®, Episil®, or other barrier devices
- Caphosol®
- Nitrates, phosphodiesterase type 5 (PDE 5) inhibitors (e.g., sildanefil, tadalafil, or similar agents) or other drugs that in the judgment of the treating investigator could create a risk of a precipitous decrease in blood pressure are prohibited until at least 24 hours after the last dose of GC4419
- Pyridostigmine or other drugs that in the judgment of the treating investigator could create a risk of increased carotid sinus sensitivity, symptomatic bradycardia, or syncopal episodes.

- Palifermin (Kepivance®) or other keratinocyte or fibroblast growth factor
- Povidone-iodine rinses
- Steroid rinses
- Sucralfate in suspension form (use of sucralfate tablets is not proscribed)
- Other biologic response modifiers – except systemic hematopoietic growth factors for the management of anemia or myelosuppression
- Concurrent approved or investigational anti-cancer therapy (e.g., chemotherapy, immunotherapy, targeted therapy, hormone and biologic therapy) other than the Protocol regimen
- Other investigational agents

All medication restrictions end after post-IMRT OM follow-up is completed unless otherwise noted.

Anti-emetic prophylaxis and hematopoietic growth factor use are permitted per ASCO guidelines. Following ASCO (and MASCC) guidelines for the prevention and management of chemotherapy-induced nausea and vomiting (CINV) is strongly encouraged.

**Statistical methods:**

With 65 patients per arm having received GC4419/placebo and completed their IMRT course (assumes 72 patients enrolled to each treatment arm with a 10% dropout rate), the study will have roughly 80-85% power to detect a reduction in duration in the experimental arm under the following assumed incidence of severe OM and percentiles of the distribution of duration of severe OM:

- GC4419 arms: incidence = 40%; duration (25th, 50th, 75$^{th}$ percentile): 0, 0, 21 days
- Control arm: incidence = 65%; duration (25th, 50th, 75$^{th}$ percentile): 0, 28, 50 days

For each active dose, duration of severe OM will be compared to the placebo duration using the van Elteren test stratified by the factors used in randomization, namely baseline HPV status and planned chemotherapy schedule.

To control the overall 2-sided Type I error rate of 0.05, testing of hypotheses for the primary and secondary endpoints will follow a fixed sequence, continuing until a preceding hypothesis fails to be rejected at the 0.05 level.

Additional details will be provided in the Statistical Analysis Plan. In the event of discrepancies of details between the protocol and the Statistical Analysis Plan, the latter will control the analyses performed.

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# 3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 1: Abbreviations and Specialist Terms**

| Abbreviation or Specialist Term | Definition |
|---|---|
| AE | Adverse Event |
| AJCC | American Joint Committee on Cancer |
| ALT | Alanine Aminotransferase |
| ANC | Absolute Neutrophil Count |
| ASCO | American Society of Clinical Oncology |
| AST | Aspartate Aminotransferase |
| BUN | Blood Urea Nitrogen |
| BSA | Body Surface Area |
| CAT | Computerized Axial Tomography |
| CINV | Chemotherapy-Induced Nausea and Vomiting |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CS | Clinically Significant |
| CT | Computerized Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTV | Clinical Tumor Volume |
| DLT | Dose-Limiting Toxicity |
| DMC | Data Monitoring Committee |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| ET | Early Termination |
| FACT-HN | Functional Assessment of Cancer Therapy – Head and Neck |
| FDA | Federal Drug Administration |
| FHNSI | FACT Head and Neck Symptom Index |
| GCP | Good Clinical Practice |
| GTV | Gross Tumor Volume |
| Gy | Gray |
| Hgb | Hemoglobin |
| HIV | Human Immunodeficiency Virus |

| Abbreviation or Specialist Term | Definition |
|---|---|
| HIPAA | Health Insurance Portability and Accountability Act |
| HNC | Head and Neck Cancer |
| HPV | Human Papilloma Virus |
| HSCT | Hematopoietic Stem Cell Transplantation |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IMRT | Intensity-Modulated Radiation Therapy |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| ISOO | International Society of Oral Oncology |
| IV | Intravenous |
| IVRS | Interactive Voice Randomization System |
| MASCC | Multinational Association of Supportive Care in Cancer |
| MTS | Mouth and Throat Soreness |
| MRI | Magnetic Resonance Imaging |
| NCI | National Cancer Institute |
| NCS | Non-Clinically Significant |
| OAE | Other Significant Adverse Event |
| OC | Oral Cavity |
| OM | Oral Mucositis |
| OMDQ | Oral Mucositis Daily Questionnaire |
| OMWQ | Oral Mucositis Weekly Questionnaire |
| OP | Oropharynx |
| PBO | Placebo |
| PD | Pharmacodynamic |
| PET | Positron Emission Tomography |
| PI | Principal Investigator |
| PK | Pharmacokinetic |
| PRO | Patient Reported Outcome |
| PTV | Planning Tumor Volume |
| QOL | Quality of Life |

| Abbreviation or Specialist Term | Definition |
|---|---|
| REB | Research Ethics Board |
| RNA | Ribonucleic Acid |
| ROS | Reactive Oxygen Species |
| RT | Radiation Therapy |
| RTOG | Radiation Therapy Oncology Group |
| SAE | Serious Adverse Event |
| SAS | Statistical Analysis System |
| SCC | Squamous Cell Carcinoma |
| SCCHN | Squamous Cell Carcinoma of the Head and Neck |
| SOD | Superoxide Dismutase |
| ULN | Upper Limit of Normal |
| WHO | World Health Organization |

# 4. INTRODUCTION

## 4.1. Background

### 4.1.1. Oral Mucositis in Patients Treated with Chemoradiation for HNC

Oral mucositis (OM) is a common, problematic, and painful complication of cancer therapy, particularly in regimens that include radiation to the head and neck.[1] Oral mucositis is readily graded using the commonly-used five-point World Health Organization (WHO) scale, in which:

- Grade 0 = No mucositis
- Grade 1 = Pain and erythema
- Grade 2 = Ulceration but no compromise in diet (able to eat solid food)
- Grade 3 = Ulceration with ability to eat only liquids
- Grade 4 = Ulceration with inability to eat/requirement for tube or parenteral feeding

A majority of patients receiving combined chemoradiotherapy for head and neck cancer (HNC) can be expected to develop severe (WHO Grade 3-4) OM,[2] and nearly all HNC patients receiving RT with concurrent cisplatin are expected to develop ulcerative OM (WHO Grade 2 or higher).[3]

Standard chemoradiotherapy for locally advanced squamous cell carcinoma of the head and neck (SCCHN), whether in the post-operative or definitive setting, currently consists of intensity-modulated radiation therapy (IMRT) plus systemic therapy. Common systemic treatment is with single-agent cisplatin, administered either q3 weeks or once weekly schedule.[4, 5, 6, 7] The monoclonal antibody cetuximab has also been shown to increase the efficacy of radiotherapy for locally advanced head and neck cancer,[8] and the combination of IMRT plus either single-agent cisplatin or single-agent cetuximab is currently being tested head-to-head for patients with human papilloma virus (HPV)-related oropharyngeal cancer in the ongoing RTOG 1016 trial.

Unpublished observations for a group of approximately 300 patients treated with intensity-modulated radiation therapy (IMRT) plus single-agent cisplatin for cancers of the oral cavity or oropharynx, without additional treatment to prevent OM, suggest that approximately 70% of patients may be expected to develop severe OM, at a median cumulative IMRT dose delivered of approximately 40 Gy (S. Sonis, Dana-Farber Cancer Institute), as summarized in Table 2. In addition, two published Phase 3 studies of palifermin in patients receiving RT plus single-agent cisplatin for SCCHN reported an overall incidence of severe (WHO Grade 3-4) OM among placebo patients of 67% in one study and 69% in the other.[9,10]

**Table 2: Cumulative Onset of WHO Grade 3-4 OM vs. Total IMRT in Patients Receiving Concurrent Single-Agent Cisplatin**

| At Total Delivered IMRT | Estimated Cumulative Incidence of Severe OM (WHO Grade 3-4) +/-5%, N= ~300 Patients, Multiple Studies |
|---|---|
| At any time during/post IMRT | 73% |
| @ total 20-29 Gy | 20% |
| @ total 30-39 Gy | 40% |
| @ total 40-49 Gy | 50% |
| @ total 50-59 Gy | 60% |
| @ total 60-70 Gy | 70% |
| Median Onset of Severe OM | 40 Gy |

Adding cetuximab to standard chemoradiation regimens for HNC increases the risk of significant OM,[7] while cetuximab without additional chemotherapy has been reported in one study to increase the risk of OM in patients receiving radiation modestly, if at all.[8]

Among patients being treated for HNC, OM follows a predictable and well-documented course.[11] By the end of the first week of treatment (typically cumulative radiation doses of 10 Gy), erythema of the oral mucosa is usually seen and patients complain of discomfort that is characterized as burning. This relatively mild pain escalates between the second and third week of treatment (radiation doses of 20 Gy to 30 Gy), when frank ulceration of the mucosa develops. Lesions at this stage often necessitate a modification in food intake and a marked increase in the need for analgesics. Individual ulcers frequently coalesce as radiation progresses resulting in confluent injury affecting many aspects of the oral mucosa. Pain intensifies and may be inadequately controlled even with aggressive narcotic therapy.[12]

Oral mucositis is a treatment-induced morbidity that has substantial impact on day-to-day functioning. In addition to the common need for, and inadequate pain control with, narcotics, the profound clinical impact of OM also includes weight loss, difficulty eating and swallowing, dehydration, need for nutritional support, and reduced performance status,[12] as well as secondary infections at sites of ulcerative OM,[13] and diminished quality of life (QOL) outcomes.[14] Patients with HNC may also suffer the additional complications of short- and long-term xerostomia, taste change, and trismus related to post-radiation fibrosis.

Besides its symptomatic toll, OM is associated with a number of serious medical complications and negative health economic outcomes. Among patients treated for HNC, even mild mucositis results in more frequent hospitalization and breaks in treatment, introducing the risk of compromised anti-tumor efficacy.[15, 16] In granulocytopenic patients, mucositis is strongly associated with an increased risk of bacteremia and sepsis.[17] Adverse health economic outcomes include increased analgesic and antibiotic use, increased number of febrile days, need for parenteral nutrition, prolonged length of hospital stay, and increased resource use and associated cost.[18]

### 4.1.2. Oral Mucositis is an Unmet Medical Need

Oral mucositis prevention and management remains a substantial unmet need. For years, there has been no substantial change in its management.[19] Current guidelines[20] from the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) limit recommended or suggested interventions to prevent OM to:

- Palifermin in the setting of high-dose chemotherapy and total body irradiation, followed by autologous hematopoietic stem cell transplantation (HSCT), for a hematological malignancy;
- Oral cryotherapy in the setting of 5-fluorouracil therapy or chemotherapy/HSCT;
- Low-level laser therapy in the setting of chemotherapy/HSCT or chemoradiotherapy for HNC;
- Benzydamine mouthwash in the setting of HNC treated with moderate-dose RT, without concomitant chemotherapy;
- Oral zinc supplements in the setting of radiation or chemoradiation;
- Oral care protocols across all cancer treatment modalities.

Narcotics and doxepin mouthwash are recommended or suggested by MASCC/ISOO for the treatment of OM-related pain. A number of other agents currently used to treat OM, while designed to palliate associated pain or manage infection, do not alter the underlying biologic processes that give rise to OM. MASCC/ISOO currently recommends or suggests *against* the use of some agents that have historically been used (e.g., antimicrobial mouthwashes, sucralfate, chlorhexidine mouthwash), citing evidence for lack of effectiveness against OM in one or more treatment settings.

At present, palifermin is the only FDA-approved drug intervention for OM but its use (patients receiving HSCT for hematologic malignancies) is limited to a very small cohort (4%) of the at-risk population; viz., OM associated with conditioning regimens prior to stem cell transplant for the treatment of hematologic malignancies.[21]

A number of medical devices are in the market, but generally lack sufficient data to allow recommendation. The mucoadhesive MuGard™ is indicated as a palliative treatment for the management of OM[22] but requires administration four to six times per day for optimal effect and does not alter the mechanism of OM. The oral gel Gelclair® has a similar use and effect for OM or oral irritation due to other causes but does not affect the mechanism of OM. Caphosol® (supersaturated calcium phosphate rinse) is indicated for xerostomia or as an adjunct to standard oral care for OM[23] but failed to reduce the incidence of ulcerative or severe OM in a recently-published Phase 2 study.[24] The lipid-based oral barrier rinse Episil® and the bacteriostatic rinse GelX® (zinc gluconate-taurine complex) may be used for pain related to OM but do not affect the mechanism causing OM.

## 4.2. GC4419

GC4419 is a novel, highly stable manganese-containing macrocyclic ligand complex with a molecular weight of 483, whose activity mimics that of naturally occurring superoxide dismutase

(SOD) enzymes. It is therefore a prototype of a new class of drugs termed selective SOD mimetics.

GC4419 selectively removes superoxide anions without reacting with other reactive oxygen species, including nitric oxide, hydrogen peroxide, and peroxynitrite. In addition, unlike native SOD, GC4419 is not deactivated by nitration. Nonclinical data have identified GC4419 as a promising new radioprotective, anti-cancer and anti-inflammatory agent. Thus, GC4419 was active as a radio-protectant in animal models of cancer radiation therapy and added to the activity of chemotherapeutic agents in animal models of cancer. Importantly, GC4419 did not interfere with the anti-tumor effects of either radiation therapy or chemotherapy in animal models of cancer.

GC4419 is being developed for the initial indication of "Reduction of the Severity and Incidence of Radiation and Chemotherapy Induced Oral Mucositis" under IND 111,539 with the Division of Oncology Products I, United States Food and Drug Administration.

### 4.2.1. Biological Rationale for GC4419 in Radiation/Chemotherapy Induced OM

Under normal circumstances superoxide (O2-) is a by-product of mitochondrial cellular respiration and is also produced by activated phagocytes. Since superoxide is extremely reactive with biological molecules, it is quite toxic to cells. In all studied species, this potentially toxic superoxide burden is normally contained by a complement of Superoxide Dismutase (SOD) enzymes.[25] In vertebrates, SOD enzymes are present in the cytoplasm (SOD1 Cu/Zn based), mitochondria (SOD2, Mn based) and extracellular spaces (SOD3, Cu/Zn based). Superoxide dismutases are a class of oxidoreductase enzymes that dismutate superoxide into molecular oxygen and hydrogen peroxide.

The control of the free radical flux derived from oxygen is jeopardized in many circumstances in which superoxide production is excessive or if the breakdown of superoxide is compromised. This over-production of superoxide can overwhelm the body's ability to eliminate it via catalytic dismutation and lead to a variety of superoxide initiated or mediated disease states, including OM.

Ionizing radiation damages cells by transferring sufficient energy to intracellular atoms or biomolecules to modify their normal properties and functions. Since approximately 70% of an average cell consists of water, radiolytic hydrolysis is by far the primary triggering event following the exposure of cells and tissues to ionizing irradiation, e.g., as in radiation therapy (RT) for the treatment of cancer.[26]

Radiolytic hydrolysis leads to the formation of a number of reactive oxygen species (ROS), including predominantly the superoxide anion (O2-). Therapeutic radiation damages cancer cells by abruptly but transiently increasing tissue ROS, including superoxide. Normal cells in the radiation field counter these damaging effects by detoxifying ROS via their intact redox protective enzyme systems (SOD, catalase, glutathione peroxidase), converting hydrogen peroxide into water and molecular oxygen, and by the activation of DNA repair mechanisms. In cancer cells, it has been suggested that exogenous SOD and SOD mimetics, by reducing intracellular superoxide (a proliferation trigger) and increasing hydrogen peroxide (an apoptosis trigger) shifts the critical cellular redox balance reducing the proliferative drive and increasing the apoptotic drive.[27]

Recent research has demonstrated that the pathogenesis of mucositis involves more than just direct clonogenic cell death induced non-specifically on rapidly dividing basal epithelial cells. Rather, basal epithelial cell death is mediated by a wide range of mechanistic pathways; at least 14 canonical pathways have been identified as being involved in HNC treatment toxicities.[28] The generation of reactive oxygen species (ROS) by chemoradiation, for example, leads to a number of signaling pathways in the submucosa that then target the epithelium and result in loss of epithelial renewal and the development of ulceration.[29] ROS, and in particular O2•-, are believed to play a central role in the initiation of tissue injury and up-regulation of inflammatory cytokines, with subsequent signal amplification and mucosal inflammation and ulceration.[30] Furthermore, differences in polymorphisms that encode for glutathione S-transferase, an enzyme that provides protection from ROS, have been associated with increased risk for radiation- and chemotherapy-induced injury to both the oral mucosa and skin.[31]

Taken as a whole, this suggests that an agent that efficiently and rapidly removes O2•- offers a treatment paradigm for preventing or controlling OM. Numerous published studies indicate that OM, esophagitis, pneumonitis, fibrosis, or other normal-tissue radiation damage may be reduced by treatment with liposomally encapsulated exogenous MnSOD or a MnSOD transgene, exogenous Cu/Zn SOD, or a dismutase mimetic enantiomerically related to GC4419.[32, 33, 34, 35, 36]

## 4.3. Pre-Clinical GC4419 Data

### 4.3.1. Pre-Clinical Data with GC4419 in Hamster Models for Radiation-Induced OM

Pre-clinically, GC4419 has been shown to reduce the duration of severe OM in the hamster cheek pouch model. When administered 30 min before and 12 hours after irradiation (40 Gy) of the everted buccal cheek pouch of Syrian golden hamsters, GC4419, like its enantiomer GC4403, accelerated the resolution of OM and reduced the percentage of animal days with severe OM (a mucositis score ≥3), in a dose-dependent fashion, compared with a vehicle control group.[37] Effective plasma concentrations of GC4419 in this well-established animal model of OM were similar to those previously found achievable in normal human volunteers.[38]

In a separate study in the same model assessing fractionated radiation, hamsters received a total of 60 Gy in eight fractions of 7.5 Gy each over 10 days, on Days 0-3 and 6-9. GC4419, 10 or 30 mg/kg i.p, was administered 30 minutes before irradiation by two schedules: on Days 0-3 and 6-9; or on Days 0, 2, 6, and 8 (10 animals per group). GC4419 significantly reduced severe OM, but only when administered at a dose of 30 mg/kg before each irradiation.[39]

### 4.3.2. GC4419 is not Tumor Protective in Non-Clinical Cancer Models.

Importantly, GC4419 does not interfere with the antitumor efficacy of radiation therapy or cancer chemotherapeutic agents in any in vitro or in vivo models evaluated to date. This supports the findings for this differential effect on cancer and normal cells is due to differences in H2O2 sensitivity between these cells, as noted above. SOD enzymes in normal cells rapidly convert O2•- to H2O2 which is then rapidly detoxified to water by catalase, glutathione peroxidase and related enzymes. Cancer cells may be deficient in these enzymes, but also tend to be especially sensitive to elevated H2O2. The addition of an SOD mimetic (such as GC4419) more rapidly drives O2•- to H2O2, creating a burden that is markedly more toxic to tumor cells than normal cells. In vitro, GC4419 protects a variety of normal cell types from the effects of

radiation while sensitizing lung and head-and-neck cancer cell lines, consistent with the literature on SOD enzyme effects. GC4419 did not antagonize the growth-inhibitory effects of cisplatin on the cisplatin-sensitive CT26 tumor cell line. In fact, at concentrations >1 μM cisplatin, GC4419 enhanced the cisplatin effect. As expected, GC4419, when added alone, inhibited the O2•- dependent proliferation of CT26 cells. In addition, Galera has evaluated GC4419 as a single agent against multiple tumor cell lines in vitro and, in every case, tumor cell growth and proliferation was either inhibited or not affected (data on file, Galera Therapeutics, Inc.).

In vivo, GC4419 does not diminish, but may enhance, the anti-tumor effects of radiation or chemotherapy. Notable are results in the human lung tumor xenograft, H1299, and the human HNC tumor xenograft, FaDu/HTB-43. In the H1299 model, GC4419 appeared modestly to increase the antitumor effect of cisplatin plus radiation given in fractions of approximately 2 Gy. In the FaDu model, GC4419 neither enhanced nor antagonized the anti-tumor effect of radiation. In the FaDu model, in parallel cohorts of tumor-bearing animals, plasma concentrations of GC4419 assayed 0, 5, 15, 30, and 60 minutes following irradiation demonstrated plasma exposures of GC4419 that exceeded the levels shown to be efficacious in the previously described OM model in hamsters (data on file, Galera Therapeutics, Inc.).

Further, results from ongoing Galera-sponsored studies (M. Story, University of Texas/Southwestern, personal communication) suggest that GC4419 may more greatly radiosensitize tumors when radiation is given by a hypofractionated schedule. In another experiment in the H1299 model, a single dose of 20 mg/kg GC4419 caused a tumor growth delay of 22 days vs. vehicle control, comparable to results with single agent cisplatin (21 day tumor growth delay). A single radiation fraction (day 0) of 18 Gy produced a 32-day tumor growth delay compared to vehicle. The combination of GC4419 and 18 Gy of radiation produced a tumor growth delay of 90 days compared to vehicle and 57 days compared to radiation alone. These results were similar to those obtained by the combination of cisplatin and radiation and were not statistically different from results when GC4419 was added to the combination of radiation and cisplatin.

Galera has conducted tumor growth delay studies in several other in vivo tumor models, including colon, HNC, lung and melanoma. In every case, tumor growth was either slowed or not affected, and in no case has GC4419 interfered with the anti-tumor effects of chemotherapy (cisplatin, gemcitabine, cyclophosphamide, paclitaxel, irinotecan, and doxorubicin) or radiotherapy (data on file, Galera Therapeutics, Inc.).

Results of experiments with GC4419 in cancer tumor models are further described in the GC4419 Investigator's Brochure. Additional non-clinical studies are planned to further elucidate mechanisms of any anti-tumor interaction between radiation and GC4419.

## 4.4. Phase I Study of GC4419, GT-001

### 4.4.1. Clinical Data with GC4419 in Radiation/Chemotherapy Induced OM

GC4419 has been studied in a Phase 1b/2a trial, GT-001 (NCT01921426), in combination with IMRT and single agent cisplatin, in the treatment of patients with squamous cell carcinoma of the oral cavity (OC) or oropharynx (OP) for whom the planned IMRT/cisplatin regimen is medically indicated. In the IMRT regimen, patients received approximately 2 Gy of IMRT once daily, Monday-Friday, up to a total of approximately 70 Gy administered over 7 weeks.

Cisplatin was administered either every 3 weeks for 3 doses (80-100 mg/m$^2$), or weekly for 6-7 doses (30-40 mg/m$^2$). GC4419 was administered by 60-minute IV infusion each day (M-F) prior to that day's IMRT fraction, with IMRT administered within 60 minutes of the end of GC4419 infusion.

The primary objective of the GT-001 clinical study was to characterize the safety profile of GC4419 when administered with the IMRT/platinum regimen, with key secondary objectives of reduction in the incidence, severity, and/or duration of OM experienced by patients. The trial followed a serial cohort (3+3) dose escalation design.

Under an early version of protocol GT-001 patients received GC4419 prior to each of the first 14 or 20 doses of IMRT. Serial cohorts of patients were assigned to daily doses of 15, 30, 50, 75, or 112 mg (absolute dose). After FDA review of a Type A meeting request (IND serial 0016, submitted April 2, 2014 with FDA Meeting Preliminary Comments April 28, 2014) the protocol was amended to provide for serial patient cohorts to receive GC4419 prior to the first 25, 30, or all 35 dose fractions of IMRT, at daily doses previously shown not to exceed the maximum tolerated dose (MTD). Under this amendment, serial cohorts of patients were assigned to receive 112 mg/d for 25 or 30 doses, 90 mg/day for 30 or 35 doses, and 30 mg/d for 35 doses. Studying longer durations of dosing was based on the hypothesis that administration of GC4419 throughout the duration of IMRT would be needed for optimal efficacy against OM.

A total of 46 patients were enrolled. Of these, 45 were evaluable for safety and 43 were evaluable for OM (Table 3):

**Table 3: GT-001 Enrollment**

| Dose Cohort | # enrolled | # evaluable for safety | # evaluable for OM |
|---|---|---|---|
| 15 mg/d x 14 doses | 4 | 4 | 4 |
| 30 mg/d x 14 doses | 3 | 3 | 3 |
| 50 mg/d x 14 doses | 4 | 4 | 4 |
| 75 mg/d x 14 doses | 3 | 3 | 3 |
| 112 mg/d x 14 doses | 8 | 7 | 6 |
| 112 mg/d x 20 doses | 3 | 3 | 3 |
| 112 mg/d x 25 doses | 3 | 3 | 3 |
| 112 mg/d x 30 doses | 5 | 5 | 4** |
| 90 mg/d x 30 doses | 3 | 3 | 3 |
| 90 mg/d x 35 doses | 6 | 6 | 6 |
| 30 mg/d x 35 doses | 4 | 4 | 4 |

**one patient enrolled at 112 mg/d x 30 doses actually received 87 mg/d, per protocol provision, and is included with others at 90 mg/d x 30 doses in presentations of OM efficacy

### 4.4.2. Oral Mucositis Clinical Data from GT-001

As of July 8, 2015, treatment was complete for all patients and unaudited OM data were available for the 43 patients evaluable for OM. The OM evaluations indicate that, compared with historical expectations:

- The overall incidence of severe (WHO Grade 3 or 4) OM appears reduced;

- Severity of OM (specifically, Grade 4 OM) appears to be lowered when GC4419 treatment is extended for 6-7 weeks;
- Onset of severe OM appears delayed;
- Duration of severe OM appears reduced, particularly with the longer treatment schedules.

In general, efficacy to reduce the incidence and severity of OM appeared greatest with more prolonged GC4419 dosing schedules. However, there was not a clear relationship between absolute daily dose and OM results; excellent efficacy was apparent even for patients who received 30 mg/d.

The overall incidence of Grade 3-4 OM (all cohorts, pooled) is summarized, in comparison with the matched historical data, in Table 4, below:

**Table 4: Cumulative Onset of WHO Grade 3-4 OM vs. Total IMRT in GT-001, Compared with Unpublished Experience from S. Sonis**

| At Total Delivered IMRT | Week of Therapy | Expected Cumulative Incidence of Severe (WHO Grade 3-4) OM (+/-5%) | GC4419 Results All Cohorts, N=43 |
|---|---|---|---|
| At any time during/post IMRT | --- | 73% | 51% (22/43)[1] |
| @ total 20-29 Gy | 3 | 20% | 5% (2/43) |
| @ total 30-39 Gy | 4 | 40% | 12% (5/43) |
| @ total 40-49 Gy | 5 | 50% | 26% (11/43) |
| @ total 50-59 Gy | 6 | 60% | 37% (16/43) |
| @ total 60-70 Gy | 7 | 70% | 47% (20/43) |

[1]Two patients had first severe OM at a post-IMRT visit; Gy to onset of severe OM set at 70 for these 2 patients
Sources: Sonis, personal communication; Monitored, unaudited Galera GT-001 clinical data

It is noteworthy that only 2 of 43 patients had experienced Grade 3 OM (no Grade 4) by the end of the third week of IMRT, and only 5 of 43 had experienced Grade 3 OM (no Grade 4) by the end of the fourth week of IMRT. This compares favorably with the published experience of Le et.al.[9] and Henke et.al.[10] in which approximately 20% of patients receiving placebo and approximately 15% of patients receiving palifermin had developed Grade 3 or 4 OM by the end of 3 weeks, and approximately 40% of patients receiving placebo and approximately 30% of patients receiving palifermin had developed Grade 3 or 4 OM by the end of 4 weeks.[9,10]

However, a single metric such as overall incidence does not fully characterize the OM efficacy data for GC4419. Figure 1, Figure 2 and Figure 3 demonstrate each individual patient's OM experience over time (one row per patient). In the aggregate, these results appear to confirm that, as treatment duration is increased, the incidence of severe OM is lower than expected, while severe OM, when it occurs, is delayed in onset, lower in severity (with Grade 4 OM rare in patients receiving 6-7 weeks of GC4419), and shorter in duration.

Table 5 tabulates OM results by several measures, vs the historical matched data and the published placebo data of Le and Henke. These measures include incidence of severe OM through the "landmark" point of 60 Gy delivered to tumor (approximately 6 weeks), a fixed reference point in the treatment course.

**Figure 1: OM scores by visit for individual patients; cohorts receiving 14 doses (3 weeks) GC4419, GT-001 trial**

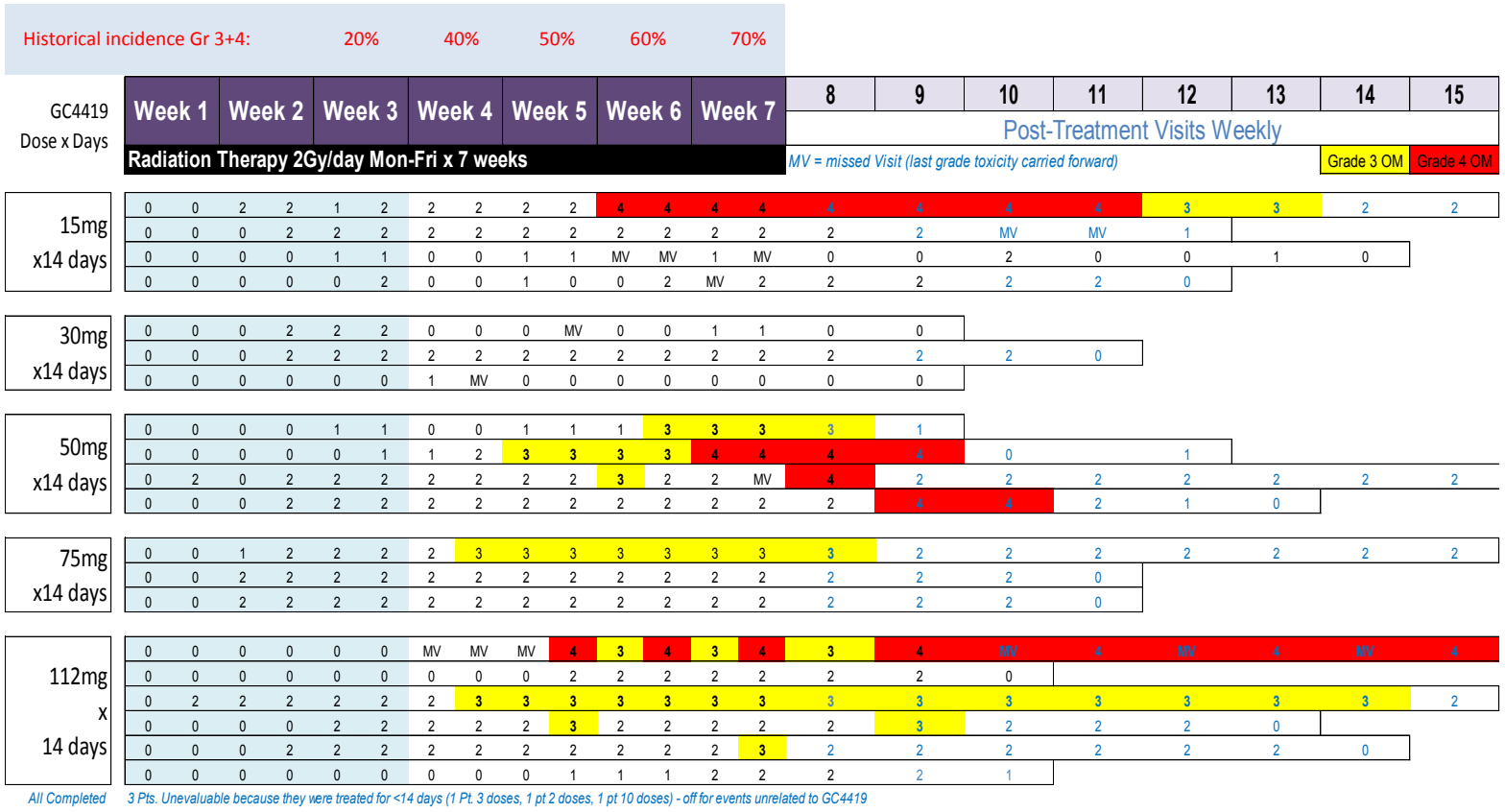

**Figure 2: OM scores by visit for individual patients; cohorts receiving 112 mg/d of GC4419 for 20-30 doses (4-6 weeks), GT-001 trial**

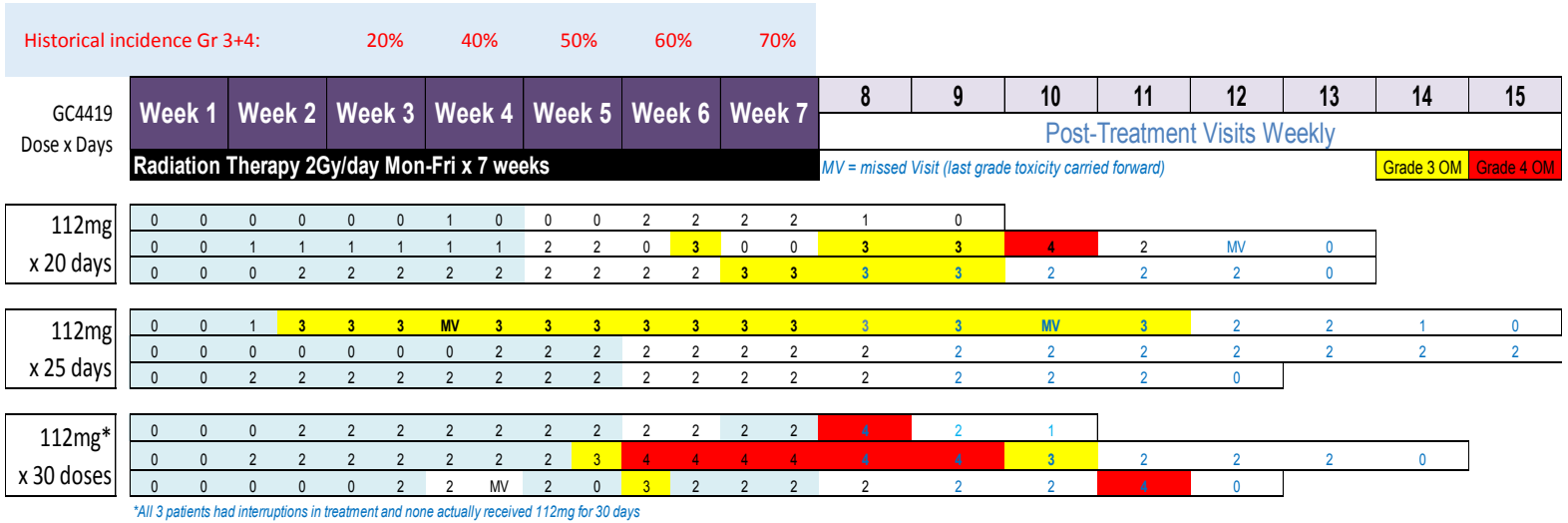

**Figure 3: OM scores by visit for individual patients; cohorts receiving 30 or 90 mg/d of GC4419 for 6-7 weeks, GT-001 trial**

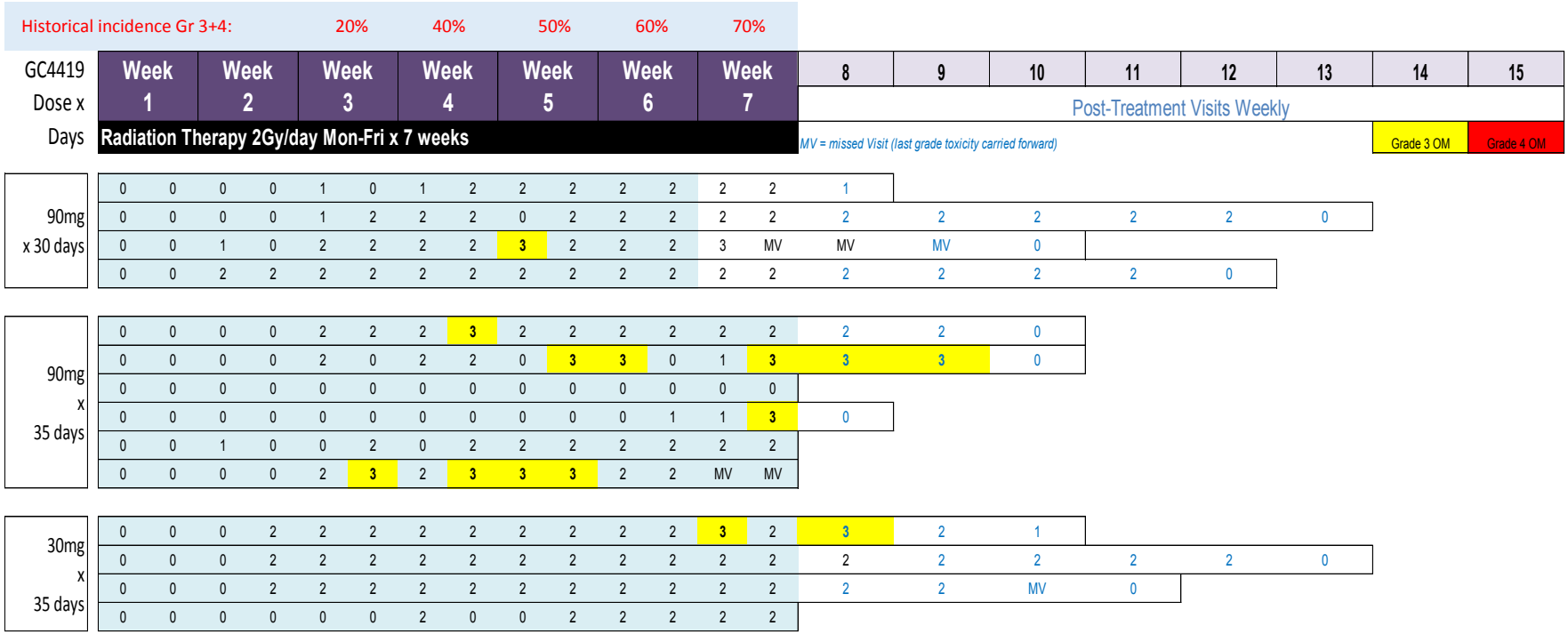

**Table 5: OM parameters for GC4419 (GT-001 trial) compared with historical matched and published control data**

| SEVERE ORAL MUCOSITIS (Grade 3&4) Comparison of Key Efficacy Parameters | | Comparative Historical Control Data | | | GC4419 data | |
|---|---|---|---|---|---|---|
| | | Matched Data Set | Placebo data from published Phase III trials | | Partial treatment (3 weeks) | Full Treatment (6-7 weeks) |
| | | S. Sonis | Le et al (ref 9) | Henke et al (ref 10) | | |
| # Patients | | ≈300 | 94 | 94 | 20 | 14 |
| **INCIDENCE** | Grade 3+4 Incidence through 60 Gray | 60% | 57% | 62% | 40% | 29% |
| **INTENSITY** | Grade 4 Overall Incidence | 20% | 19% | 26% | 25% | 0% |
| **ONSET** | Median Time to Onset of Grade 3-4 (treatment days) | 28 | 35 | 32 | >54 | >50 |
| | Median Radiation Dose to Onset (Gray) | 40 Gy | Not stated | Not stated | 70 Gy[1] | 70 Gy[1] |
| **DURATION** | Median Duration of Grade 3+4 OM (Days) | 28 | 26 | 22 | 4.5 | 2.5 |

[1] All patients included. Assigns a value of 70 Gy to patients who never developed severe OM.
Sources: Sonis, personal communication; Galera monitored, unaudited data for GT-001 trial; references 9 and 10

### 4.4.3. Clinical Safety Data with GC4419

The most common adverse events observed in the GT-001 study were nausea, fatigue, dysgeusia, oropharyngeal pain, decreased white blood cell count, constipation, dry mouth, anemia, vomiting, diarrhea, decreased lymphocyte count, and decreased appetite. These and other adverse events observed are characteristic of the cisplatin/IMRT regimen in this patient population.

The following mild to moderate adverse events were reported as possibly related to GC4419 for >10% of patients in the GT-001 study: nausea, vomiting, dry mouth, diarrhea, fatigue, dyspepsia, gastroesophageal reflux disease, dizziness, dysgeusia, weight loss, decreased appetite, headache, paresthesia, and hiccups.

The following more severe adverse events were reported as possibly related to GC4419 in the GT-001 study: anemia, nausea, vomiting, gastroenteritis, low white blood cell count, low neutrophil count, weight loss, decreased appetite, arthritis, and reduced range of motion. As of 21-Dec-2016 the following additional severe adverse events have been reported as possibly related to GC4419 in the GT-201 study: hypotension, diarrhea, unexplained fever, and bradycardia/syncope.

Potentially mechanism-related facial tingling or paresthesia, possibly due to nitric oxide potentiation, was reported for several patients in the GT-001 study and appears related to GC4419 dose, occurring in 11/19 (58%) patients receiving 112 mg per dose, 5/9 (55%) patients receiving 90 mg/dose, but only 2/18 (11%) at lower doses. This facial tingling/paresthesia was mild to moderate, and when it occurred it did so during GC4419 infusion with resolution shortly after the end of the infusion. It was neither treatment-limiting nor troublesome to patients, and does not pose a meaningful safety risk.

Per their reported assessments, investigators considered two patients to have potentially dose-limiting toxicities (DLTs), both at a daily dose of 112 mg:

- One patient receiving 112 mg for 14 doses had an episode described as gastroenteritis (principally nausea and vomiting) requiring hospitalization. This event occurred during the first three weeks of IMRT, and was reported as possibly related to GC4419 because of the temporal association with days of GC4419 treatment, although the patient's symptoms were not infusion-related. Furthermore, the treating investigator reported that the event "probably" was attributable to cisplatin.
- One patient enrolled to the 112 mg x 30 dose cohort experienced two episodes of nausea and vomiting requiring hospitalization, first after the fourth week of protocol therapy, then again after rechallenge with GC4419 and IMRT through the fifth week of treatment. The treating investigators reported that the patient's vomiting was possibly related to GC4419 but principally due to the presence of thick secretions complicating swallowing. The patient also experienced Grade 3 hyponatremia that was initially reported as possibly related to GC4419, but that appears from the clinical events to be attributable to GI loss and poor intake of solutes. While this patient's events were reported as possibly related to GC4419, they may not constitute true dose-limiting toxicities of GC4419. Including these two cases, through August 6, 2015 a total of 49 event terms have been reported as serious adverse events (SAEs) for 23 patients. In some cases, a single medical event was reported as several event terms with identical or overlapping onset dates. Only in the two cases described above were the events reported as possibly related to GC4419. Other SAEs were judged not related to GC4419, but attributable to the combination of platinum and IMRT or to comorbidities and concomitant medications. SAEs event terms reported for more than one patient include fever (5 patients), vomiting (5 patients), febrile neutropenia (4 patients), nausea (3 patients), and dehydration (2 patients).

Pharmacokinetic (PK) sampling has been performed on Week 1 Day 2 and on Week 3 Day 3. Preliminary results shown in Table 6 below reflect available data for 32 patients from the GT-001 study, with analysis of additional patients (e.g., treated at 90 mg/day) in progress. Results are consistent with modeled predictions (data not shown), and demonstrate increases in GC4419 $C_{max}$ and AUC that are approximately dose-proportional. There has been minimal accumulation of GC4419 in plasma with repeated dosing. Exposure to active metabolites (which are substantially less active than the parent drug) is low compared with exposure to the parent drug GC4419 (data not shown).

**Table 6: Pharmacokinetic parameters of GC4419 from Clinical Study GT-001**

| Dose Level (mg) | $C_{(max)}$ (ng/mL) (Mean [SD]) | | $AUC_{(0\text{-}inf)}$ (ng·h/mL) (Mean [SD]) | |
|---|---|---|---|---|
| | Week 1 | Week 3 | Week 1 | Week 3 |
| 15 (n=4) | 474 [182] | 604 [308] | 883 [347] | 905 [466] |
| 30 (n=6) | 963 [152] | 991 [266] | 1650 [187] | 1810[408] |
| 50 (n=4) | 1450 [760] | 1620 [569] | 2780 [1570] | 3000 [1370] |
| 75 (n=3) | 2380 [940] | 3260 [406] | 4100 [2080] | 5000 [395] |

| Dose Level (mg) | $C_{(max)}$ (ng/mL) (Mean [SD]) | | $AUC_{(0\text{-}inf)}$ (ng·h/mL) (Mean [SD]) | |
|---|---|---|---|---|
| 112 (n=15) | 3410 [688] | 4130 [1290] | 6340 [1630] | 8090 [2660] |

## 4.5. Randomized Phase II Study of GC4419, GT-201

In the present three-arm, randomized (1:1:1), placebo-controlled phase 2 trial, two doses of GC4419 (a "low" dose of 30 mg and a "high" dose of 90 mg) will be evaluated against placebo in patients with locally advanced, non-metastatic squamous cell HNC of the oral cavity or oropharynx. All patients will receive a backbone regimen of cisplatin, either administered q3 weeks, 80-100 mg/m$^2$ or weekly 30-40 mg/m$^2$ (investigator's choice), plus IMRT administered in 2.0-2.2 Gy daily fractions, to a total dose of 60-72 Gy.

The goals of the Phase 2 trial are to identify sufficient efficacy of GC4419, in the form of reduced duration, incidence, and severity of OM; to suggest clinical benefit and indicate that confirmation of such benefit is likely in a subsequent pivotal trial; and to inform the design of that trial. Accordingly, the design of the Phase 2 trial, including the sample and target effect sizes, is intended to provide data sufficiently robust for GT-201 to guide the design of a future pivotal, registration-directed Phase 3 trial of GC4419 in the present indication.

GT-201 is a placebo-controlled, double-blind trial. Galera believes that the estimated incidences of severe OM as communicated by Sonis (Table 2) are likely to be accurate, because the data supporting them are pooled from a set of patients matched for tumor site, IMRT, and single-agent cisplatin treatment, and because they appear to agree closely with published data, including the placebo experience in the two similarly-designed trials conducted with palifermin. However, because of the risk of bias, the possibility of reductions of severe OM arising solely from ongoing refinements in the delivery of radiation therapy, and the early stage of GC4419's development justifying equipoise, the placebo-controlled design has been chosen. Similarly, this trial is double-blinded to reduce the risk of bias in the primary and secondary endpoints.

# 5. TRIAL OBJECTIVES AND PURPOSE

## 5.1. Primary Objective

The primary objective of this study will be 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.

### 5.1.1. Rationale for Primary Endpoint

The WHO scale is commonly used to assess OM in clinical care and research settings. It was developed as a standard toxicity reporting index. It has evolved into the most accepted outcome for efficacy testing of drugs as it has been shown to meet key characteristics for clinical studies:

- Accurate reflection of the severity and course of the objective and subjective changes of mucositis.
- Easy to teach with a minimal inter-observer variability.
- Does not require measurement of lesions.
- Sensitive enough to discriminate treatment efficacy.
- Clinically meaningful and easily interpreted endpoints for clinicians, patients and regulatory agencies.
- The WHO scale has been used as the primary efficacy endpoint for many studies and is accepted internationally.

There is precedent for severe OM on the WHO scale being used as the basis for drug approval. Palifermin (Kepivance®) is indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support, when the preparative regimen is predicted to result in WHO Grade > 3 mucositis in the majority of patients. Approval of palifermin was based on a reduction in the number of days during which patients experienced severe oral mucositis (Grade 3/4 on the WHO (World Health Organization) scale); other analyses included the incidence, duration, and severity of oral mucositis and the use of opioid analgesia.[43] Additional studies of agents to reduce OM—notably the two published studies of palifermin in the HNC population[9, 10] also have used the WHO scale.

The duration of severe OM is planned as the single primary endpoint of this Phase 2 trial. Secondary and exploratory endpoints (see sections 5.2 and 5.3, below) are expected to provide important and clinically relevant data supporting the primary endpoint, as well as data to guide the selection of a primary endpoint for a future pivotal trial.

Because of the nature of the WHO grading scale (See Section 20), improvement of meaningful magnitude in the primary endpoint implies clinical benefit. While ulcerative (Grade 2) OM is very common, its functional consequences may be open to question. However, by definition, WHO Grade 3 OM entails a change in diet, and WHO Grade 4 OM includes inability to eat, requiring parenteral or tube feedings.

It may be noted here that many reports of OM in clinical trials use the NCI-CTCAE, in which the grading of OM is different from the WHO scale (Table 7). Whereas the WHO criteria have been stable for years, NCI criteria have changed markedly with every new version. The NCI criteria have found their greatest application in describing mucositis as an AE associated with anti-cancer regimens, not as an instrument to assess intervention efficacy.

**Table 7: Comparison of WHO Scale vs. NCI-CTCAE v4 for Oral Mucositis**

| OM Grade | WHO Scale | NCI-CTCAE v4 |
|---|---|---|
| 0 | No mucositis | No mucositis |
| 1 | Pain and erythema | Asymptomatic or mild symptoms; intervention not indicated |
| 2 | Ulceration but no compromise in diet (able to eat solid food) | Moderate pain; not interfering with oral intake; modified diet indicated |
| 3 | Ulceration with ability to eat only liquids | Severe pain; interfering with oral Intake |
| 4 | Ulceration with inability to eat/requirement for tube or parenteral feeding | Life-threatening consequences; urgent intervention indicated |

As noted, the WHO scale will be used in GT-201. Separate grading of OM according to the CTCAE will not be performed.

## 5.2. Secondary Objectives

- To evaluate and compare the safety of GC4419 at the treatment assignment of each respective arm
- 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 30$^{th}$ 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 onset of severe OM expressed as the number of IMRT fractions delivered at onset of severe OM
- To evaluate and compare the effect of treatment assignment on tumor outcomes (locoregional failure, distant metastases, progression-free survival, overall survival)

## 5.3. 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 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, 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 assessments (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 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

# 6. INVESTIGATIONAL PLAN

## 6.1. Overall Study Design

GT-201 is a randomized, double-blind, placebo-controlled, multi-center study conducted in the US and Canada to evaluate GC4419 administered IV to reduce the duration, incidence, and severity of radiation induced oral mucositis in patients receiving chemoradiation for SCCHN, limited to the oral cavity or oropharynx.

## 6.2. Treatment Plan and Duration of Therapy

Patients will be randomized equally to one of three treatment arms:

Arm A: 30 mg GC4419 per day (60 min IV infusion, to complete within 60 minutes prior to IMRT), concurrent with daily fractions of IMRT (2.0-2.2 Gy) to a total of 60-72 Gy over approximately seven weeks, plus cisplatin administered 80-100 mg/m$^2$ once every three weeks for 3 doses or 30-40 mg/m$^2$ once weekly for 6-7 doses (investigator's choice)

Arm B: 90 mg GC4419 per day (60 min IV infusion, to complete within 60 minutes prior to IMRT), concurrent with daily fractions of IMRT (2.0-2.2 Gy) to a total of 60-72 Gy over approximately seven weeks, plus cisplatin administered 80-100 mg/m$^2$ once every three weeks for 3 doses or 30-40 mg/m$^2$ once weekly for 6-7 doses (investigator's choice)

Arm C: Placebo daily (60 min IV infusion, to complete within 60 minutes prior to IMRT), concurrent with daily fractions of IMRT (2.0-2.2 Gy) to a total of 60-72 Gy over approximately seven weeks, plus cisplatin administered 80-100 mg/m$^2$ once every three weeks for 3 doses or 30-40 mg/m$^2$ once weekly for 6-7 doses (investigator's choice)

Planned radiation treatment fields must include at least two oral sites (buccal mucosa, floor of mouth, tongue, soft palate) that are each planned to receive a total of ≥ 50 Gy. Note, unavoidable doses of at least 50 Gy, to include entrance, exit, and scatter doses, still constitutes planned radiation.

GC4419/placebo will be given intravenously in a one hour infusion. IMRT must be initiated as soon as possible upon completion of the GC4419/placebo infusion but no later than 60 minutes following the end of the GC4419/placebo infusion.

GC4419/placebo will be given beginning on the first day of radiation and continuing daily, concurrent with each dose of IMRT, to a cumulative radiation dose of approximately 60-72 Gy.

If IMRT is not administered on any given day due to a treatment break or unforeseen circumstances, GC4419/placebo should not be administered on that day. Breaks in IMRT will be determined by the patient's treating physician in accordance with standard of care. Patients should resume GC4419/placebo administration when IMRT resumes. On days when planned doses of both GC4419/placebo and IMRT are not administered (e.g., due to a holiday site closure, etc.), GC4419/placebo dosing may be extended along with IMRT to make up the missed dose(s) up to a maximum of 35 doses of GC4419/placebo. If a fraction of IMRT is not

administered for any reason after GC4419/placebo has been administered, that day's GC4419/placebo will count as one of the 35 doses.

Anti-emetic prophylaxis and hematopoietic growth factor use should be administered per ASCO guidelines. If institutional guidelines permit, cisplatin may be administered prior to or after the first day of IMRT, as long as it follows a weekly or tri-weekly schedule. On days in which chemotherapy and GC4419/placebo are administered, the administration sequence should be GC4419/placebo, IMRT, prehydration, and cisplatin if possible. Patients treated with induction chemotherapy prior to concomitant chemoradiation are not eligible for this study.

### 6.2.1. Rationale for GC4419 Dose and Schedule Selection

Data from the GT-001 trial indicate that the acute toxicity of GC4419 and the overall adverse event profile in combination with IMRT/cisplatin are as expected. GC4419 does not appear to increase the toxicity of IMRT/cisplatin. The acute toxicity of GC4419 was acceptable at all doses tested, and consistent with prior expectations as described in the Investigator's Brochure. A true "maximum tolerated dose" of GC4419 by the common definition used in oncology Phase 1 trials (>1/6 patients with DLT) was not exceeded in the GT-001 trial. Although dose-limiting toxicities were suggested in two patients receiving 112 mg/dose, the relationship of the events to GC4419 is questionable in each case. However, the overall incidence of Grade 3 nausea at 112 mg was nominally greater than at lower doses. Even if not strictly dose-limiting, nausea is highly undesirable for the indication currently under study. In addition, circumoral paresthesia, although mild, was dose-related. Therefore, to provide an additional margin of safety and reduce the possibility of adverse events that could increase the possibility of breaking study blinding, an upper dose of 90 mg of GC4419 will be used in the present trial. Safety was acceptable at this dose when administered for 30-35 doses over six-seven weeks. Accordingly, the available safety data support the doses selected for the present trial for administration daily on weekdays for a full course of IMRT.

Also of note is that Phase 1 data have not indicated a clear dose-response relationship with regard to either safety or potential efficacy in preventing OM, although there did appear to be a positive relationship between the total duration of GC4419 treatment and the incidence, onset, and duration of severe OM.

The small cohort sizes and overall Phase 1 sample size preclude conclusions about a dose-response relationship. As a next step in exploring such relationships, Galera will study 30 mg as a "low" dose in one of the two active treatment arms in GT-201.

### 6.2.2. Rationale for Cisplatin/IMRT Treatment Plan

Meta-analyses have indicated superior survival for HNC patients treated with concurrent chemoradiotherapy compared with standard fractionation (M-F) radiation therapy alone. While not all available regimens have been tested directly against one another, the benefit appears superior for single-agent cisplatin over other chemotherapy regimens,[40] and concurrent IMRT plus platinum monotherapy was chosen as one arm of the ongoing RTOG 1016 trial in human papilloma virus-associated oropharyngeal cancer. The other arm of that trial uses IMRT plus cetuximab, as a potentially less-toxic, equally efficacious regimen to IMRT/cisplatin, based on the results from the trial of Bonner et. al.,[8] and other studies. The incidence of severe OM may

be lower when IMRT is combined with cetuximab than with cisplatin; in the Bonner study, [NCI-CTCAE] Grade 3-5 OM was reported in 56% of patients receiving IMRT plus cetuximab. Survival data for RTOG 1016 are anticipated in 2020.[41] For purposes of the GT-201 study, the still-standard cisplatin/IMRT regimen has been chosen as it poses a significant medical need by virtue of the high incidence of associated severe OM. In the event that GT-201 yields positive results with regard to OM, the combination of GC4419, IMRT, and cetuximab may be studied in a separate, future trial. It should be noted that RTOG 0522 determined that adding cetuximab to IMRT plus cisplatin did not increase antitumor efficacy, but did increase toxicity.[7]

Standard fractionation (five fractions/week, delivered M-F) IMRT has been chosen for the GT-201 trial. Although accelerated fractionation (six fractions/week, combined with two rather than three doses of cisplatin q3 weeks), has been studied, prospective lead investigators for GT-201 have advised that standard fractionation remains the widely-used standard, and in the interest of using a chemoradiation regimen that is as uniform and commonly-used as possible, the standard fractionation approach is being retained. It is noted that accelerated fractionation appears substantially to increase the incidence of severe OM.[42]

Galera believes that the q3 weeks cisplatin regimen has not been directly compared with the once-weekly cisplatin regimen in combination with IMRT for HNC cancer in a clinical trial. These two regimens appear to be used interchangeably based on investigator preference and clinical assessment of the risk of cisplatin toxicity to the patient. The data supporting the information in Table 2 includes patients treated with both cisplatin schedules, but these data do not indicate a difference in the incidence of severe OM based on the cisplatin schedule used (Sonis, personal communication). However, and on advice of the Division of Oncology of the U.S. Food and Drug Administration, enrolled patients will be stratified based on the cisplatin regimen to be used.

### 6.2.3. Rationale for Tumor Follow-up and Analysis

Although the mechanism of action and existing nonclinical data (in vitro and in vivo) with GC4419 uniformly indicate otherwise, there is a theoretical potential for GC4419 to protect the tumor from the therapeutic effects of concurrent chemoradiation. Patient candidates for GT-201 will be informed of this potential risk and the existing data as part of the consent process and document. There has been no suggestion of tumor protection so far in GT-001 [data not shown].

Fakhry et.al. have recently published an analysis comparing time to and patterns of progression for HPV-positive and HPV-negative patients treated in RTOG 0129 or RTOG 0522.[46] The rate of progression was similar in the two groups and is summarized in Table 8.

After a median follow up of four years, the majority of progression events was found to have occurred in the first year after protocol therapy, and the vast majority of all progressions observed occurred by the end of three years.

**Table 8: Time to Tumor Progression in RTOG 0129 and RTOG 0522 (Fakhry et.al. - ref 46)**

| | HPV-positive patients | HPV-negative patients |
|---|---|---|
| Median time to progression (months) | 8.2 | 7.3 |
| Progression within first year post treatment | 65% | 63% |
| Progression within first two years post treatment | 82% | 86% |
| Progression within first three years post treatment | 86% | 93% |

This information suggests that tumor control data at two years after protocol treatment may provide a strong initial indication that results are consistent with expectations. As such, patients in this Phase 2 trial will be followed for tumor progression and overall survival for two years after completing treatment.

# 7. SELECTION AND WITHDRAWAL OF SUBJECTS

Approximately 216 total patients from investigational sites in US and Canada will be enrolled to achieve 195 evaluable patients, with 65 evaluable patients per treatment arm. Patients appropriate for this trial will be identified by the Principal Investigator (or designee) who will make a preliminary determination of the patient's eligibility for the trial in accordance with the provisions of the study protocol. Once a patient is enrolled to the study, the Sponsor or designee will assign a unique patient identification number that does not contain any Personal Health Information that will be used to reference the patient and corresponding data that is collected.

## 7.1. Subject Inclusion Criteria

Patients are required to meet the following inclusion criteria before entering the trial:

1. Pathologically-confirmed diagnosis of squamous cell carcinoma of the head and neck, defined as SCC of the oral cavity or oropharynx that will be treated with cisplatin plus concurrent IMRT

   Note: Patients with unknown primary tumors whose treatment plan matches the requirements specified in Inclusion Criteria 2 and 3 below are eligible for the trial.

2. Treatment plan to receive a continuous course of IMRT delivered as single daily fractions of 2.0 to 2.2 Gy with a cumulative radiation dose between 60 Gy and 72 Gy. Planned radiation treatment fields must include at least two oral sites (buccal mucosa, floor of mouth, tongue, soft palate) that are each planned to receive a total of ≥50 Gy. Patients who have had prior surgery are eligible, provided they have fully recovered from surgery, and patients who may have surgery in the future are eligible.

   Note: Unavoidable doses of at least 50 Gy, to include entrance, exit, and scatter doses, still constitutes planned radiation.

3. Treatment plan to receive standard cisplatin monotherapy administered either every three weeks (80-100 mg/m$^2$ for 3 doses) or weekly (30-40 mg/m$^2$ for 6-7 doses). The decision on which cisplatin regimen to use in combination with IMRT and GC4419 will be at the discretion of the investigator.
4. Aged 18 years or older
5. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
6. Adequate hematologic function as indicated by:
   - Absolute neutrophil counts (ANC) ≥ 1,500/mm$^3$
   - Hemoglobin (Hgb) ≥ 9.0 g/dL
   - Platelet count ≥ 100,000/mm$^3$
7. Adequate renal and liver function as indicated by:
   - Serum creatinine acceptable for treatment with cisplatin per institutional guidelines
   - Total bilirubin ≤ 1.5 x upper-normal limit (ULN)

- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN
- Alkaline phosphatase ≤ 2.5 x ULN

8. Human papilloma virus (HPV) status in tumor has been documented, using tumor immunohistochemistry for p16 or other accepted test
9. Serum pregnancy test negative for females of childbearing potential
10. Males and females must agree to use effective contraception starting prior to the first day of treatment and continuing for 30 days after the last dose of GC4419
11. Properly obtained written informed consent

## 7.2. Subject Exclusion Criteria

Patients will be excluded if they meet any of the following exclusion criteria:

1. Tumor of the lips, larynx, hypopharynx, nasopharynx, sinuses, or salivary glands
2. Metastatic disease (Stage IV C)
3. Prior radiotherapy to the region of the study cancer or adjacent anatomical sites or more than 25% of total body marrow-bearing area (potentially interfering with chemotherapy tolerance)
4. Prior induction chemotherapy
5. Receiving any approved or investigational anti-cancer agent other than those provided for in this study
6. Concurrent participation in another interventional clinical trial or use of another investigational agent within 30 days of study entry

   Note: Patients who are participating in non-interventional clinical trials (e.g., QOL, imaging, observational, follow-up studies, etc.) are eligible, regardless of the timing of participation.
7. Requirement for significantly modified diet (liquids and/or nothing by mouth) due to compromised oral/pharyngeal function at baseline
8. Complete reliance on parenteral or gastrointestinal tube-delivered nutrition at baseline

   Note: Patients who have gastrostomy tubes prophylactically placed are eligible. Patients receiving supplemental nutrition through a gastrostomy tube at baseline may be eligible depending on diet.
9. Malignant tumors other than HNC within the last five years, unless treated definitively and with low risk of recurrence in the judgment of the treating investigator
10. Active infectious disease excluding oral candidiasis
11. Presence of oral mucositis (WHO Score ≥ Grade 1) at study entry
12. Known history of HIV or active hepatitis B/C (patients who have been vaccinated for hepatitis B and do not have a history of infection are eligible)

13. Female patients who are pregnant or breastfeeding
14. Known allergies or intolerance to cisplatin and similar platinum-containing compounds
15. Requirement for concurrent treatment with nitrates or other drugs that may, in the judgment of the treating investigator, create a risk for a precipitous decrease in blood pressure
16. Medical history that includes any condition, or requires the use of concomitant medications which, in the investigator's judgment, are associated with or create a risk of increased carotid sinus sensitivity, symptomatic bradycardia, or syncopal episodes.

## 7.3. Rationale for Patient Population

Eligibility will be limited to patients with squamous cell tumors of the oral cavity or oropharynx in an attempt to keep the evaluation of OM as uniform as possible and to facilitate comparison with the Phase 1 data and the assumptions derived from the matched data base described in Table 2. Although some trials, such as the trials of palifermin for OM in patients with HNC cancer, have included other anatomic sites (e.g., laryngeal, hypopharyngeal), exclusion of these from the current trial may simplify the evaluation of OM (e.g., by reducing the need for endoscopy) for the immediate goal of obtaining a clearer assessment of the efficacy of GC4419 in the proposed indication. Patients with locally advanced squamous cell cancer of the oral cavity or oropharynx remain appropriate candidates for concurrent chemoradiation as standard of care, with single-agent cisplatin perhaps the most widely accepted and widely used standard regimen.

Eligibility will include patients scheduled to receive the prescribed IMRT/cisplatin regimen either as definitive therapy or post-operatively. Both groups may be candidates for IMRT/cisplatin as standard care and the incidence of severe OM is expected to be similar for both groups. In addition, both have been included in the Phase 1 trial, GT-001.

Patients with unknown primary tumor whose IMRT/cisplatin treatment plans conform to study requirements will be eligible, as most of these patients are considered likely to have oropharyngeal or oral cavity primary tumors.

## 7.4. Screen Failures

A patient is considered to be a screen failure if the patient signs the informed consent form but withdraws consent or is deemed ineligible before being randomly assigned to a treatment arm. The reason why the patient was precluded from the clinical trial will be collected. All patients who sign the informed consent form for this study, including screening failures, will be listed on the Screening, Enrollment, and Discontinuation Log which is further detailed in the Regulatory Binder.

## 7.5. Randomization Failures

A patient is considered to be a randomization failure if the patient signs the informed consent form and is randomized to a treatment arm but withdraws consent or is deemed ineligible prior to receiving their first dose of IMRT and GC4419/placebo. Basic demographic and disease history

information will be collected for randomization failures, as well of the reason the patient was precluded from the clinical trial. All randomization failures will be listed on the Screening, Enrollment, and Discontinuation Log which is further detailed in the Regulatory Binder.

## 7.6. Subject Withdrawal Criteria

In accordance with the Declaration of Helsinki, a patient has the right to withdraw from the study at any time for any reason. The investigator may also, at his/her discretion, discontinue a patient from participating in this study at any time. Additionally, study treatment may be discontinued for any of the following reasons:

- Adverse Event
- Medical requirement to administer a contra-indicated medication
- Patient non-compliance
- Discontinuation of the study at the request of Galera Therapeutics, Inc.

The primary reason for ceasing treatment with the randomized therapy (GC4419 or placebo) will be clearly documented in the patient's medical record and recorded on the appropriate CRF page. Once a patient discontinues, the patient will not be allowed to be retreated.

If a patient discontinues randomized therapy as a result of an adverse event (AE) or serious adverse event (SAE), every attempt should be made to keep the patient in the study and continue to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the patient or investigator, the patient may be withdrawn from the study.

## 7.7. Study and Site Closure

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. In terminating the study, Galera Therapeutics, Inc. and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or site staff, as appropriate:

- Return of all study data to Galera Therapeutics, Inc. (as applicable)
- Resolution of all data queries
- Accountability, reconciliation, and arrangements for all unused study drug
- Review of site study records for completeness
- Shipment of laboratory samples (as applicable)

In addition, Galera Therapeutics, Inc. reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. If Galera Therapeutics, Inc. determines such action is needed, Galera Therapeutics, Inc. will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, Galera Therapeutics,

Inc. will provide advance notification to the investigator of the impending action prior to it taking effect.

Galera Therapeutics, Inc. will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IRB/IEC/REB promptly and provide the reason for the suspension or termination. If the study is prematurely discontinued, all study data must be returned to Galera Therapeutics, Inc.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and Galera Therapeutics, Inc.

# 8. TREATMENT OF SUBJECTS

## 8.1. Concomitant Medications

All concomitant therapies (e.g., prescription and over-the-counter medications) taken by patients from 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. Additionally, any concomitant therapies if used to treat any serious or related adverse event will be recorded in the CRF.

Note that narcotic medications will be captured separately in a pain medication diary and entered into a specific segment of the CRF, apart from other concomitant medications. Narcotic use will only be recorded from the Baseline Visit through the Last Day of IMRT Visit.

Anti-emetic prophylaxis and hematopoietic growth factors should be used per ASCO guidelines.

If a patient withdraws consent for the study or is removed from the study completely (i.e., the patient is no longer participating in any study procedures or follow-up) no further data should be collected after the date of the patient's study discontinuation.

### 8.1.1. Prohibited Medications

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

- Low-level laser treatment for OM
- Amifostine (Ethyol®)
- Benzydamine (Difflam®)
- Cetuximab (Erbitux®)
- Glutamine applied topically
- GM-CSF applied topically
- 'Magic mouthwashes' or 'Miracle mouthwashes' are permitted, provided they do not contain:
    - Chlorhexidine
    - Hydrogen peroxide
    - Diphenhydramine (Benadryl®)
    - Tetracycline
    - Any other listed disallowed medications
    - Notes:
        - Topical lidocaine preparations are permitted

    - Diphenhydramine (Benadryl®) administered as tablets for by injection is permitted; only diphenhydramine liquid formulation is prohibited
- MuGard™, Gelclair®, Episil®, or other barrier devices
- Caphosol®
- Nitrates, phosphodiesterase type 5 (PDE 5) inhibitors (e.g., sildanefil, tadalafil, or similar agents) or other drugs that in the judgment of the treating investigator could create a risk of a precipitous decrease in blood pressure are prohibited until at least 24 hours after the last dose of GC4419
- Pyridostigmine or other drugs that in the judgment of the treating investigator could create a risk of increased carotid sinus sensitivity, symptomatic bradycardia, or syncopal episodes
- Palifermin (Kepivance®) or other keratinocyte or fibroblast growth factor
- Povidone-iodine rinses
- Steroid rinses
- Sucralfate in suspension form (use of sucralfate tablets is not proscribed)
- Other biologic response modifiers – except systemic hematopoietic growth factors for the management of anemia or myelosuppression
- Concurrent approved or investigational anti-cancer therapy (e.g., chemotherapy, immunotherapy, targeted therapy, hormone and biologic therapy) other than the Protocol regimen
- Other investigational agents

All medication restrictions end after post-IMRT OM follow-up is completed unless otherwise noted.

Patients who receive prohibited medications prior to completion of post-IMRT OM follow-up will not automatically be removed from the study; however, administration of a prohibited medication is a significant deviation from the protocol and must be reported to the Medical Monitor as soon as possible and the presiding IRB/IEC/REB (per institutional guidelines). The decision for study continuation or discontinuation will be made at that time on a case-by-case basis and in consideration of the clinical requirement and circumstances.

A standard oral care regimen is recommended, consisting of aggressive oral hygiene, frequent saline rinsing, and the use of daily topical fluoride. Mouthwashes or rinses containing sodium bicarbonate, clotrimazole (Mycelex), nystatin, fluconazole (Diflucan), viscous xylocaine, and/or viscous lidocaine are permitted. If a patient uses “Magic Mouthwashes” or “Miracle Mouthwashes,” all ingredients must be recorded in the patient’s medical record in order to confirm the mouthwashes did not contain the prohibited ingredients listed above.

Anti-emetic prophylaxis and hematopoietic growth factor use are permitted per ASCO guidelines. Following ASCO (and MASCC) guidelines for the prevention and management of chemotherapy-induced nausea and vomiting (CINV) is strongly encouraged.

## 8.2. Treatment Compliance

Compliance with GC4419/placebo dosing, including administration details (e.g., volume, start, stop times, etc.) should be documented in the source documents and recorded on the Case Report Form (CRF).

## 8.3. Randomization and Blinding

### 8.3.1. Treatment Assignment

Patients will be randomly assigned to one of the three study arms through an interactive voice randomization system (IVRS) or web-based randomization system. The system will assign a patient a unique randomization number that will remain consistent for the duration of the study. See the Pharmacy Binder for additional information regarding patient randomization and the IVRS system.

### 8.3.2. Stratification

Central randomization will be stratified according to the following criteria:

- HPV status at baseline: positive vs. negative
- Initial chemotherapy schedule: q3 weeks or weekly cisplatin

### 8.3.3. Blinding

Treatment should remain blinded until the end of the Post-active Phase of the study. Only in the case of an emergency, when knowledge of the investigational product is essential for the clinical management or welfare of the patient, may the investigator unblind a patient's treatment assignment prior to the end of the Post-active Phase. The investigator will, whenever possible, discuss options with the Medical Monitor, on-call physician, or appropriate Galera Therapeutics, Inc./CRO study personnel before unblinding. If the blind is broken for any reason and the investigator is unable to contact Galera Therapeutics, Inc. prior to unblinding, the investigator must notify Galera Therapeutics, Inc./CRO as soon as possible following the unblinding incident without revealing the subject's study treatment assignment, unless the information is important to the safety of patients remaining in the study. In addition, the investigator will record the date and reason for revealing the blinded treatment assignment for that subject in the appropriate section of the CRFs.

If a serious adverse event (SAE; as defined in Section 12.1.2) is reported to Galera Therapeutics, Inc./CRO, Galera Therapeutics, Inc. staff may unblind the treatment assignment for the individual patient. If an expedited regulatory report to one or more regulatory agencies is required, the report will identify the patient's treatment assignment. When applicable, a copy of the regulatory report may be sent to investigators in accordance with relevant regulations, Galera Therapeutics, Inc. policy, or both.

# 9. STUDY DRUG MATERIALS AND MANAGEMENT

## 9.1. Description of Study Drug

**GC4419**

GC4419 (manganese,dichloro[(4aS,13aS,17aS,21aS)-1,2,3,4,4a,5,6,12,13,13a,14,15,16,17,17a,18,19,20,21a-eicosahydro-11,7-nitilo-7H-dibenzo[b,h][1,2,7,10]tetraazacylcoheptadecine-κN5,κN13,κN18,κN21,κN22]-) is a water soluble, highly stable, low molecular weight manganese-containing macrocyclic ligand complex whose activity mimics that of naturally occurring SOD enzymes.

GC4419 is formulated as a clear solution at two concentrations to support the active arms:

- Arm A: 30 mg GC4419: 3 mg/mL in 26 mM sodium bicarbonate-buffered 0.9 wt. % saline for parenteral administration.
- Arm B: 90 mg GC4419: 9 mg/mL in 26 mM sodium bicarbonate-buffered 0.9 wt. % saline for parenteral administration.

There are no other excipients. GC4419 is packaged as an 11 mL ± 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.

**Placebo**

- Arm C: 26 mM sodium bicarbonate-buffered 0.9 wt. % saline for parenteral administration.

There are no other excipients. Placebo is packaged as a clear solution of 11 mL ± 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.

## 9.2. Study Drug Packaging and Labeling

GC4419 (either concentration) and placebo will be presented in kits of 35 single-use vials, which represent 35 daily doses to be administered IV concurrent with IMRT. To maintain the blind, each concentration of GC4419, as well as placebo, will be packaged into amber vials and will appear generally identical; that is, there will be no distinguishing features in or on the packaging that could permit the identification of GC4419 concentration or placebo.

## 9.3. GC4419

GC4419 is packaged as an 11 mL ± 0.1mL aliquot in a 10 mL amber glass vial with a S-127 4432/50 gray stopper and a 20 mm red flip-off seal. Each bottle will be labeled with the appropriate language, including the required regulatory text.

## 9.4. Placebo

Placebo is packaged as an 11 mL ± 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. Each bottle will be labeled with the appropriate language, including the required regulatory text.

## 9.5. Study Drug Storage

### GC4419 and Placebo

GC4419 solutions must be stored at 2°C to 8°C at all times until use. GC4419 solutions must not be frozen at any time. Temperature excursions above freezing and up to 25°C or down to 0.1°C for four hours are accepted; however, Galera Therapeutics, Inc. or its designee must be notified immediately of the temperature excursion to ensure proper oversight.

Once prepared, the IV bags containing GC4419/saline mixtures must also be stored at 2°C to 8°C until use, and must be administered to patients within 24 hours of preparation. GC4419 dosing solutions must not be frozen at any time. If freezing of the material is evident, that supply must be quarantined per institutional guidelines and Galera Therapeutics, Inc. or its designee must be notified immediately.

## 9.6. Study Drug Preparation

### GC4419 and Placebo

GC4419 will be provided to the study site in single use, sterile, pyrogen-free vials ready for dose preparation. Proper mixing with normal saline is required. Standard aseptic techniques will be used to maintain sterility.

Assignment of treatment arm will be randomized 1:1:1 with respect to treatment arms A, B and C. GC4419 (either concentration) and placebo will be presented in kits of 35 single-use vials, which represent 35 daily doses to be administered IV concurrent with IMRT.

To prepare daily IV solutions, investigational pharmacists will extract of 10 mL from a single vial and add to 250 mL normal saline. Note that there is no extraction of saline (i.e., the infusion solution volume will be 250 mL saline + 10mL volume of GC4419/placebo). No additional modifications or adjustments are to be made to the infusion solution.

Further information and preparation details will be provided in a separate pharmacy manual.

Note: Investigational staff who prepare infusion solutions cannot be oral evaluators.

## 9.7. Administration

### GC4419 and Placebo

GC4419 or Placebo/saline mixture will be administered intravenously at an infusion rate that totals 60 min (± 6 min to account for saline overfill) for the total dose assigned. Infusions of GC4419/placebo must be administered using an infusion pump (i.e., not by drip rate). Infusion pump models are not specified and may be per institutional preference/standard.

To facilitate administration of GC4419 according to the study schedule, an indwelling venous access device may be used, at the discretion of the treating investigator. If an indwelling venous access device is placed to facilitate administration of GC4419, this fact will be recorded with the study data, as will information about the date of placement, type of device, and subsequent complications or adverse events related to the use of the device.

IMRT must be initiated as soon as possible upon completion of the GC4419/placebo infusion, but no later than 60 minutes following the end of the infusion.

GC4419/placebo will be given beginning on the first day of radiation and continuing daily, concurrent with each dose of IMRT, to a cumulative radiation dose of approximately 60-72 Gy.

Table 9 outlines the chemoradiation and GC4419/placebo administration schedules. Please note chemotherapy is not required to be administered on the study days listed in Table 9 as long as it follows a weekly or tri-weekly schedule.

If IMRT is not administered on any given day due to a treatment break or unforeseen circumstances, GC4419/placebo should not be administered on that day. Breaks in IMRT will be determined by the patient's treating physician in accordance with standard of care. Patients should resume GC4419/placebo administration when IMRT resumes. On days when planned doses of both GC4419/placebo and IMRT are not administered (e.g., due to a holiday site closure), GC4419/placebo dosing may be extended along with IMRT to make up the missed dose(s) to a maximum of 35 doses of GC4419/placebo. If a fraction of IMRT is not administered for any reason after GC4419/placebo has been administered, that day's GC4419/placebo will count as one of the 35 doses.

**Table 9: Chemoradiation and GC4419 Example Administration Schedule: 35 Doses of GC4419 (7 Week Schedule)**

| Treatment | Week 1 | | | | | | Week 2 | | | | | | Week 3 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Days 6&7 | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Days 13&14 | Day 15 | Day 16 | Day 17 | Day 18 | Day 19 | Days 20&21 |
| **GC4419/ Placebo[1]** | X | X | X | X | X | | X | X | X | X | X | | X | X | X | X | X | |
| **Cisplatin[2]** | | | | | | | | | | | | | | | | | | |
| Tri-Weekly | X | | | | | | | | | | | | | | | | | |
| Weekly | X | | | | | | X | | | | | | X | | | | | |
| **Radiation[3]** | X | X | X | X | X | | X | X | X | X | X | | X | X | X | X | X | |

| Treatment | Week 4 | | | | | | Week 5 | | | | | | Week 6 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day 22 | Day 23 | Day 24 | Day 25 | Day 26 | Days 27&28 | Day 29 | Day 30 | Day 31 | Day 32 | Day 33 | Days 34&35 | Day 36 | Day 37 | Day 38 | Day 39 | Day 40 | Days 41&42 |
| **GC4419/ Placebo[1]** | X | X | X | X | X | | X | X | X | X | X | | X | X | X | X | X | |
| **Cisplatin[1]** | | | | | | | | | | | | | | | | | | |
| Tri-Weekly | X | | | | | | | | | | | | | | | | | |
| Weekly | X | | | | | | X | | | | | | X | | | | | |
| **Radiation[2]** | X | X | X | X | X | | X | X | X | X | X | | X | X | X | X | X | |

| Treatment | Week 7 | | | | | |
|---|---|---|---|---|---|---|
| | Day 43 | Day 44 | Day 45 | Day 46 | Day 47 | Days 48&49 |
| GC4419/ Placebo[1] | X | X | X | X | X | |
| Cisplatin[2] Tri-Weekly | | | | | X | |
| Weekly | X[4] | | | | | |
| Radiation[3] | X | X | X | X | X | |

[1] Intravenous GC4419/placebo is administered by a 60-minute intravenous infusion (±6 min) once a day for the first 35 days of IMRT (Monday through Friday). IMRT must be initiated as soon as possible upon completion of GC4419/placebo infusion, but no later than 60 minutes post GC4419/placebo infusion. On Day 1/Baseline, chemotherapy prehydration and infusion should be administered after GC4419/placebo infusion and IMRT, if possible. If IMRT is not received on any given day due to a treatment break or unforeseen circumstances, GC4419/placebo should not be administered on that day. Patients should resume GC4419/placebo administration when IMRT resumes. If a patient is scheduled to receive IMRT on a weekend day (e.g., to make-up for a holiday site closure), the investigator should contact the Medical Monitor for a discussion prior to IMRT administration.

[2] Cisplatin monotherapy should be administered in a standard q3 weeks regimen (80-100 mg/m$^2$) or weekly regimen (30-40 mg/m$^2$). Anti-emetic prophylaxis and hematopoietic growth factor use should be administered per ASCO guidelines. If institutional guidelines permit, cisplatin may be administered prior to or after the first day of IMRT. On days in which chemotherapy and GC4419/placebo are administered, the administration sequence should be GC4419/placebo, IMRT, prehydration, and then cisplatin, if possible. Patients treated with induction chemotherapy prior to concomitant chemoradiation are not eligible for this study.

[3] Eligible patients will be scheduled to receive a continuous course IMRT delivered in single daily fractions of 2.0 to 2.2 Gy, five days per week (Monday through Friday), with a cumulative radiation dose between 60 Gy and 72 Gy. Planned radiation treatment fields must include at least two oral sites (buccal mucosa, floor of mouth, tongue, soft palate) that are each planned to receive $\geq$ 50 Gy.

[4] The 7th dose of cisplatin will only be administered if the patient is on the 7-dose weekly cisplatin schedule (weekly cisplatin schedule may be 6 or 7 doses, depending on investigator choice).

## 9.8. Study Drug Accountability

### GC4419 and Placebo

The investigator is responsible for ensuring adequate accountability of all used and unused GC4419/placebo. This includes acknowledgment of receipt of each shipment of GC4419/placebo (quantity and condition), patient dispensing records, and quantity of GC4419/placebo returned or destroyed. Dispensing records will document quantities received from Galera Therapeutics, Inc. and quantities dispensed to patients, including container number or lot number, date dispensed, patient identifier number, patient initials, and the initials of the person dispensing the medication. Any GC4419/placebo that is prepared but not used must also be recorded in the dispensing records.

All GC4419/placebo supplies and associated documentation will be reviewed and verified by the study monitor. All GC4419/placebo and used containers are to be retained by the site until notified by the study monitor, who will instruct the site in the disposal and/or destruction of all used GC4419/placebo supplies. Copies of all forms, documenting drug receipt at the study site, drug transportation to satellite sites, and drug return to Galera Therapeutics, Inc., together with

drug accountability records, will be retained according to the regulations governing record retention.

The investigator will not allow GC4419/placebo to be given to any patient not included in the study or any unauthorized person.

## 9.9. Study Drug Handling and Disposal

**GC4419 and Placebo**

After completion of the study, all unused study drug will be inventoried and if possible, destroyed locally at the site. GC4419/placebo should not be returned directly to Galera Therapeutics, Inc. unless specifically requested by Galera Therapeutics, Inc. The study monitor will instruct the site in the disposal and/or destruction of all used and unused GC4419/placebo supplies. Destruction of any GC4419/placebo should be documented appropriately.

# 10. TOXICITY MANAGEMENT

## 10.1. Dose Delays and Dose Modifications for Toxicity

The following toxicities require a 25% dose reduction in GC4419/placebo:

- Grade 3 flushing
- Grade 2 or greater hypotension within two hours after the start of GC4419/PBO infusion
- Grade 3 or 4 infusion reaction with GC4419
- Grade 4 vomiting despite optimal antiemetic therapy per current ASCO and MASCC guidelines

Two dose reductions for toxicity will be permitted per patient. After the first event, the patient will be re-challenged at 75% of the original dose (7.5 mL GC4419/placebo in 250 mL normal saline). After the second event, the patient will be re-challenged at 50% of the original dose (5.0 mL GC4419/placebo in 250 mL normal saline). Patients who are unable to tolerate GC4419/placebo infusions following two dose reductions must be discontinued from the study treatment but may continue with cisplatin/IMRT at the discretion of the treating investigator.

For other toxicities (including those attributable to cisplatin and IMRT), management will be per institutional and ASCO guidelines and investigator judgment.

Galera strongly recommends that treatment modifications for cisplatin related toxicities should be managed by reducing the dose and/or altering the schedule of cisplatin administration. Such modifications may be made per the judgment of the treating investigator. However, substitution of other systemic agents (e.g., carboplatin with or without paclitaxel, cetuximab, etc.) is not consistent with the protocol and should not be done without prior consultation with the Galera Medical Monitor to determine the patient's eligibility for continuing protocol treatment.

## 10.2. Supportive Care Guidelines

Necessary supportive measures for optimal medical care will be given throughout the study. Supportive care medications may be administered at the investigator's discretion and recorded in the CRF (including administration of prophylactic antiemetic medication if deemed appropriate by the investigator). However, medications are subject to the exclusions listed in Section 8.1.1.

### 10.2.1. Supportive care for chemotherapy-induced nausea and vomiting (CINV)

Medication to prevent or manage chemotherapy-induced nausea and vomiting (CINV) should follow recent guidelines from ASCO and MASCC (Appendix 7, Section 25). It should be noted that single-agent IV cisplatin is considered a "high risk" treatment for the purposes of these guidelines. Therefore, the use not only of a 5-$HT_3$ receptor antagonist and dexamethasone, but also an $NK_1$ antagonist (aprepitant or fosaprepitant) is recommended.

Supportive care for CINV should be optimized, per ASCO and MASCC guidelines, before GC4419 dose is reduced for nausea and vomiting.

# 11. ASSESSMENTS

The study procedures to be conducted for each patient enrolled in the study are described in the text that follows and presented in Section 19.

Any deviation from protocol procedures should be explained in the source documents. The sponsor (or designee) and the site's institutional review board (IRB – as required by the IRB's policies and procedures) should be notified as soon as possible of any substantial deviations potentially affecting patient safety, study drug administration or the assessment of safety, efficacy and tolerability parameters.

## 11.1. Safety Assessments

Safety will be assessed on the basis of treatment-emergent AEs, physical examination findings, clinical laboratory tests, electrocardiogram (ECG) measurements, and vital sign measurements.

### 11.1.1. Clinical Assessments

The following clinical assessments are defined when referenced in the schedule of events for this study:

- 12-Lead ECG: ventricular rate, P-R interval, QRS interval, QT interval, and QTc
- Vital signs: measured following two minutes of rest in the sitting position – temperature, systolic and diastolic blood pressures, heart rate and respiration rate
- Weight and Height: measured in kilograms (kg) and centimeters (cm), respectively
- Performance Status: ECOG (see Section 22 for conversion criteria for Karnofsky to ECOG)

### 11.1.2. Laboratory Assessments

All protocol required clinical laboratory assessments should be performed at the central laboratory.

The investigator must assess all abnormal clinical laboratory results for clinical significance in a timely fashion. A notation of clinically significant (CS) or non-clinically significant (NCS) with initials and date will be documented on the respective laboratory report next to any abnormal value. Information on laboratory AE reporting can be found in Section 12.

The following laboratory assessments are defined when referenced in the schedule of events for this study:

- 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.
- Serum Chemistry Profile: glucose, BUN, creatinine, sodium, potassium, calcium, albumin, total protein, direct bilirubin, total bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), chloride, phosphate, bicarbonate.
- Serum Pregnancy Test: required for all females of childbearing potential. Lack of childbearing potential must be noted in the source documents, if applicable.

## 11.2. Oral Mucositis Assessments

OM assessments will be completed at the Screening Visit (within 28 days of IMRT start), Baseline Visit, and twice weekly (no less than 48 hours apart) within each five-day IMRT treatment period. The extent of patients' OM will be assessed by a trained evaluator and scored using the WHO OM toxicity grading scale. All patients must have an oral assessment on the last day of IMRT treatment. If a patient withdraws for any reason prior to the end of IMRT, a complete oral assessment should be done on that day.

If a patient has a WHO score ≥ 2 at the completion of IMRT, the patient will be evaluated at weekly (± 2 days) intervals until the WHO score returns to ≤ 1 or until the Week 8 Post-IMRT Follow-up Visit, whichever comes first. Post-IMRT Follow-up Visit should occur at intervals of 7 ± 2 calendar days from the last day of IMRT (i.e., 7, 14, 21 days, etc.) and not 7 days from the previous Post-IMRT OM Visit.

Study site personnel will be provided with specific training and instructions regarding OM assessment performance, grading, and documentation. Designated trained study staff (oral evaluators) will conduct all assessments using a standardized and consistent method. To reduce inter-observer variability, the fewest possible number of evaluators should be involved in the assessments of each patient. The oral evaluators will use a Sponsor-provided headlamp for all oral assessments conducted for this study.

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

- Solid foods are defined as foods that need to be chewed. Examples include meat, grains and vegetables.
- Liquids are defined as foods that take the shape of their container. Examples include fruit juices, soups, pureed foods, mashed potatoes, cooked cereals (oatmeal), baby food, Jell O®, pudding, and ice cream.
- Nothing by mouth is defined as no eating or drinking, except enough liquid to allow for taking medications.

The WHO scoring scale is appended in Section 20.

## 11.3. Radiation Therapy Quality Assurance

Quality assurance for IMRT will be conducted by a prospective review of the overall treatment plan, at the time of patient screening, by a radiation oncologist who is not an investigator on the trial. In addition to IMRT treatment, dosimetry and dose volume histograms will be collected after simulation. Confirmation of appropriate planned doses to oral cavity and oropharynx sub-sites for eligibility will be confirmed. Galera plans to collect the following information from all investigators:

- Institutional policy/radiation oncologists plan regarding the margins used to determine Gross Tumor Volumes, (GTV), Clinical Target Volumes (CTV) and Planning Target Volumes (PTV)
- What elective volumes are to be treated
- What nodal levels are to be treated

This information will be available for summary and retrospective analysis at the end of the study.

## 11.4. Patient Reported Outcomes (PRO)

### 11.4.1. Oral Mucositis Daily Questionnaire (OMDQ)

Patients will be required to personally complete the OMDQ. The OMDQ will be contained in the patient diary and will be completed daily, including weekend days, during the IMRT treatment period. If a patient is required to continue weekly visits after the last day of IMRT based on his/her WHO score, the OMDQ will be completed at the time of those visits. As any manipulation of the patient's mouth may influence PRO responses, the OMDQ must be completed prior to the oral assessment.

The mouth and throat soreness (MTS) question of the OMDQ contains five response categories from 0 (no soreness) to 4 (extreme soreness). In a study conducted by Stiff et al. (2006), the OMDQ MTS question two score was found to be highly correlated with the WHO Scale and patients reported the onset, peak and resolution of oral pain one to three days earlier than physicians using the clinical assessment.

The OMDQ has been used in the Phase 1 trial, GT-001, with excellent patient compliance. The OMDQ was used in past trials in OM, notably the registration trial of palifermin.[44] In that trial, there was high patient compliance (>80%), and good test-retest and internal consistency reliability. Changes in MTS-related scores—particularly for question two ("During the last 24 hours, how much mouth and throat soreness did you have?") paralleled changes in the WHO OM score and were higher in patients with severe (Grade 3-4) OM than for patients with Grade 1-2 OM. Changes in MTS-related scores on the OMDQ preceded changes in the WHO scoring by one to two days, perhaps reflecting the timing of visits to assess and record the WHO score.

It may be further noted that a weekly counterpart to the OMDQ—the OMWQ—has been reported to be more responsive to early changes in symptoms than less symptom-focused instruments such as the FACT-HN and the FHNSI.[45]

The OMDQ can be found in Appendix 3, Section 21. Results from the OMDQ are an exploratory endpoint of this study.

## 11.5. Health and Economic Outcomes

Several health and economic outcomes, including the incidence and duration of opioid use, insertion of and need for use of gastrostomy tube feedings, use and complications of indwelling venous access catheters, and unplanned office visits, emergency room visits, or hospitalizations, will be assessed throughout the study.

### 11.5.1. Pain Medication Diary

Questions regarding analgesic use will be contained in the patient pain medication diary, which will be completed daily, including weekend days, during the IMRT treatment period (Baseline Visit through Last Day of IMRT Visit). In addition, general concomitant medications will be recorded by study personnel on weekdays during IMRT treatment. To measure opiate analgesic use for oral pain, patients will be required to record in the pain medication diary each time any opiate analgesics are administered (either by self or investigational staff).

Unaided written completion of the pain medication diary by the patient should always be encouraged and should be considered the standard method of data collection for the study. However, diary responses should be recorded using one or more of the methods described below if the patient is unable to fully complete the diary him/herself:

1. From the patient in the form of a verbal response recorded in the diary with the assistance of:
    a. A spouse, family member, or other personal caretaker
    b. Study coordinator, study nurse, or investigator
2. From the patient's medical record if:
    a. The patient is hospitalized, or otherwise incapacitated
    b. The patient supplies incomplete information

Adequate documentation (i.e. emergency room or inpatient hospitalization reports, documentation of a prescription on file, etc.) must be on file in the patient's medical record and available for review by the site monitor.

## 11.6. Pharmacokinetic (PK) Measurements

Sparse PK sampling will be sought from all patients for GC4419 and its two metabolites, GC4520 and GC4570.

Plasma samples for GC4419 PK measurements will be collected in two cycles: Study Days 1 and 2, and Study Days 22 and 23. On Study Days 1 and 22, four samples will be drawn as follows:

1. The first sample will be drawn prior to GC4419 administration.
2. The second sample will be drawn within 10 minutes after the end of GC4419 infusion.
3. The third sample will be drawn within 10 minutes after the end of IMRT.
4. The fourth and final sample will be drawn between 60 and 180 minutes after the end of GC4419 infusion. If cisplatin is being administered on the same day as PK sampling, it is preferred that the PK sample be drawn prior to cisplatin administration, but not required.

On Study Days 2 and 23 only one PK sample will be drawn. This sample should be drawn approximately 24 hours after the previous day's GC4419 infusion but prior to the GC4419 infusion on Days 2 and 23.

Table 10 below summarizes the PK sample collection time points. Note that this schedule may be adjusted to accommodate mid/late-week study starts and holidays. Adjustments in the PK schedule must be approved by Galera, and will not be considered a protocol deviation by the

Sponsor if pre-approved. Time of actual blood draws for PK assessment must be recorded in the source notes. Plasma PK samples will be sent to a central laboratory for analysis and interpretation. Further details on PK sample collection, processing, and shipping are provided in a separate manual. Volumes and start/stop times for administration of IV fluids will be collected on PK sampling days.

**Table 10: Pharmacokinetic Sampling Schedule to Assess GC4419, Metabolites GC4570 and GC4520**

| | Day 1 | Day 2 | Day 22 | Day 23 |
|---|---|---|---|---|
| Pre-GC4419 | X | X[1] | X | X[1] |
| End of Infusion-GC4419 (+10min) | X | | X | |
| Post-IMRT (+10min) | X | | X | |
| 60 – 180 min Post End of Infusion-GC4419[2] | X | | X | |

[1]Approximately 24 hours after previous day's GC4419 infusion.
[2]If cisplatin is being administered on this day, it is preferred that the PK sample be drawn prior to cisplatin administration, but not required.

## 11.7. Biological Surrogate Markers of Mucositis

Preliminary data obtained during the ongoing Phase 1 study provide preliminary evidence of GC4419's biological activity. Consequently, biological surrogate markers of mucositis will be assessed in all patients enrolled in the study. Correlation between levels of circulating cytokines and proteins and clinical endpoints will be assessed by analysis of blood samples collected for all patients during the active phase of the study. Refer to Appendix 1, Section 19 for the schedule of biomarker assessments for each treatment schedule. For patients who consent separately, RNA samples for the assessment of gene expression patterns prior to receiving the first dose of GC4419 and upon completion of GC4419 doses will be collected during screening and on the last day of IMRT. Additional details regarding the processing and handling of biomarker samples will be provided in a separate manual.

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.

## 11.8. Tumor Status Assessment

### 11.8.1. Clinical Tumor Assessment

The patient's tumor status will be assessed clinically at the following time points:

- Last day of IMRT
- Every 3 months, ± 30 days, throughout the 1st year post-IMRT (Months 3, 6, 9, and 12)
- Every 4 months, ± 30 days, throughout the 2nd year post-IMRT (Months 16, 20, and 24)

The following tumor status information will be collected at each of the above time points:

- Survival

- Disease progression
- Development of second primary tumors
- Additional malignancies

If disease progression is suspected at any of the above visits, a laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure), should be conducted. If disease progression is not suspected, a neck and oral exam is sufficient.

### 11.8.2. Tumor Imaging

#### 11.8.2.1. Pre-Treatment Tumor Imaging

Radiographic tumor imaging must occur within 60 days prior to the first day of IMRT (Baseline). One of the following imaging combinations is recommended:

- CT scan of the neck with contrast plus chest CT with or without contrast
- MRI scan of the neck with contrast plus chest CT with or without contrast
- CT scan of the neck with contrast plus PET/CT of the neck and chest with or without contrast
- MRI scan of the neck with contrast plus PET/CT of the neck and chest with or without contrast

If the patient has no evidence of disease at Baseline, it should be clearly indicated.

#### 11.8.2.2. Post-Treatment Tumor Imaging

Radiographic imaging must be performed 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.

When possible, the same imaging technique (i.e., CAT, PET, or MRI) that was used for pre-treatment tumor imaging at the time of staging should be used for post-treatment tumor imaging.

## 11.9. Xerostomia and Trismus Assessments

To assess trismus, the maximum opening of the mouth that a patient can achieve will be assessed by measuring the distance in millimeters between the incisal edges of the mandibular and maxillary incisors at midline using a Sponsor-provided ruler.

To assess xerostomia, patients will mark their response on a 100 mm visual analog scale (VAS See Section 24) anchored on the left with negative responses (very dry; extremely uncomfortable; very difficult) and on the right with positive responses (not dry; comfortable; easy).

The assessments for trismus and xerostomia will be performed and recorded at Baseline and at Months 3, 6, 9, 12, 16, 20, and 24 Post-IMRT.

## 11.10. Schedule of Time and Events

A schedule of study assessments table is located in Appendix 1, Section 19. Minor changes to the assessment schedule may be made to accommodate holidays, administrative closures, etc., which if necessary, are not considered as significant deviations by the Sponsor. Sites should contact the Sponsor (or its representative) prospectively to address rescheduling protocol assessments and data handling.

## 11.11. Screening Phase

The following screening observations and procedures will be completed within 28 days of IMRT and GC4419 start:

- Confirm patient eligibility by reviewing inclusion/exclusion criteria
- Obtain a signed IRB/IEC/REB-approved informed consent
- Obtain medical history, smoking and alcohol use
- Obtain HNC history; HNC history should include:
    - HPV status and strain (s) if known
    - Pre-treatment tumor imaging (See Section 11.8.2.1; may be completed within 60 days prior to the first day of IMRT)
    - Prior treatments
    - Confirmation of histopathological diagnosis of SCC
- Conduct a complete physical examination, including height
- Ensure a dental examination was conducted for IMRT clearance and potential sources of mucosal irritation (e.g., tooth extraction) were eliminated. The dental exam must occur within the 28-day screening period. The exam must be performed by a licensed clinician, but not necessarily by a dentist. For edentulous patients, the patient must be cleared for IMRT per SOC (i.e., oral exam).
- Conduct OM assessment and record the WHO score
- Record planned IMRT and chemotherapy parameters
- Measure vital signs, body weight, and ECOG Performance Status
- Conduct a 12-lead ECG
- Record concomitant medications from date of randomization
- Record adverse events from date of randomization
- Record/update medical conditions and illnesses that have occurred since the patient signed the ICF
- Draw blood for laboratory measurements
    - Chemistry profile
    - Hematology profile

- Biomarker sample for pro-inflammatory cytokine analysis (See Sections 11.7 and 19)
- For patients who consent separately: RNA sample (PAXgene) for genomic studies (See Sections 11.7 and 19)
- Serum pregnancy test for women of childbearing potential

All questions related to patient eligibility should be directed to Galera's Medical Monitor or designee.

## 11.12. Active Phase

### 11.12.1. Baseline/Day 1 (First Day of IMRT and GC4419)

Prior to receiving the first dose of GC4419 the following observations and procedures will be conducted for all patients:

- Confirm continued patient eligibility by reviewing inclusion/exclusion criteria
- Measure vital signs, body weight, and ECOG Performance Status
- Conduct 12-lead ECG
- Provide and review instructions for completion of the daily diary (OMDQ & analgesic recording)
- Provide the daily diary for recording the OMDQ
- Have the patient complete the OMDQ and review completion
- Conduct OM assessment (OMDQ must be completed prior to the OM assessment) and record the severity using the WHO score
- Conduct trismus assessment
- Conduct xerostomia assessment
- Record BSA (used to confirm cisplatin dosing)
- Ensure concomitant medications have been recorded from date of randomization
- Ensure adverse events have been recorded from date of randomization
- Record placement of an indwelling venous catheter (at baseline, or at any time during the study)
- Record use and/or placement of gastrostomy tube
- Record/update medical conditions and illnesses that have occurred since the patient signed the ICF
- Draw blood for laboratory measurements
  - Chemistry profile
  - Hematology profile
  - PK sampling (See Section 11.6 and Table 10)
  - Biomarker sample for pro-inflammatory cytokine analysis (See Sections 11.7 and 19)

Administer the first GC4419 dose by continuous intravenous infusion over 60 minutes. IMRT must begin as soon as possible but no later than 60 minutes following the end of GC4419 dosing. Following IMRT, hydration and chemotherapy pre-medications should be administered per institutional guidelines prior to cisplatin administration.

### 11.12.2. Day 2 of IMRT and GC4419

Prior to GC4419 administration the following observations and procedures will be conducted for all patients:

- Record concomitant medications
- Record adverse events
- Ensure the daily diary is completed
- PK sampling (Section 11.6 and Table 10)

Administer the second GC4419 dose by continuous intravenous infusion. IMRT must begin as soon as possible but no later than 60 minutes following the end of GC4419 dosing.

### 11.12.3. Days 3 to 5 of IMRT and GC4419

Prior to GC4419 administration the following observations and procedures will be conducted for all patients on **Days 3, 4, and 5 unless otherwise noted**:

- Record concomitant medications
- Record adverse events
- Ensure the daily diary is completed; on Friday provide daily diary pages for the patient to complete at home over the weekend

Prior to GC4419 administration the following observations and procedures will be conducted for all patients on **Day 3, 4, or 5 unless otherwise noted**:

- Conduct second OM assessment for the week (OMDQ must be completed prior to the OM assessment) and record the severity using the WHO score
- Record use and/or placement of gastrostomy tube
- Draw blood for laboratory measurements
    - Chemistry profile
    - Hematology profile

Administer GC4419 dose by continuous intravenous infusion. IMRT must begin as soon as possible but no later than 60 minutes following the end of GC4419 dosing.

### 11.12.4. Week 2

Prior to GC4419 administration the following observations and procedures will be conducted for all patients on **all IMRT days**:

- Record concomitant medications

- Record adverse events
- Ensure the daily diary is completed; on Friday provide daily diary pages for the patient to complete at home over the weekend

Prior to GC4419 administration the following observations and procedures will be conducted for all patients **twice during this week, at least 48 hours apart**:

- Conduct OM assessment (OMDQ must be completed prior to the OM assessment) and record the severity using the WHO score
- Record use and/or placement of gastrostomy tube
- Record unscheduled office visits, ER visits, or hospitalizations

Prior to GC4419 administration the following observations and procedures will be conducted for all patients **once this week**:

- For patients receiving weekly cisplatin, record BSA (used to confirm cisplatin dosing)
- Draw blood for laboratory measurements
    - Chemistry profile
    - Hematology profile

Prior to GC4419 administration the following observations and procedures will be conducted on the **day of the second OM assessment only**:

- Draw blood for laboratory measurements
    - Biomarker sample for pro-inflammatory cytokine analysis (See Sections 11.7 and 19)

Administer GC4419 dose by continuous intravenous infusion. IMRT must begin as soon as possible but no later than 60 minutes following the end of GC4419 dosing.

### 11.12.5. Week 3

Prior to GC4419 administration the following observations and procedures will be conducted for all patients on **all IMRT days**:

- Record concomitant medications
- Record adverse events
- Ensure the daily diary is completed; on Friday provide daily diary pages for the patient to complete at home over the weekend

Prior to GC4419 administration the following observations and procedures will be conducted for all patients **twice during this week, at least 48 hours apart**:

- Conduct OM assessment (OMDQ must be completed prior to the OM assessment) and record the severity using the WHO score
- Record use and/or placement of gastrostomy tube

- Record unscheduled office visits, ER visits, or hospitalizations

Prior to GC4419 administration the following observations and procedures will be conducted for all patients **once this week**:

- For patients receiving weekly cisplatin, record BSA (used to confirm cisplatin dosing)
- Draw blood for laboratory measurements
    - Chemistry profile
    - Hematology profile

Administer GC4419 doses by continuous intravenous infusion. IMRT must begin as soon as possible but no later than 60 minutes following the end of GC4419 dosing.

### 11.12.6. Week 4

Prior to IMRT administration the following observations and procedures will be conducted for all patients on **all IMRT days**:

- Record concomitant medications
- Record adverse events
- Ensure the daily diary is completed; on Friday provide daily diary pages for the patient to complete at home over the weekend

Prior to IMRT administration the following observations and procedures will be conducted for all patients **twice during this week, at least 48 hours apart**:

- Conduct OM assessment (OMDQ must be completed prior to the OM assessment) and record the severity using the WHO score
- Record use and/or placement of gastrostomy tube
- Record unscheduled office visits, ER visits, or hospitalizations

Prior to GC4419 administration the following observations and procedures will be conducted for all patients **once this week**:

- Perform symptom-directed PE
- Measure vital signs, body weight, and ECOG Performance Status
- Record BSA (used to confirm chemotherapy dosing)
- Draw blood for laboratory measurements
    - Chemistry profile
    - Hematology profile

Prior to GC4419 administration the following observations and procedures will be conducted for all patients on the **day of the second OM assessment only**:

- Draw blood for laboratory measurements

- Biomarker sample for pro-inflammatory cytokine analysis (See Sections 11.7 and 19)

Prior to GC4419 administration the following observations and procedures will be conducted for all patients on **Days 22 and 23 only**:

- Draw blood for laboratory measurements
  - PK sampling (Section 11.6 and Table 10)

Prior to GC4419 administration the following observations and procedures will be conducted for all patients on **Day 22 only**:

- Conduct 12-lead ECG

Administer GC4419 doses by continuous intravenous infusion. IMRT must begin as soon as possible but no later than 60 minutes following the end of GC4419 dosing.

### 11.12.7. Week 5

Prior to GC4419 administration the following observations and procedures will be conducted for all patients on **all IMRT days**:

- Record concomitant medications
- Record adverse events
- Ensure the daily diary is completed; on Friday provide daily diary pages for the patient to complete at home over the weekend

Prior to GC4419 administration the following observations and procedures will be conducted for all patients **twice during this week, at least 48 hours apart**:

- Conduct OM assessment (OMDQ must be completed prior to the OM assessment) and record the severity using the WHO score
- Record use and/or placement of gastrostomy tube
- Record unscheduled office visits, ER visits, or hospitalizations

Prior to GC4419 administration the following observations and procedures will be conducted for all patients **once this week**:

- For patients receiving weekly cisplatin, record BSA (used to confirm cisplatin dosing)
- Draw blood for laboratory measurements
  - Chemistry profile
  - Hematology profile

Administer GC4419 doses by continuous intravenous infusion. IMRT must begin as soon as possible but no later than 60 minutes following the end of GC4419 dosing.

### 11.12.8. Week 6

Prior to IMRT administration the following observations and procedures will be conducted for all patients on **all IMRT days**:

- Record concomitant medications
- Record adverse events
- Ensure the daily diary is completed; on Friday provide daily diary pages for the patient to complete at home over the weekend

Prior to IMRT administration the following observations and procedures will be conducted for all patients **twice during this week, at least 48 hours apart**:

- Conduct OM assessment (OMDQ must be completed prior to the OM assessment) and record the severity using the WHO score
- Record use and/or placement of gastrostomy tube
- Record unscheduled office visits, ER visits, or hospitalizations

Prior to IMRT administration the following observations and procedures will be conducted for all patients on the **once this week**:

- For patients receiving weekly cisplatin, record BSA (used to confirm cisplatin dosing)
- Draw blood for laboratory measurements
    - Chemistry profile
    - Hematology profile

Prior to IMRT administration the following observations and procedures will be conducted for all patients on the **day of the second OM assessment only this week**:

- Draw blood for laboratory measurements
    - Biomarker sample for pro-inflammatory cytokine analysis (See Sections 11.7 and 19)

Administer GC4419 doses by continuous intravenous infusion. IMRT must begin as soon as possible but no later than 60 minutes following the end of GC4419 dosing.

### 11.12.9. Week 7 (plus additional IMRT weeks, if needed)

Prior to IMRT administration the following observations and procedures will be conducted for all patients on **all IMRT days**:

- Record concomitant medications
- Record adverse events
- Ensure the daily diary is completed; on Friday provide daily diary pages for the patient to complete at home over the weekend

Prior to IMRT administration the following observations and procedures will be conducted for all patients **twice during this week, at least 48 hours apart**:

- Conduct OM assessment (OMDQ must be completed prior to the OM assessment) and record the severity using the WHO score
- Record use and/or placement of gastrostomy tube
- Record unscheduled office visits, ER visits, or hospitalizations

Prior to IMRT administration the following observations and procedures will be conducted for all patients **once this week**:

- Draw blood for laboratory measurements
    - Chemistry profile
    - Hematology profile
- Measure vital signs, body weight, and ECOG Performance Status
- If receiving cisplatin this week, record BSA (used to confirm cisplatin dosing)

Administer GC4419 doses by continuous intravenous infusion. IMRT must begin as soon as possible but no later than 60 minutes following the end of GC4419 dosing.

### 11.12.10. Last Day of IMRT or Early Termination Visit

Prior to IMRT administration the following observations and procedures will be conducted for all patients on the last day of IMRT or if the patient terminates study participation early:

- Conduct a complete physical examination
- Measure vital signs, body weight, and ECOG status
- Conduct clinical tumor status assessment
- Conduct 12-lead electrocardiogram (ECG)
- Ensure the daily diary is completed
- Conduct OM assessment (OMDQ must be completed prior to the OM assessment) and record the severity using the WHO score
- Record any concomitant medications
- Record adverse events
- Record use and/or placement of gastrostomy tube
- Draw blood for laboratory measurements
    - Chemistry profile
    - Hematology profile
        - Note: 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.

- Biomarker sample for pro-inflammatory cytokine analysis (See Sections 11.7 and 19)
- For patients who consent separately: RNA sample (PAXgene) for genomic studies (See Sections 11.7 and 19)

### 11.12.11. Post-IMRT Weeks 1 through 8

If a patient has a WHO score ≥ 2 at the completion of IMRT, the patient will be evaluated at weekly (± 2 days) intervals until the WHO score returns to ≤ 1 or until the Week 8 Post-IMRT Follow-up Visit, whichever comes first. Post-IMRT Follow-up Visit should occur at intervals of 7 ± 2 calendar days from the last day of IMRT (i.e., 7, 14, 21 days, etc.) and not 7 days from the previous Post-IMRT Visit. At each visit, the following should be completed:

- Administer the OMDQ
- Conduct OM assessment (OMDQ must be completed prior to the OM assessment) and record the severity using the WHO score
- Record adverse events and concomitant medications through 30 days following the last dose of IMRT, cisplatin, or GC4419/placebo (i.e., whichever occurs last)

## 11.13. Post-Active Phase

All patients will be followed for two years Post-IMRT. Patients will be seen every 3 months throughout the first year Post-IMRT (Months 3, 6, 9, and 12) and every 4 months throughout the second year Post-IMRT (Months 16, 20, and 24), ± 30 days for each visit. At each of these visits the patient should be seen by a Radiation Oncologist, Medical Oncologist, ENT, or Head & Neck Surgeon and the following assessments should be conducted:

- Clinical tumor assessment (See Section 11.8.1)
- Xerostomia and Trismus assessments (See Section 11.9)

Radiographic imaging must be performed 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.

As indicated in Section 11.8.2.2, radiographic imaging is highly recommended if disease progression is suspected by the treating physician at any of the above time points. If radiographic imaging is performed, both local/regional recurrence and distant metastases should be evaluated. Biopsy of any lesion(s) suspicious for tumor recurrence is also recommended.

When possible, the same imaging technique (i.e., CAT, PET, or MRI) that was used for pre-treatment tumor imaging at the time of staging should be used for post-treatment tumor imaging.

# 12. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. Throughout the study, AEs will be recorded in the source documents and on the appropriate pages of the CRF regardless of whether the AEs are considered related to GC4419/placebo. To avoid confusion, the AE should be recorded in standard medical terminology.

## 12.1. Definitions

The following definitions of terms are guided by the International Conference on Harmonization and the US Code of Federal Regulations and are included here verbatim.

### 12.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

**Examples of an AE include:**

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity (grade) of the condition.
- New conditions detected or diagnosed after investigational product administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae associated with a suspected interaction of the investigational product with a concomitant medication.
- Signs, symptoms, or the clinical sequelae associated with a suspected overdose of either investigational product or a concurrent medication.

### 12.1.2. Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening – *NOTE: The term 'life-threatening' in the definition of 'serious' refers to any adverse drug experience [adverse event] that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death. [emphasis added]*

- Requires inpatient hospitalization or prolongation of hospitalization – NOTE*: In general, hospitalization signifies that the patient or subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.*
- Results in persistent or significant disability/incapacity – *NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions*.

OR

- Is a congenital abnormality/birth defect.

## 12.2. Adverse Event Reporting Requirements

### 12.2.1. Serious Adverse Events

All events meeting the criteria for Serious Adverse Events (see Section 12.1.2) must be reported by investigational sites within 24-hours of becoming aware of the event. In order to determine the sponsor's timeline for notifying regulatory authorities and investigators per Federal Regulations, an event term, serious criteria, and causality is required at the time of the initial report. Specific SAE reporting instructions are provided in a separate manual.

The investigator is responsible for notifying the IRB/IEC/REB in writing of serious events as soon as is practical in accordance with the policy of the IRB/IEC/REB.

### 12.2.2. All Adverse Events (AEs) Regardless of Seriousness

Any adverse medical condition or laboratory abnormality with an onset date before the date of randomization is considered to be pre-existing in nature, and part of a patient's medical history. Adverse medical conditions that begin on or after date of randomization will be considered an adverse event, including SAEs, and followed for 30 days after the last dose of IMRT, cisplatin, or GC4419/placebo (i.e., whichever occurs last), hereafter referred to as the "30 Day Follow-up Period". Similarly, new events will be reported as AEs/SAEs if the start date is within 30 Day Follow-up Period. Increases in toxicity grade of pre-existing conditions that occur on or after the date of randomization are also considered an adverse event.

All adverse events must be recorded in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to randomized therapy.

### 12.2.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than

expected for the patient's condition, or that are present or detected at the time of randomization and do not worsen, will not be reported as AEs or SAEs.

Laboratory abnormalities should only be recorded in the Adverse Event section of the CRF if at least one of the following criteria is met:

- Meets the criteria of an SAE
- Resulted in a dose reduction and/or delay in the administration of GC4419/placebo, IMRT, and/or cisplatin
- Treatment is initiated for the abnormality
- Investigational product was discontinued
- Grade 3 or Grade 4 per National Cancer Institute Common Terminology Criteria for Adverse Event Version 4.03 (NCI CTCAE v4.03)

All other abnormal laboratory findings will be captured via laboratory CRF pages and noted in shift tables.

Abnormal assessments (e.g., ECGs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definitions as defined in Section 12.1.

### 12.2.4. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Oral mucositis and xerostomia will not be reported as AEs as they are captured as study endpoints in the CRF. Progressive disease found by scan or on clinical evaluation should be captured on the applicable lesion CRF pages and not as an AE.

### 12.2.5. Grading of Adverse Events

The severity of adverse events will be designated as mild, moderate, severe, life threatening, or fatal per NCI CTCAE version 4.03. If not specifically addressed in NCI CTCAE version 4.03, use Table 11 below:

**Table 11: Adverse Event Severity**

| Grade | Criteria[1] |
|---|---|
| Mild – Grade 1 | Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| Moderate – Grade 2 | Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[2] |
| Severe – Grade 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[3] |
| Life Threatening – Grade 4 | Life-threatening consequences; urgent intervention indicated |
| Death – Grade 5 | Death related to adverse event |

[1] A Semi-colon indicates 'or' within the description of the grade.

[2] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[3] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

## 12.3. Relationship to Study Drug

All AEs will be categorized by the investigator with respect to their relationship to GC4419/placebo. The relationship between GC4419/placebo and the AE may be considered related, possibly related, or unrelated. The criteria for each category are listed below:

- **Related:** It is likely that GC4419/placebo caused or contributed to the cause of the adverse event or laboratory abnormality, when the temporal sequence from the time of GC4419/placebo administration, the known consequences of the patient's clinical/state condition or study procedures, the effects of discontinuing or reintroducing GC4419/placebo on the adverse event, and other medically relevant factors are considered.
- **Possibly Related:** There is a reasonable possibility that the adverse event or laboratory abnormality was caused by GC4419/placebo, when the temporal sequence from the time of GC4419/placebo administration, the known consequences of the patient's clinical state/condition or study procedures, and other medically relevant factors are considered.
- **Unrelated:** The investigator has a high level of certainty that the patient's clinical state/condition, study procedures, or other medically relevant factors other than treatment with GC4419/placebo caused the adverse event or laboratory abnormality. This relationship category should only be used when a clear precipitating cause exists and it is not reasonably possible that the event is caused by treatment with GC4419/placebo.

If the relationship between the AE/SAE and the investigational product is determined to be "possibly related" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

## 12.4. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient and provide further information on the patient's condition. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Non-serious AEs that have not resolved by the end of the 30 Day Follow-up Period will be considered ongoing, and marked as such in the CRF. All SAEs will be followed until they resolve or a new baseline is established, at which point the appropriate CRF page(s) or SAE Report Form(s) will be updated.

Routine collection of AEs will stop at the end of the 30 Day Follow-up Period; however, collection of clinical data will continue on AEs of interest or as clinical circumstances warrant that exceed the 30 Day Follow-up Period, per below and described in other sections of the Protocol:

- Oral Mucositis: up to 8 weeks post last IMRT dose (Section 11.12.11)
- Xerostomia and Trismus: through 12 months post last IMRT dose (Section 11.9)
- Medical events, which in the opinion of the investigator, serious and are believed to be a result of study participation to warrant notifying the sponsor (Sections 12.5 and 12.6). In these circumstances, the investigator should contact the Galera Medical Monitor (or designee) directly to discuss the case, and how it should be reported.

As reasonably requested by Galera Therapeutics, Inc., the investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. If a patient dies during participation in the study or during a recognized follow-up period, Galera Therapeutics, Inc. will be provided with a copy of any post-mortem findings, including histopathology.

## 12.5. Post-Study Reporting Requirements

Although such information may not be routinely sought or collected by Galera Therapeutics, Inc., serious adverse events that occur after the patient has completed a clinical study may be reported. Such cases will be evaluated for expedited reporting.

## 12.6. Pregnancy

The risks of treatment with GC4419 during pregnancy have not been evaluated. Male subjects and female subjects of childbearing potential who engage in sexual intercourse should use a barrier method of contraception throughout the study and for 30 days following the last dose of GC4419/placebo.

### 12.6.1. Time Period for Collecting Pregnancy Information

As permitted by IRB/EC/REB policies, any pregnancy that occurs from the first dose of GC4419/placebo up to 30 days after last dose should be reported using the appropriate form within 2 weeks of learning of the patient's pregnancy. The patient will be followed throughout the course of the pregnancy. Generally, follow-up will be no longer than six to eight weeks following the estimated delivery date. Any premature termination of the pregnancy should be reported. If a pregnancy is identified outside the 30 days after last dose, the investigator may report using clinical judgment.

### 12.6.2. Action to be Taken if Pregnancy Occurs in a Female Partner of a Male Patient

The investigator will attempt to collect pregnancy information on any female partner of a male study patient who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to Galera Therapeutics, Inc. within 2 weeks of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will

be forwarded to Galera Therapeutics, Inc. Generally, follow-up will be no longer than six to eight weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported. If a pregnancy is identified outside the 30 days after last dose, the investigator may report using clinical judgment.

## 12.7. Recording Adverse Events

All AEs must be recorded on the appropriate CRF regardless of the severity or relationship to GC4419/placebo. All AEs that meet the seriousness criteria should also be recorded on the SAE Report Form. All SAEs must be reported to the sponsor or delegated organization within the timeline stated in Section 12.2.

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

- Medical and surgical history
- Physical examinations including vital signs
- Clinical laboratory test results
- Patient verbal reports to the investigational staff and documented in the medical chart
- Patient diary

All clinical events, including both observed (such as any reaction at sites of application) and volunteered problems, complaints, or symptoms, are to be recorded. The need to capture this information is not dependent upon whether the clinical event is associated with GC4419/placebo use. AEs resulting from concurrent illnesses, reactions to concurrent medications or symptomatic progression of disease states are also to be recorded.

The information to be recorded for AEs will include:

- The specific type of event in standard medical terminology – diagnosis if known, is preferred over symptoms
- Duration of the clinical event (start and stop dates)
- Severity (Grade 1, 2, 3, 4, or 5) of the clinical event
- Seriousness (SAE) criteria, if applicable
- Relationship of the AE to GC4419/placebo as defined in Section 12.3
- Management of GC4419/placebo administration and other action taken to alleviate the clinical events
- Clinical outcome of the AE

If an adverse event changes in grade within the date of randomization through the 30 Day Reporting Period, the event should be recorded as a new AE.

## 12.8. Regulatory Reporting of Adverse Events

Galera Therapeutics, Inc. will have final determination of reportability and is responsible for notifying the relevant regulatory authorities of certain events. The investigator will report all

SAEs that occur at his/her site to the IRB per the site's IRB regulations. AEs will be reported to regulatory authorities in compliance with 21 CFR 312.32, local and regional law and established guidance by the Sponsor or its designee. The format of the reports will be dictated by the local and regional requirements.

Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB/IEC/REB of these additional SAEs in accordance with local or central IRB/IEC/REB procedures. Copies of each report will be kept in the investigator's files and adequate documentation will be provided to Galera Therapeutics, Inc. including documentation that the IRB/IEC/REB was notified of each safety report.

# 13. STATISTICS

## 13.1. General Considerations

A separate Statistical Analysis Plan will provide technical details of the statistical analyses to be performed, in addition to the specifications in this protocol. In the event of discrepancies between the protocol and the Statistical Analysis Plan, the latter will control the analyses performed.

All statistical analyses will be conducted with the SAS® software package version 9.2 or higher.

### 13.1.1. Randomization and Stratification

Eligible patients will be randomized 1:1:1 to the three treatment arms. Randomization will be stratified by:

1. Tumor human-papilloma virus (HPV) status. It is now accepted that tumor HPV status is a strong independent prognostic factor for survival of patients with oropharyngeal cancer,[45] and that HPV-positive disease is fundamentally different from HPV-negative disease. HPV-positive oropharyngeal cancer tends to present with early T stage and advanced N stage. Whether the risk of severe OM is different for patients with HPV-positive disease compared with those with HPV-negative disease has not been established; review of the data supporting the information in Table 2 suggests that the risks are similar for the two groups (Sonis, personal communication). However, stratification by tumor HPV status is common in trials that are not limited to HPV-positive disease but include patients with oropharyngeal cancer.
2. Assigned cisplatin schedule (q3 weeks or weekly). Historical data supporting also do not suggest differences in risk of OM based on the cisplatin schedule (q3 weeks or weekly). However, based on correspondence with the Food and Drug Administration, patients will be stratified by cisplatin schedule in this study.

It may be noted that the historical data supporting Table 2 also do not suggest a difference in OM risk associated with, T stage (although this factor may be co-distributed with HPV status) (Sonis, personal communication). Similarly, whether smoking status affects the risk of OM is not certain. In GT-201, information about smoking (current/past/never, pack-years) will be collected and its association with OM assessed in the final data analysis. However, stratification based on T stage, smoking status, or factors other than tumor HPV status and cisplatin schedule is not planned.

## 13.2. Sample Size

Approximately 216 patients will be enrolled to ensure that 65 patients per arm receive study drug and complete their IMRT course, with an assumed proportion of early discontinuations of 10%.

The primary objective of the study will test the following hypothesis: separately for each active arm:

- $H_0$: the distribution of duration of severe OM in the active arm = the distribution of duration of severe OM in the placebo arm

- $H_1$: the distribution of duration of severe OM in the active arm ≠ the distribution of duration of severe OM in the placebo arm

Sample size has been calculated using an overall two-sided alpha of 0.05.

With 65 patients per arm having received GC4419/placebo and completed their IMRT course (assumes 72 patients enrolled to each treatment arm with a 10% dropout rate), the study will have roughly 80-85% power to detect a reduction in duration in the experimental arm under the following assumed incidence of severe OM and percentiles of the distribution of duration of severe OM:

- GC4419 arms: incidence = 40%; duration (25th, 50th, 75th percentile): 0, 0, 21 days
- Control arm: incidence = 65%; duration (25th, 50th, 75th percentile): 0, 28, 50 days

## 13.3. Analysis Populations

The intent-to-treat (ITT) population includes 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.

Analyses on other efficacy populations (e,g., a modified intent-to-treat (mITT) population, or an "evaluable" or "per protocol" population) may be conducted. Such analyses will be specified in the Statistical Analysis Plan for this study.

The safety population will include all patients who receive at least one dose of GC4419. Only patients with clear documentation that no GC4419 was received may be excluded from analysis. Patients will be analyzed according to the dose received.

## 13.4. Definition of Endpoints

### 13.4.1. Primary Endpoint

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 instance of ≥ Grade 3 OM. Subjects with complete study follow-up for severe OM who do not develop severe OM will be considered to have durations of 0 days.

### 13.4.2. Secondary Endpoints

- 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)
- Evaluate and compare the safety of GC4419 at the treatment assignment of each respective arm
- Cumulative incidence of severe OM from the first IMRT fraction through the last IMRT fraction
- Cumulative incidence of Grade 4 OM from the first IMRT fraction through the last IMRT fraction

- Onset of severe OM: number of IMRT fractions delivered at onset of severe OM
- Effect of treatment assignment on tumor outcomes (locoregional failure, distant metastases, progression-free survival, overall survival)—see also Section 13.9

### 13.4.3. Exploratory Endpoints

- Duration of severe OM, excluding those without severe OM (i.e., durations of 0 days)
- Onset to severe OM, expressed in cumulative IMRT dosage and time (days)
- Onset to 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 (see Section 24)
    - 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, Section 21)

- 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 $25^{th}$-$75^{th}$ 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

## 13.5. Safety Analysis

Adverse events will be grouped by system organ class, high level term, and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Incidence by subject will be tabulated for all treatment emergent, serious, severe, and treatment related adverse events. Detailed listings will be provided for all serious adverse events, deaths, and withdrawals due to adverse events.

Laboratory measurements, vital signs, and ECG parameters will be summarized by treatment group at each of the protocol specified time points.

Further details will be provided in the trial's Statistical Analysis Plan.

## 13.6. Primary Efficacy Analysis

Duration will be compared between each active arm and placebo by a van Elteren test, stratified by the factors used in randomization, namely baseline HPV status and planned chemotherapy schedule.

Differences in duration will be described by presenting each group's incidence of severe OM and the percentiles of the duration of severe OM, both with and without inclusion of subjects without severe OM.

### 13.6.1. Multiplicity

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.

### 13.6.2. Handling of Missing Data

Investigators should make reasonable attempts to continue to collect WHO OM scores for inclusion in the study database for subjects who discontinue from study drug but continue to receive further IMRT fractions.

The trial's Statistical Analysis Plan will discuss the imputation strategy for subjects who lack WHO OM scores, who discontinue from the trial without complete follow-up of WHO OM scores, and whose resolution date of severe OM is unknown.

### 13.6.3. Covariate Adjustment

Because the trial's randomization is stratified by baseline HPV status and planned chemotherapy schedule, the primary analysis will be stratified by these factors. The Statistical Analysis Plan will contain guidelines for combining strata should the size of any of the four strata be unacceptably small.

## 13.7. Secondary Efficacy Analyses

### 13.7.1. Cumulative Incidence Endpoints

Incidence endpoints will be analyzed by Cochran-Mantel-Haenszel tests stratified by the factors used in randomization.

### 13.7.2. Onset of Severe OM: Number of IMRT Fractions Delivered at Onset of Severe OM, Time (days), and Cumulative IMRT Delivered at Onset of Severe OM

Onset of severe OM will be compared using a stratified logrank test, where time is substituted by the cumulative IMRT fractions received. Subjects without severe OM will be censored at their last IMRT fraction. Kaplan-Meier estimates will be presented in a figure.

Similar supportive analyses of the endpoint will be performed using days on study and using cumulative RT dosage as the unit of time.

## 13.8. Exploratory Efficacy Analyses

### 13.8.1. Instances of severe OM lasting ≥ 7 days

Instances of severe OM lasting seven or more days will be compared by a van Elteran test. The proportion of subjects with episodes of severe OM lasting seven or more days will be compared by a Cochran-Mantel-Haenszel test.

Further exploratory efficacy analyses are described in the Statistical Analysis Plan.

## 13.9. Analysis of Tumor Endpoints

### 13.9.1. Local or Regional Progression

Local (primary site) or regional (neck) progression is defined as clinical or radiographic evidence of progressive disease at the primary site or neck. The location of progressive disease should be separately distinguished (local vs. neck) if possible. Progression of local or regional disease should be confirmed by biopsy when possible but may be clinically assessed and documented in the clinical record at the judgment of the treating clinicians. Tumor reappearing with the initial and immediate adjoining anatomical region of the primary will be considered local recurrence.

### 13.9.2. Distant Metastasis

Clear evidence of distant metastases (lung, bone, brain, etc.): biopsy is recommended where possible. Multiple lung nodules/masses are considered distant metastases from the index cancer unless proven otherwise.

The frequencies of locoregional and distant failure will be tabulated and standard Kaplan-Meier plots will be made for time-to-event endpoints (OS, PFS, locoregional failure over time, distant metastases over time). Other exploratory analyses of the time-to-event endpoints may also be performed; e.g., ratio or difference of t-year event rates, ratio or difference of percentiles of survival functions, and ratio or difference of restricted mean survival times or restricted time lost.[47]

### 13.9.3. Second Primary Neoplasm

A solitary, speculated lung mass/nodule is considered a second primary neoplasm unless proven otherwise.

Frequency of second primary neoplasms will be tabulated.

## 13.10. Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will perform periodic unblinded safety reviews while patients in the trial receive study drug. The DMC will make recommendations regarding the conduct of the study, i.e., to continue enrollment, to hold enrollment until further review, to amend the protocol, or to stop the study early.

# 14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

## 14.1. Study Monitoring

In accordance with International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the consistency of the data recorded in the electronic CRFs.

The monitor is responsible for routine review of the electronic CRFs at regular intervals throughout the study, to verify adherence to the protocol, and the completeness, consistency and accuracy of the data being entered on them. The monitor should have full access to any patient records needed to verify the entries on the electronic CRFs. The investigator agrees to cooperate with the monitor to assure that any follow-up items identified in the course of these monitoring visits are resolved.

During site visits, the monitor will:

- Check the progress of the study;
- Review study data collected;
- Conduct source document verification;
- Identify any issues and address their resolution.
- This will be done in order to verify that the:
    - Data are authentic, accurate, and complete;
    - Safety and rights of subjects are being protected;
    - Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

## 14.2. Audits and Inspections

Authorized representatives of Galera Therapeutics, Inc., a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Galera Therapeutics, Inc. audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact Galera Therapeutics, Inc. immediately if contacted by a regulatory agency about an inspection.

## 14.3. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

## 14.4. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by Galera Therapeutics, Inc. or its representatives. All protocol modifications must be submitted to the IRB/IEC/REB in accordance with local requirements. Approval must be obtained before changes can be implemented.

## 14.5. Information Disclosure

### 14.5.1. Ownership

All information provided by Galera Therapeutics, Inc. or its representatives, and all data and information generated by the site as part of the study (other than a subject's medical records), are the sole property of Galera Therapeutics, Inc.

### 14.5.2. Confidentiality

All information provided by Galera Therapeutics, Inc. or its representatives, and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. Information related to this study is subject to the confidentiality provisions of the Clinical Research Agreement between the investigative site and Galera Therapeutics, Inc.

### 14.5.3. Publication

All publication or presentation rights for the findings of the clinical investigation under this protocol shall be governed by the appropriate terms of the Clinical Research Agreement between the investigational site and Galera Therapeutics, Inc.

# 15. QUALITY CONTROL AND QUALITY ASSURANCE

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

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Galera Therapeutics, Inc. or its representatives may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

# 16. ETHICS

## 16.1. Ethical Conduct of the Study

The investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki" (version October 2008), International Conference on Harmonisation (ICH) guidelines, in particular ICH GCP E6, or with the laws and regulations of the country in which the research is conducted, whichever affords the greatest protection to the study patient. The investigator will also assure that the basic principles outlined in "ICH Guideline for Good Clinical Practice" as published in the Federal Register May 9, 1997, and all applicable Federal regulations including 21 CFR parts 50, 54, 56 and 312 are adhered to.

## 16.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research Ethics Board (REB) Approval

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted, by the investigator, to an IRB/IEC/REB. Approval from the IRB/IEC/REB must be obtained and a copy must be provided to Galera Therapeutics, Inc. or its representatives before initiating the conduct of any study procedures including screening or enrolling any patients into the trial.

No modifications or deviations from this protocol other than those that are deemed medically necessary by the Principal Investigator or designated sub-investigator are to be made without prior, written approval by Galera Therapeutics, Inc. Significant protocol deviations will be reported to Galera Therapeutics, Inc. and to the IRB/IEC/REB in accordance with its reporting policy.

Any modifications made to the protocol by the sponsor after receipt of IRB/IEC/REB approval must be submitted to the committee for approval prior to implementation.

## 16.3. Written Informed Consent

In accordance with regulatory and local IRB/IEC/REB requirements, before study procedures are performed, patients will be informed about the study and required to sign the IRB/IEC/REB approved ICF. This form will be signed after adequate explanation of the aims, methods, objective and potential hazards of the study and prior to undertaking any study-related procedures. The Sponsor or its designee will provide an ICF template to the investigator. The Sponsor or its designee must approve changes to the ICF template prior to submission to the IRB/IEC/REB. Informed consent will be obtained according to the applicable IRB/IEC/REB requirements. No patient is to be screened or treated until an ICF, written in a language in which the patient is fluent, has been obtained. The signed ICF will be retained with the study records. Each patient will also be given a copy of his/her signed ICF.

# 17. DATA HANDLING AND RECORDKEEPING

## 17.1. Case Report Forms

All required study data must be recorded on the electronic CRF provided by Galera Therapeutics, Inc. or its representatives. The data recorded onto the electronic CRF is derived from the source documents. The investigator shall ensure that all data in the electronic CRF is accurate and consistent with the source documents or that any discrepancies of the electronic CRF with source documents are explained (ICH E6 4.9.2).

Electronic case report forms will be accessed by the study center for collection of all study data, and a copy of the electronic CRF will be provided to the site for the investigator files. For each patient who receives study drug, the electronic CRF must be completed by site staff and must be signed electronically by the principal investigator in a timely fashion after data collection. If a patient withdraws from the study, the electronic CRFs should be promptly completed and the reason for withdrawal must be noted. If a patient is withdrawn from the study because of a drug-related toxicity, thorough efforts should be made to clearly document the outcome.

## 17.2. Retention/Inspection of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

Records of drug receipt and disposition, electronic file of CRFs, source documents, reports of this investigation and other study documentation must be maintained by the investigator for a period of at least two years following the date on which the investigational drug is approved by FDA or other applicable regulatory agency for marketing for the purposes that were the subject of the clinical investigations. If no application is to be filed, records must be retained until two years following the date that the study is discontinued and the FDA or other applicable regulatory agency is notified. If the application is not approved by the FDA or other applicable regulatory agency for such indication, records must be retained for two years after notification by Galera Therapeutics, Inc. of the FDA or other applicable regulatory agency decision. The records must be available for copying and inspection if requested by regulatory authorities.

Galera Therapeutics, Inc. should be notified in writing at least 30 days prior to the disposal or transfer to another location or party of any study records related to this protocol.

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# 19. 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 | X |
| Xerostomia assessment[16] | | X | | | | | | | | | | 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, 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 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.

# 20. APPENDIX 2: WHO SCORE

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

# 21. APPENDIX 3: ORAL MUCOSITIS DAILY QUESTIONNAIRE

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

0 1 2 3 4 5 6 7 8 9 10

Worst Possible — Halfway Between Worst Possible and Perfect Health — Perfect Health

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

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

*If you circled 0, please skip to question 5*

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

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

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

0 1 2 3 4 5 6 7 8 9 10

0 = No Soreness; 10 = Worst Possible

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

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

*If you circled 0, STOP here*

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

0 1 2 3 4 5 6 7 8 9 10

0 = No Diarrhea; 10 = Worst Possible Diarrhea

# 22. APPENDIX 4: PERFORMANCE STATUS CONVERSION

| **Performance Status Conversion: ECOG - Karnofsky** | | | |
|---|---|---|---|
| **ECOG** | | **Karnofsky** | |
| Score | Description | Score | Description |
| 0 | Fully active, able to carry on all pre-disease performances without restriction. | 100 | Normal, no complaints, no evidence of disease |
| | | 90 | Able to carry on normal activity, minor signs or symptoms of disease. |
| 1 | Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, office work | 80 | Normal activity with effort, some signs or symptoms of disease |
| | | 70 | Cares for self, unable to carry on normal activity or do active work |
| 2 | Ambulatory and capable of all self-care, but unable to carry out any work activities; Up and about more than 50% of waking hours | 60 | Requires occasional assistance, but is able to care for most of his/her needs |
| | | 50 | Requires considerable assistance and frequent medical care |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours | 40 | Disabled, requires special care and assistance |
| | | 30 | Severely disabled, hospitalization indicated; Death not imminent |
| 4 | Completely disabled; Cannot carry on any self-care; Totally confined to bed or chair | 20 | Very sick, hospital indicated, death not imminent |
| | | 10 | Moribund, fatal processes progressing rapidly |
| 5 | Death | 0 | Death |

# 23. APPENDIX 5: NATIONAL CANCER INSTITUTE-COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS, VERSION 4

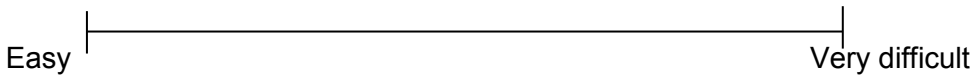
See the following website link for the complete NCI-CTCAE Version 4:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40_conversion

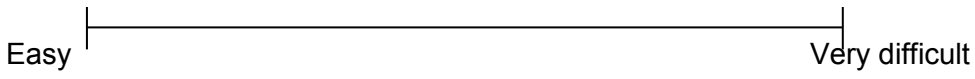
# 24. APPENDIX 6: XEROSTOMIA ASSESSMENT (LEVEQUE, 1993)

Instructions: For each question below, mark your answer by placing a vertical (up & down) line on the horizontal (left to right) scale.

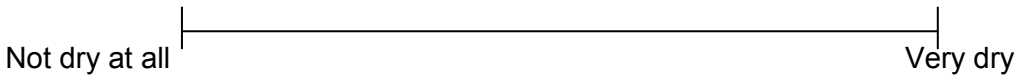
1. **Rate the difficulty you experience in speaking due to dryness.**



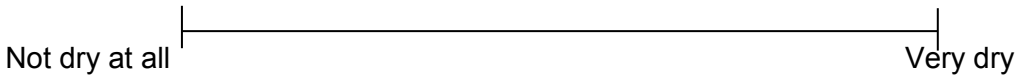

2. **Rate the difficulty you experience in swallowing due to dryness.**



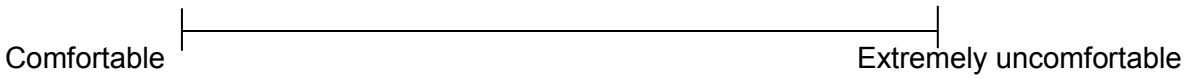

3. **Rate the dryness of your mouth.**




4. **Rate the dryness of your throat.**




5. **Rate the mouth and tongue discomfort you have due to dryness.**



# 25. APPENDIX 7. RECOMMENDED REGIMENS FOR HIGH-RISK CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV) PER ASCO AND MASCC GUIDELINES

Note: Both ASCO and MASCC define single-agent IV cisplatin as a "high risk" regimen for CINV.

***ASCO:***

http://www.instituteforquality.org/sites/instituteforquality.org/files/antiemetic_dosing_clinical_tool_9_21_11_correction_may_2014.pdf, accessed 27 March 2015

| Drug Class | Agent | Dose on Day of Chemotherapy | Dose(s) on Subsequent Days |
|---|---|---|---|
| $NK_1$ Antagonist | Aprepitant | 125 mg oral | 80 mg oral; days 2 and 3 |
| | Fosaprepitant | 150 mg IV | Day 1 only |
| 5-$HT_3$ Receptor Antagonist | Granisetron | 2 mg oral OR 1 mg or 0.01 mg/kg IV | Day 1 only |
| | Ondansetron | 8 mg oral twice daily OR 8 mg or 0.15 mg/kg IV | |
| | Palonosetron | 0.50 mg oral OR 0.25 mg IV | |
| | Dolaseetron | 100 mg oral ONLY | |
| | Tropisetron | 5 mg oral OR IV | |
| | Ramosetron | 0.3 mg IV | |
| Corticosteroind if aprepitant is used* | Dexamethasone | 12 mg oral OR IV | 8 mg oral OR IV; days 2-3 OR days 2-4* |
| Corticosteroid if fosaprepitant is used* | Dexamethasone | 12 mg oral OR IV | 8 mg oral OR IV day 2; 8 mg oral OR IV twice daily on days 3-4* |

*Presumes patients are receiving an NK1 antagonist. If they are not, the **dexamethasone dose should be adjusted** to 20 mg on day 1 and 16 mg on days 2-4.

Special Note Regarding the 2/Nov/15 Guideline Update: The oral combination of netupitant and palonosetron (NEPA) plus dexamethasone is an additional treatment option in this setting. (http://jco.ascopubs.org/content/early/2015/10/26/JCO.2015.64.3635.full)

In the event that the 2015 Guidelines are updated, the new recommendations should be followed effective immediately upon issuance.

***MASCC:*** http://www.mascc.org/assets/Guidelines-Tools/mascc_antiemetic_english_2014.pdf, accessed 26 March 2015

Guideline for the prevention of acute nausea and vomiting: To prevent acute nausea and vomiting following chemotherapy of high emetic risk, a three-drug regimen including single doses of a 5-HT3 receptor antagonist, dexamethasone 12 mg, and aprepitant 125 mg (or fosaprepitant 150 mg) given before chemotherapy is recommended. (Dosing of 5-HT-3 receptor antagonist and dexamethasone as per ASCO guidelines, except no recommendation made for ramositron.)

Guideline for the prevention of delayed nausea and vomiting: In patients receiving cisplatin treated with a combination of aprepitant (or fosaprepitant*), a 5-HT3 receptor antagonist and dexamethasone to prevent acute nausea and vomiting, the combination of dexamethasone and aprepitant (80 mg orally per day for the 2 days following chemotherapy)* is suggested to prevent delayed emesis, on the basis of its superiority to dexamethasone alone.

- *However, if fosaprepitant is used in Day 1, only dexamethasone is required at days 2 - 4 post-chemotherapy

**Additional note:** NEPA (a fixed-dose combination of netupitant and palonosetron) has been approved by the FDA in October 2014 and may be considered.

# 26. APPENDIX 8: SUMMARY OF CHANGES IN AMENDMENT 6

The GT-201 Protocol Amendment 5, dated 8 May 2017, is replaced by this Protocol Amendment 6, dated 19 October 2017. This Protocol Amendment 6 applies to all sites.

Listed below are a summary of substantive changes incorporated into Amendment 6. Administrative changes, such as cross-linking and typographical/grammatical corrections have also been made, which may not be summarized. A red-line version which identifies all non-formatting changes (i.e., "was-is" document) is incorporated by reference to this document as, "GT-201: Redline Changes from Protocol Amendment 5 to Protocol Amendment 6" (Note: The page numbers in the final version may not match exactly the page numbers in the redline version due to the listing of previous and new text).

1. **Change:** Change method of handling multiple comparisons from the prior Hochberg method to a fixed sequence analysis approach. As part of the change in multiple testing, add as secondary endpoints incidence of Grade 4 OM and onset of severe OM, expressed as number of IMRT fractions at onset.

   **Rationale:** In consultation with scientific, statistical, and regulatory advisors, the Sponsor has determined that a fixed sequential approach provides a more appropriate way to assess the effects of the two active doses of GC4419. Note: this change is made prior to database lock or study unblinding, and is not informed by examination of the study data.

2. **Change:** Specify that, in the event of discrepancies between the protocol and the Statistical Analysis Plan, the latter will control the evaluations conducted.

   **Rationale:** Clarification.

3. **Change:** Change "28%" to "29%" in Table 5, which summarizes severe OM results from GT-001.

   **Rationale:** Correct a previous rounding error.

4. **Change:** Move incidence of Grade 4 OM and onset of Grade 3-4 OM from exploratory to secondary endpoints.

   **Rationale:** Consistency with the adoption of fixed sequential hypothesis testing, in which these endpoints are now included in the testing sequence.