CLINICAL STUDY PROTOCOL

Study Title:	An Open Label Multi-Center Study of the Effects of Superoxide Dismutase Mimetic GC4419 when Administered to Reduce the Incidence and Severity of Severe Oral Mucositis (SOM) Associated with Chemoradiotherapy for Locally Advanced, Non-Metastatic Head and Neck Cancer
Sponsor:	Galera Therapeutics, Inc. 2 West Liberty Boulevard, Suite 110 Malvern, PA 19355 USA
IND Number:	111,539
Protocol ID:	GTI-4419-202
EudraCT Number:	2019-002745-38
Medical Monitor:	Jon T. Holmlund, MD
Protocol Version/Date:	Version 3.0/ 02September2020
Previous Version/Date:	Version 2.0/ 03August2020 Version 1.0/ 23July2019

STUDY ACKNOWLEDGEMENT

Study Title: An Open Label Multi-Center Study of the Effects of Superoxide Dismutase Mimetic GC4419 when Administered to Reduce the Incidence and Severity of Severe Oral Mucositis (SOM) Associated with Chemoradiotherapy for Locally Advanced, Non-Metastatic Head and Neck Cancer

Protocol No. GTI-4419-202 Final Protocol Date: 02September2020

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

DocuSigned by:
Jon Holmlund
Signer Name: Jon Holmlund
Signing Reason: I approve this document
Signing Time: September 3, 2020 | 3:49:30 PM EDT
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Jon T. Holmlund, MD
Chief Medical Officer
Galera Therapeutics, Inc.

Investigator Statement:

I have read the attached protocol dated 02September2020 and agree to abide by all provisions set forth therein. I will provide copies of the protocol and other pertinent information to all individuals responsible to me who will assist with the study.

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

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, Inc.

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 (avasopasem manganese)

Name of Active Ingredient:

GC4419 (avasopasem manganese)

Title of Study:

An Open Label Multi-Center Study of the Effects of Superoxide Dismutase Mimetic GC4419 when Administered to Reduce the Incidence and Severity of Severe Oral Mucositis (SOM) Associated with Chemoradiotherapy for Locally Advanced, Non-Metastatic Head and Neck Cancer

Number of Study Center(s):

Approximately 30 centers in selected countries in Europe

Estimated Enrollment Period:

Approximately 12 months

Studied period (years):	**Phase of development:** 2
First subject enrolled: June 2020 Estimated date last subject enrolled: 4th quarter 2020 Estimated date for primary results: 2nd quarter 2021	

Objectives:

Primary Objective:

- To assess the safety and tolerability of GC4419 administered intravenously (IV) to subjects receiving post-operative or definitive therapy with single-agent cisplatin plus Intensity-Modulated Radiation Therapy (IMRT) for locally advanced, non-metastatic squamous cell carcinoma (SCC) of the head and neck

Secondary Objective:

- To assess the incidence of severe oral mucositis (SOM; World Health Organization Grade 3 or 4) in the study population

Endpoints:

Primary Endpoint:

- Frequency, duration, and severity of AEs and serious AEs (SAEs);
- Incidence and shifts of clinically significant laboratory abnormalities

Secondary Endpoints:

- Cumulative incidence of SOM, defined as any occurrence of WHO Grade 3-4 OM, from the first IMRT fraction through the end of the study treatment period (last day of IMRT)
- Cumulative incidence of WHO Grade 4 OM and days of Grade 4 OM from the first IMRT fraction through the end of the study treatment period (last day of IMRT)
- Cumulative incidence of SOM, and days of SOM, from the first IMRT fraction through two weeks after the end of IMRT

Methodology:

GTI-4419-202 is an open-label, multi-center international study conducted to evaluate the effects of GC4419 when administered IV in combination with IMRT/cisplatin to subjects with head and neck cancer, who are at high risk for SOM.

Subjects will receive 90 mg GC4419 per day (60 min IV infusion to complete within 4 hours 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 100 mg/m^2 once every three weeks for 3 doses or 40 mg/m^2 once weekly for 6-7 doses (Investigator's choice)

Note: Planned radiation fields must include at least 2 oral sites (left and right buccal mucosa, floor of mouth, left and right lateral tongue, soft palate) with each site receiving a cumulative dose of at least 50 Gy.

If IMRT is not administered on any given day due to a treatment break or unforeseen circumstances, GC4419 should not be administered on that day.

All subjects will be assessed twice weekly for OM per WHO grading criteria until 28 days post end of study treatment period (last day of IMRT).

Number of subjects (planned):

Up to 70 total subjects

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. Pathologically-confirmed diagnosis of locally advanced squamous cell carcinoma of the head and neck 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 study.
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 of 60-72 Gy. Planned radiation fields must include at least 2 oral sites (left and right buccal mucosa, floor of mouth, left and right lateral tongue, soft palate) with each site receiving a cumulative dose of at least 50 Gy.

   Note: Unavoidable doses of at least 50 Gy, to include entrance, exit, and scatter doses, still constitute planned radiation.
3. 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.
4. Treatment plan to receive standard cisplatin monotherapy administered either every three weeks (100 mg/m^2 for 3 doses) or weekly (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.
5. Age 18 years or older
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2

7. 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
8. Adequate renal and liver function as indicated by:
   - Serum creatinine acceptable for treatment with cisplatin per institutional guidelines
   - Total bilirubin ≤ 1.5 × upper-normal limit (ULN)
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN
   - Alkaline phosphatase ≤ 2.5 × ULN
9. Serum pregnancy test negative for women of childbearing potential
10. Males and females must agree to use highly effective method of contraception starting prior to the first day of treatment and continuing after the last dose of GC4419 for 30 days (females) or 90 days (males)
11. Properly obtained written informed consent

Exclusion Criteria:

1. Metastatic disease
2. 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)
3. Prior induction chemotherapy or plans for chemotherapy to be administered only sequentially, not concurrently, with IMRT
4. Planned concurrent chemotherapy other than single agent cisplatin
5. Receiving any approved or investigational anti-cancer agent other than those provided for in this study
6. Concurrent participation in another interventional clinical study or use of another investigational agent within 30 days of first dose of GC4419

   Note: Patients who are participating in non-interventional clinical studies (e.g., QOL, imaging, observational, follow-up studies, etc.) are eligible, regardless of the timing of participation.
7. Inability to eat soft solid food at baseline for reasons other than mouth soreness after surgery or dental procedures
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 head and neck cancer (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 at baseline. Subjects with mouth or throat pain solely due to post-operative effects are eligible, however.
12. Known history of human immunodeficiency virus (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 9 mg/mL in 26 mM sodium bicarbonate-buffered 0.9 wt. % saline for parenteral administration (drug product). GC4419 will be presented in single use 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 100 mg/m^2 once every three weeks for 3 doses or 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 (M-F), for approximately 7 weeks. GC4419 will be administered within 4 hours prior to each IMRT treatment.

Reference therapy, dosage and mode of administration:

Not applicable

Criteria for evaluation:

Safety:

National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE), version 5.0

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

Efficacy:

WHO Criteria for OM

Toxicity Management:

Toxicity requiring 25% GC4419 dose reduction:

- Grade 2 or greater hypotension within 2 hours after the start of GC4419 infusion
- Grade 3-4 adverse events (AEs) judged by the Investigator to be likely attributable to the study infusion.

Dose reductions of GC4419 should be done in increments of 25% of the starting dose. Two dose reductions for toxicity will be permitted per subject. Subjects unable to tolerate GC4419 after 2 dose reductions must discontinue treatment with GC4419 but should continue with cisplatin/IMRT and other study assessments and procedures, with the concurrence of the treating Investigator, if the subject maintains informed consent to do so.

For other toxicities (including those attributable to cisplatin and IMRT): management per institutional and American Society of Clinical Oncology (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.

Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Cavity (ISOO) Oral Care Education Materials and patient instructions for oral hygiene will be strongly recommended, and a summary appended to the protocol (Appendix 6).

OM will NOT be considered an AE requiring dose modification for the purposes of this study.

Concomitant Medications/Treatments:

Investigators may prescribe concomitant medication or supportive therapy deemed necessary to provide adequate supportive care for complications other than OM, e.g., antiemetics, systemic antibiotics, hydration to prevent renal damage, etc.

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

Oral care per MASCC/ISOO Oral Care Education Materials (summarized in Appendix 6) is strongly recommended for all subjects as part of standard of care.

Oral topical lidocaine is permitted.

Diphenhydramine (Benadryl®) administered as tablets or by injection is permitted.

The following must not be used:

- Nitrates, phosphodiesterase type 5 (PDE 5) inhibitors (e.g., sildenafil, 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 another keratinocyte or fibroblast growth factor
- Amifostine (Ethyol®)
- Benzydamine (Difflam®, Pharixia®, Tantum Verde)
- Low-level laser treatment
- Glutamine applied topically
- GM-CSF applied topically
- 'Mouthwashes' that include the following:
    - Chlorhexidine
    - Hydrogen peroxide
    - Diphenhydramine (Benadryl®) liquid formulation
    - Tetracycline
    - Any other listed disallowed medications
- MuGard™, Gelclair®, Episil®, or other barrier devices
- Caphosol®
- Povidone-iodine rinses
- Steroid rinses
- Sucralfate in suspension form (use of sucralfate tablets is not proscribed)
- 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 IMRT is completed unless otherwise noted.

Statistical methods:

The primary objective of this study is to further assess the safety profile of GC4419, with efficacy objectives of cumulative incidence of SOM, days of SOM, and tumor outcome key secondary efficacy endpoints. No formal statistical hypothesis testing is prespecified for the primary safety objectives. A sample size of up to 70 subjects has been selected to obtain adequate safety and efficacy subject data to compare with observed data in North American studies and historical controls for IMRT with Cisplatin. These results will also contribute to pooled analysis of an overall minimum safety database of 300 subjects with head and neck cancer who will, across all studies of GC4419, have received a full course of GC4419 at the intended dose (90 mg), schedule (1-hour infusion, 5 days/week, prior to IMRT), and duration (single course of 6-7 weeks) in combination with concurrent IMRT and cisplatin. The overall safety database size of 300 will allow for detection with 95% probability of adverse events of 1% true incidence in at least 1 subject.

As this is the first study of this drug in EU, the efficacy analysis will allow for comparison to North American results and historical controls and confirm uniformity in applying OM scoring procedures used for WHO criteria that could be used to inform future development programs.

Safety and efficacy will be assessed on an “intent to treat” (ITT) population consisting of all enrolled subjects who receive at least one dose of GC4419, and on a "per protocol" population consisting of subjects who receive at least 60 Gy of IMRT and at least 5 weeks (25 doses) of GC4419. Overall rates of adverse events, serious adverse events, and SOM/Grade 4 OM incidence will be summarized descriptively.

2. TABLE OF CONTENTS

LIST OF TABLES

3. GLOSSARY

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
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulation
CINV	Chemotherapy-Induced Nausea and Vomiting
CRF	Case Report Form
CRT	Chemo-Radiotherapy
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Federal Drug Administration
GCP	Good Clinical Practice
Gy	Gray
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HNC	Head and Neck Cancer
HPV	Human Papilloma Virus
HSCT	Hematopoietic Stem Cell Transplantation
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

Abbreviation or Specialist Term	Definition
IMRT	Intensity-Modulated Radiation Therapy
IND	Investigational New Drug
IRB	Institutional Review Board
ISOO	International Society of Oral Oncology
ITT	Intent-to-Treat
IV	Intravenous
IXRS	Interactive Voice and Web Response System
MASCC	Multinational Association of Supportive Care in Cancer
M-F	Monday to Friday
MnSOD	Manganese Superoxide Dismutase
NCI	National Cancer Institute
NCS	Non-Clinically Significant
NEPA	Netupitant-palonosetron
OC	Oral Cavity
OM	Oral Mucositis
OP	Oropharynx
PK	Pharmacokinetic
QOL	Quality of Life
REB	Research Ethics Board
ROS	Reactive Oxygen Species
RT	Radiation Therapy
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SCC	Squamous Cell Carcinoma
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SOD	Superoxide Dismutase
SOM	Severe Oral Mucositis
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCD	Tumor cure dose
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 (Sonis 2009). Oral mucositis is readily graded using the commonly-used five-point World Health Organization (WHO) scale (Appendix 2).

Most patients receiving combined chemoradiotherapy for head and neck cancer (HNC) can be expected to develop severe (WHO Grade 3-4) OM (SOM) (Sonis, Elting et al. 2004), and nearly all HNC patients receiving radiation therapy (RT) with concurrent cisplatin are expected to develop ulcerative OM (WHO Grade 2 or higher) (Traynor, Richards et al. 2010). The consequences for patients developing SOM are especially serious, because, by definition, Grade 3-4 OM entails compromise to nutrition and/or hydration, and may require surgical procedure, RT interruption, and/or hospitalization.

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 (Mendenhall, Amdur et al. 2006; Salama, Seiwert et al. 2007; Ang, Zhang et al. 2014; Nguyen-Tan, Zhang et al. 2014). The monoclonal antibody cetuximab has also been shown to increase the efficacy of radiotherapy for locally advanced head and neck cancer (Bonner, Harari et al. 2006). However, recently reported results from the RTOG 1016 study in human papilloma virus (HPV)-associated oropharyngeal cancer showed survival after IMRT plus cetuximab to be inferior to that obtained with IMRT/cisplatin (Trotti, et al. 2018).

Published observations for patients treated with RT for HNC, without additional treatment to prevent OM, indicate that approximately 50% of patients receiving RT alone (Bonner, Harari et al, 2006), and that approximately 70% of patients receiving RT plus single-agent cisplatin may be expected to develop SOM, with a median duration of approximately 3-4 weeks among those who develop SOM, a median time to onset of approximately 28-35 days after the start of therapy, and a cumulative incidence of approximately 10% per week/10 Gy. Data for the placebo groups in two published Phase 3 studies of Kepivance® (palifermin) in patients receiving RT plus single-agent cisplatin for SCCHN (Henke, Alfonsi et al. 2011; Le, Kim et al. 2011), and results for patients receiving IMRT plus platinum plus placebo in a more recent report (Kudrimoti, Curtis et al. 2016) support these observations. Adding cetuximab to standard chemoradiation regimens for HNC increases the risk of significant OM (Ang, Zhang et al. 2014).

Among patients being treated for HNC, OM follows a predictable and well-documented course (Sonis 2011). 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 (Elting, Cooksley et al. 2007).

OM 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 (Elting, Cooksley et al. 2007), as well as secondary infections at sites of ulcerative OM (Bodey, Rodriguez et al. 1978), and diminished quality of life (QOL) outcomes (Elting, Keefe et al. 2008). Patients with HNC may also suffer the additional complications of short- and long-term xerostomia, taste change, and trismus related to post-radiation fibrosis. These consequences are particularly pronounced in patients manifesting severe OM, and especially in the 20-30% who suffer Grade 4 and require artificial alimentation, usually via a percutaneous gastrostomy tube.

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 (Vera-Llonch, Oster et al. 2006; Russo, Haddad et al. 2008). In granulocytopenic patients, mucositis is strongly associated with an increased risk of bacteremia and sepsis (Ruescher, Sodeifi et al. 1998). 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 (Nonzee, Dandade et al. 2008).

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 (Keefe 2006). Current guidelines (Lalla, Bowen et al. 2014) 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:

- Kepivance® (palifermin) in the setting of high-dose chemotherapy and total body irradiation, followed by autologous hematopoietic stem cell transplantation (HSCT), for a hematological malignancy. However, Kepivance® is not licensed/approved for the treatment of OM associated with HNC;
- 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. Several other agents currently used to treat OM symptoms, 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.

Further, no approved product is available in the US (or elsewhere) for OM in the vast majority of these patients, especially those with solid tumors such as SCCHN. At present, palifermin is the only FDA-approved (licensed) product for OM but its indicated use (patients receiving HSCT for hematologic malignancies) is limited to a very small cohort (4%) of the total population at risk for OM: a cohort associated with conditioning regimens prior to stem cell transplant for the treatment of hematologic malignancies. The approval specifically excludes patients with solid tumors (Spielberger, Stiff et al. 2004).

A few medical devices are on the market, but they generally lack sufficient data to allow recommendation. The mucoadhesive MuGard™ is indicated as a palliative treatment for the management of OM but requires administration 4 to 6 times per day for optimal effect and does not alter the mechanism of OM (MuGard prescribing information). 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 but failed to reduce the incidence of ulcerative or severe OM in a recently-published Phase 2 study (Rao, Trotti et al. 2014). 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.

Therefore, current standard of care for patients with solid tumors consists of oral care protocols and palliative approaches to deal with painful symptoms. An urgent need remains for novel products, like GC4419, aimed at reducing the incidence and severity of severe OM.

4.2. GC4419 Overview

GC4419 is a novel, highly stable manganese-containing macrocyclic ligand complex with a molecular weight of 483 g/mol, 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 (O2•-) 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.

GC4419 is being developed for the initial indication of reduction of the incidence and severity of severe OM induced by RT, with or without systemic therapy, under IND 111,539 with the Division of Dermatology and Dental Products (DDDP), United States FDA.

By efficiently and rapidly removing O2•- , GC4419 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 manganese (Mn) SOD or a MnSOD transgene, exogenous Cu/Zn SOD, or a dismutase mimetic enantiomerically related to GC4419 (Delanian, Baillet et al. 1994; Epperly, Defilippi et al. 2000; Guo, Seixas-Silva et al. 2003; Murphy, Fey et al. 2008; Thompson, Chu et al. 2010).

GC4419 was studied extensively in nonclinical settings, in different animal models, and various human xenograft and murine syngeneic tumor models (for details see the Investigator's Brochure). Nonclinical data have identified GC4419 as a promising new radioprotective, anti-cancer and anti-inflammatory agent. 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 was studied in a Phase 1b/2a clinical study, GT-001 (NCT01921426, Anderson, Sonis, et al. 2018) and Phase 2b study, GT-201 (NCT02508389). In study GT-001, GC4419 was administered throughout the full 6- to 7-week course of chemo-radiotherapy (CRT) at doses of either 30 or 90 mg, Monday-Friday (M-F), and appeared to substantially reduce the duration, incidence, and overall severity (defined here as the incidence specifically of Grade 4) of severe OM compared with historical expectations (data are based on 43 evaluable subjects). Further, GC4419 did not appear to increase the known toxicity of the CRT regimen (IMRT plus concurrent cisplatin), nor did it appear to interfere with tumor response to CRT assessed through 1 year post therapy (for details see Anderson, Sonis, et al. 2018 and the Investigator's Brochure). These results supported the design of the randomized, double-blind, placebo-controlled, Phase 2b study GT-201, with two GC4419 doses of 30 and 90 mg selected for comparison with placebo and administered 5 days/week. As in GT-001, patients eligible for GT-201 were required to have locally advanced squamous cell carcinoma of the oral cavity (OC) or oropharynx (OP), with their standard care calling for concurrent IMRT and cisplatin. Results from 223 randomized subjects indicated that GC4419 at daily dose of 90 mg resulted in statistically significant reduction on the primary endpoint, severe OM duration, for subjects on the 90 mg arm compared to placebo, as determined by the non-parametric Van Elteren test. The median duration of SOM, as defined in the protocol, was 1.5 days for subjects receiving 90 mg of GC4419 vs 19 days for subjects receiving placebo (p=0.024). Also, the incidence of SOM during the IMRT treatment period was 43% for subjects receiving 90 mg of GC4419 vs 65% for subjects receiving placebo (nominal p value=0.009), a relative reduction of approximately 34%. The safety profile of GC4419 in combination with the IMRT/platinum regimen in GT-201 study was acceptable; safety results with both the 90 mg dose and the 30 mg dose were similar to those with placebo (Anderson et al, 2019). Two year follow up for standard tumor outcomes (progression-free survival, overall survival, local control, distant metastasis-free rate) did not vary among the three study arms (Anderson et al, 2020).

Based on these results, a randomized, double-blind, placebo-controlled Phase 3 trial, GTI-4419-301, has been initiated in the US and Canada. This study is of substantially the same design as GT-201, and is limited to patients with tumors of the oral cavity and oropharynx, as was the case in GT-001 and GT-201. GTI-4419-301 is a 2-arm study, with eligible subjects randomized in a 3:2 ratio to 90 mg of GC4419 or placebo in combination with IMRT/cisplatin. In accordance with discussions with regulatory authorities, the primary endpoint of GTI-4419-301 is the incidence of SOM during the study treatment period (through the last fraction of IMRT). Secondary efficacy endpoints are incidence of Grade 4 OM through the study treatment period, and the number of days of SOM or Grade 4 OM, defined as was "duration" of SOM in GT-201. The sample size is 335 randomized subjects who receive at least one dose of GC4419 or placebo.

However, additional data will be needed to permit assessment of the safety of GC4419 at the intended dose, schedule, and duration of administration, in combination with IMRT/cisplatin, to

identify adverse events with an overall frequency of approximately 1%. The present study will obtain these data along with further exploratory information about the incidence of SOM in patients receiving 4419 plus IMRT/cisplatin for a range of head and neck cancers.

Additional details about the pathogenesis of OM, the mechanism of action of GC4419, and the results of non-clinical testing as well as the clinical trials GT-001 and GT-201 are provided in the Investigator's Brochure.

5. STUDY OBJECTIVES, ENDPOINTS AND PURPOSE

5.1. Objectives

Primary Objective:

- To assess the safety of GC4419 administered intravenously (IV) to subjects receiving post-operative or definitive therapy with single-agent cisplatin plus Intensity-Modulated Radiation Therapy (IMRT) for locally advanced, non-metastatic squamous cell carcinoma (SCC) of the head and neck

Secondary Objective:

- To assess the incidence of severe oral mucositis (SOM; World Health Organization Grade 3 or 4) in the study population

5.2. Endpoints

Primary Endpoint:

- Frequency, duration, and severity of AEs and serious AEs (SAEs);
- Incidence and shifts of clinically significant laboratory abnormalities

Secondary Endpoints:

- Cumulative incidence of SOM, defined as any occurrence of WHO Grade 3-4 OM, from the first IMRT fraction through the end of the study treatment period (last day of IMRT)
- Cumulative incidence of WHO Grade 4 OM and days of Grade 4 OM from the first IMRT fraction through the end of the study treatment period (last day of IMRT)
- Cumulative incidence of SOM, and days of SOM, from the first IMRT fraction through two weeks after the end of IMRT.

5.2.1. Rationale for WHO Scale of OM (Secondary Endpoints)

The WHO scale is commonly used to assess OM in clinical care and research settings. Originally 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 low 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 also precedent for using severe OM as defined by the WHO scale as the basis for drug approval specifically in the case of palifermin.

Because of the nature of the WHO grading scale (see Appendix 2), improvement of SOM (WHO Grade 3-4) of meaningful magnitude implies clinical benefit.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

GTI-4419-202 is an open-label, multi-center international study conducted to evaluate the effects of GC4419 when administered IV in combination with IMRT/cisplatin to subjects with head and neck cancer, who are at high risk for SOM.

6.2. Treatment Plan and Duration of Therapy

Subjects will receive 90 mg GC4419 per day (60 min IV infusion to complete within four hours 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 100 mg/m^2 once every three weeks for 3 doses or 40 mg/m^2 once weekly for 6-7 doses (Investigator's choice)

Note: Planned radiation fields must include at least 2 oral sites (left and right buccal mucosa, floor of mouth, left and right lateral tongue, soft palate) that each receive a cumulative dose of at least 50 Gy.

GC4419 will be given IV by a 60-minute infusion. IMRT must be initiated as soon as possible upon completion of the GC4419 infusion but no later than four hours following the end of the GC4419 infusion.

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

Anti-emetic prophylaxis and hematopoietic growth factor use should be administered per American Society of Clinical Oncology (ASCO) guidelines (Appendix 5). 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 are administered, the following administration sequence should be used when possible to ensure that IMRT is initiated within four hours of the stop time of GC4419 infusion: GC4419, IMRT, prehydration, and cisplatin. Patients treated with induction chemotherapy prior to concomitant chemoradiation are not eligible for this study.

All subjects will be assessed twice weekly for oral mucositis per WHO grading criteria until the end of the study treatment period (last day of IMRT).

Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Cavity (ISOO) Oral Care Education Materials and patient instructions for oral hygiene should be strongly recommended. A summary of those guidelines and instructions is appended to the protocol (Appendix 6).

6.2.1. Rationale for GC4419 Dose and Schedule Selection

The GC4419 dose (90 mg), route (IV), infusion duration (60 minutes), schedule (weekdays prior to IMRT) and treatment duration (6-7 weeks) for this study are those that are being studied in the Phase 3 trial of GC4419 and that are intended for eventual clinical use. Data from the Phase 2 GT-201 study indicate that the acute toxicity of GC4419 and the overall adverse event profile in combination with IMRT/cisplatin are acceptable and as expected. Safety results with 90 mg dose were similar to those with Placebo and GC4419 does not appear to increase the toxicity of IMRT/cisplatin. In addition, the 90 mg dose of GC4419 in study GT-201 met its primary endpoint versus Placebo in demonstrating reduced duration of severe OM, and with strong statistical significance (p=0.024). Also, of note is that Phase 2 data have indicated an apparent dose response between the 90 mg, 30 mg, and Placebo arms.

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 (Pignon, le Maitre et al. 2009). Further, recently reported results from the RTOG 1016 study in human papilloma virus (HPV)-associated oropharyngeal cancer showed survival after IMRT plus cetuximab to be inferior to that obtained with IMRT/cisplatin (Trotti, et al. 2018). Accordingly, in the current study, the still-standard cisplatin/IMRT regimen has been chosen as it poses a significant medical need by virtue of the predictable and high incidence of associated severe OM.

Standard fractionation (five fractions/week, delivered M-F) IMRT has been chosen for the current study. Although accelerated fractionation (six fractions/week, combined with two rather than three doses of cisplatin q3 weeks), has been studied, prospective lead investigators 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. Accelerated fractionation appears to increase the incidence of severe OM (Overgaard, Hansen et al. 2003).

In the event that a radiation fraction is missed because of a holiday or technical issues, administering two fractions in a subsequent day, to maintain five fractions per week, will be allowed, at the discretion of the treating investigator and consistent with institutional practice.

Cisplatin is administered concomitantly with IMRT by either a q3weekly or weekly schedule. Recent literature reviews (Sturtz, Wouters et al. 2017; Jacinto, Co, et al. 2017) have found no differences in tumor outcomes or mucositis between the two schedules. A randomized trial in the adjuvant (post-operative) setting (Noronha, Joshi, et al. 2018), in which 87% of patients enrolled had squamous cancer of the oral cavity, cited superior progression-free survival for the q3weekly arm, with no difference in mucositis. However, the weekly dose of cisplatin in that study was 30 mg/m^2. Other reports (Stojan, Vermorken et al. 2015; Nguyen-Tan, Zhang et al. 2014) have described a relationship between total cisplatin dose and overall survival in combination with RT for HNC, with a target cumulative cisplatin dose of 200 mg/m^2 or greater now appearing indicated as standard of care to obtain improved survival with RT/cisplatin over RT alone. This threshold could be missed with weekly cisplatin doses < 40 mg/m^2. In the present trial, cisplatin doses of 100 mg/m^2 by the q3week schedule, and 40 mg/m^2 by the weekly

schedule, will be required. The risk of severe OM may not be different according to cisplatin schedule, and no such difference was demonstrated in a subset analysis from GT-201 (data not shown). Either regimen will be accepted as within the IMRT/cisplatin standard of care for the patient population to be enrolled in the present study.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

Up to 70 subjects will be enrolled to ensure that the required number of subjects for program need receive a full (5+ weeks) course of GC4419, with an assumed proportion of early discontinuations, for any reason, of approximately 10-20%.

7.1. Subject Inclusion Criteria

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

1. Pathologically-confirmed diagnosis of locally advanced squamous cell carcinoma of the head and neck 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 study.
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 of 60-72 Gy. Planned radiation fields must include at least 2 oral sites (left and right buccal mucosa, floor of mouth, left and right lateral tongue, soft palate) that each receive a cumulative dose of at least 50 Gy.

   Note: Unavoidable doses of at least 50 Gy, to include entrance, exit, and scatter doses, still constitute planned radiation.
3. 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.
4. Treatment plan to receive standard cisplatin monotherapy administered either every three weeks (100 mg/m^2 for 3 doses) or weekly (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.
5. Age 18 years or older
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
7. Adequate hematologic function as indicated by:
   - Absolute neutrophil counts (ANC) $\geq$ 1,500/mm^3
   - Hemoglobin (Hgb) $\geq$ 9.0 g/dL
   - Platelet count $\geq$ 100,000/mm^3
8. Adequate renal and liver function as indicated by:
   - Serum creatinine acceptable for treatment with cisplatin per institutional guidelines
   - Total bilirubin $\leq 1.5 \times$ upper-normal limit (ULN)
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times$ ULN
   - Alkaline phosphatase $\leq 2.5 \times$ ULN
9. Serum pregnancy test negative for women of childbearing potential
10. Males and females must agree to use a highly effective contraception starting prior to the first day of treatment and continuing after the last dose of GC4419 for 30 days (females) or 90 days (males)
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. Metastatic disease
2. 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)
3. Prior induction chemotherapy or plans for chemotherapy to be administered only sequentially, not concurrently, with IMRT
4. Planned concurrent chemotherapy other than single agent cisplatin
5. Receiving any approved or investigational anti-cancer agent other than those provided for in this study
6. Concurrent participation in another interventional clinical study or use of another investigational agent within 30 days of first dose of GC4419

   Note: Patients who are participating in non-interventional clinical studies (e.g., QOL, imaging, observational, follow-up studies, etc.) are eligible, regardless of the timing of participation.
7. Inability to eat soft solid food at baseline for reasons other than mouth soreness after surgery or dental procedures
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 head and neck cancer (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 at baseline. Subjects with mouth or throat pain solely due to post-operative effects are eligible, however.
12. Known history of human immunodeficiency virus (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

Patients with locally advanced squamous cell cancer of the head and neck are 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 study, GT-001, the randomized Phase 2b study, GT-201 and the randomized Phase 3 study, GTI-4419-301.

Patients with unknown primary tumor whose IMRT/cisplatin treatment plans conform to study requirements will be eligible.

7.4. Screen Failures

A subject is considered to be a screen failure if the subject signs the informed consent form but withdraws consent or is deemed ineligible before being enrolled to active treatment. The reason why the subject was precluded from the clinical study will be collected. All subjects who sign the informed consent form for this study, including screening failures, will be entered in the IXRS.

7.5. Randomization Failures

Not applicable.

7.6. Subject Withdrawal Criteria

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

- Adverse Event (AE)
- Medical requirement to administer a contra-indicated medication
- Subject non-compliance
- Subject has a confirmed positive serum pregnancy test
- Discontinuation of the study at the request of the Sponsor

The primary reason for ceasing treatment with GC4419 will be clearly documented in the subject's medical record and recorded on the appropriate CRF page. A subject who permanently discontinues treatment with GC4419 will not be allowed to be retreated.

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

Subjects who withdraw consent for further administration of GC4419 should be encouraged to continue and complete their standard treatment with IMRT/cisplatin, and should be encouraged to continue with other study procedures.

If a subject withdraws consent, additional details about the reasons for that decision will be sought and documented.

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, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subjects' 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 the Sponsor (as applicable)
- Resolution of all data queries
- Accountability, reconciliation, and arrangements for all unused GC4419
- Review of site study records for completeness
- Shipment of laboratory samples (as applicable)

In addition, the Sponsor 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 the Sponsor determines such action is needed, the Sponsor will discuss this with the Investigator (including the reasons for taking such action) at that time. When feasible, the Sponsor will provide advance notification to the Investigator of the impending action prior to it taking effect.

The Sponsor 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/Research Ethics Board (REB) promptly and provide the reason for the suspension or termination. If the study is prematurely discontinued, all study data must be returned to the Sponsor.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the Investigator and the Sponsor.

8. GC4419

8.1. Description of GC4419

8.1.1. 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 the following concentration:

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

There are no other excipients.

8.2. Treatment Assignment

This is an open-label study.

8.3. GC4419 Packaging and Labeling

GC4419 will be presented in kits of 35 single-use vials, which represent 35 daily doses to be administered IV concurrent with IMRT.

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. Further label details will be provided in a separate Pharmacy Manual.

8.4. GC4419 Storage

GC4419 must be stored at 2°C to 8°C at all times until preparation. GC4419 must not be frozen at any time. Temperature excursions up to 25°C or down to 0.1°C for four hours are accepted; however, the Sponsor 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 be administered to subjects within 24 hours of preparation. The GC4419 Infusion Solution should spend as little time as possible outside refrigerated conditions, not exceeding more than 6 hours at ambient temperature, and must not be frozen at any time. If freezing of the material is evident, that supply must be quarantined per institutional guidelines, and the Sponsor or its designee must be notified immediately.

8.5. GC4419 Preparation

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.

GC4419 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 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 for a total volume of 260 mL). 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.

8.6. GC4419 Administration

GC4419 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 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.

IMRT must be initiated as soon as possible upon completion of the GC4419 infusion, but no later than four hours following the end of the infusion.

GC4419 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 2 outlines the chemoradiation and GC4419 administration schedules. Please note chemotherapy is not required to be administered on the study days listed in Table 2, 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 should not be administered on that day. Breaks in IMRT will be determined by the subject's treating physician in accordance with standard of care. Subjects should resume GC4419 administration when IMRT resumes. On days when planned doses of both GC4419 and IMRT are not administered (e.g., due to a holiday site closure), GC4419 dosing may be extended along with IMRT to make up the missed dose(s) to a maximum of 35 doses of GC4419. If a fraction of IMRT is not administered for any reason after GC4419 has been administered, that day's GC4419 will count as one of the 35 doses.

Table 2: Chemoradiation and GC4419 Administration Schedule
Example: 35 Doses of GC4419 (5 days/week over 7 Week Schedule)

Treatment	Week 1					Week 2					Week 3					Week 4				
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 15**	**Day 16**	**Day 17**	**Day 18**	**Day 19**	Day **22**	Day **23**	Day **24**	Day **25**	Day **26**
GC4419[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cisplatin[2]																				
Tri-Weekly	X															X				
Weekly	X					X					X					X				
Radiation[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Treatment	Week 5					Week 6					Week 7				
	Day 29	Day 30	Day 31	Day 32	Day 33	Day 36	Day 37	Day 38	Day 39	Day 40	Day 43	Day 44	Day 45	Day 46	Day 47
GC4419[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[4]				
Radiation[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Intravenous GC4419 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 infusion, but no later than four hours post GC4419 infusion. On Day 1/Baseline, chemotherapy prehydration and infusion should be administered after GC4419 infusion and IMRT, if possible, to ensure that IMRT is initiated within four hours of the GC4419 infusion stop. 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. Subjects should resume GC4419 administration when IMRT resumes. If a subject 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 (100 mg/m^2) or weekly regimen (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 are administered, the administration sequence should be GC4419, IMRT, prehydration, and then cisplatin, if possible, to ensure that IMRT is initiated within four hours of the stop time of GC4419 infusion. Patients treated with induction chemotherapy

prior to concomitant chemoradiation are not eligible for this study, nor are people for whom chemotherapy and radiation are only to be administered sequentially, not in a concurrent regimen.

[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 of 60-72 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 cumulative Gy.

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

8.7. GC4419 Accountability and Compliance

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

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

All GC4419 supplies and associated documentation will be reviewed and verified by the study monitor. Copies of all forms, documenting drug receipt at the study site, drug transportation to satellite sites, and drug return to the Sponsor, together with drug accountability records, will be retained according to the regulations governing record retention.

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

8.8. GC4419 Handling and Disposal

All used GC4419 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 supplies.

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

8.9. Concomitant Medications

All concomitant therapies (i.e., prescription and over-the-counter medications) taken by subjects from the date of enrollment through 30 days following the last GC4419, IMRT or cisplatin dose (i.e., whichever occurs last) 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.

Anti-emetic prophylaxis and hematopoietic growth factors should be used per ASCO guidelines (Hesketh, Kris et al. 2017).

Subjects who withdraw consent for GC4419 should be encouraged to continue and complete standard IMRT/cisplatin treatment and other protocol procedures.

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

8.9.1. Prohibited Medications

Investigators may prescribe concomitant medication or supportive therapy deemed necessary to provide adequate supportive care for complications other than OM (e.g., antiemetics, systemic antibiotics, hydration to prevent renal damage, etc.).

Hematopoietic growth factor use is permitted per ASCO guidelines. Following the ASCO (and MASCC) guidelines for the prevention and management of chemotherapy-induced nausea and vomiting (CINV) is strongly encouraged. See Table 6 (Appendix 5).

Oral care per MASCC/ISOO Oral Care Education Materials (summarized in Appendix 6) is strongly recommended for all subjects as part of standard of care. Oral topical lidocaine is permitted.

Diphenhydramine (Benadryl®) administered as tablets or by injection is permitted.

The following must not be used:

- Nitrates, phosphodiesterase type 5 (PDE 5) inhibitors (e.g., sildenafil, 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 another keratinocyte or fibroblast growth factor
- Amifostine (Ethyol®)
- Benzydamine (Difflam®, Pharixia®, Tantum Verde)
- Low-level laser treatment
- Glutamine applied topically
- GM-CSF applied topically
- ‘Mouthwashes’ that include the following:
  - Chlorhexidine
  - Hydrogen peroxide
  - Diphenhydramine (Benadryl®) liquid formulation
  - Tetracycline
  - Any other listed disallowed medications
- MuGard™, Gelclair®, Episil®, or other barrier devices
- Caphosol®
- Povidone-iodine rinses
- Steroid rinses

- Sucralfate in suspension form (use of sucralfate tablets is not proscribed)
- 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

In vitro, GC4419 inhibited cytochrome P450 isozyme 2D6 (CYP2D6) with an IC50 of 0.079 μM. Concurrent administration of GC4419 with CYP2D6 substrates should be done with caution, and the need for a decreased dose of the CYP2D6 substrate should be considered, especially for substrates with a narrow therapeutic range. CYP2D6 substrates include certain beta blockers (e.g., propranolol and metoprolol), antidepressants (e.g., tricyclics), antipsychotics (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide).

Mouthwashes or rinses containing sodium bicarbonate, clotrimazole (Mycelex), nystatin, fluconazole (Diflucan), viscous xylocaine, and/or viscous lidocaine are permitted. If a subject uses “Magic Mouthwashes” or “Miracle Mouthwashes,” all ingredients must be recorded in the subject’s medical record in order to confirm the mouthwashes did not contain the prohibited ingredients listed above.

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

Subjects who receive prohibited medications 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.

9. TOXICITY MANAGEMENT

9.1. Dose Delays and Dose Modifications for Toxicity

Toxicities requiring a 25% dose reduction:

- Grade 2 or greater hypotension within 2 hours after the start of GC4419 infusion
- Grade 3-4 adverse events (AEs) judged by the Investigator to be likely attributable to the study infusion.

Dose reductions of GC4419 should be done in increments of 25% of the starting dose. Two dose reductions for toxicity will be permitted per subject. After the first event, the subject will be re-challenged at 75% of the original dose (7.5 mL GC4419 in 250 mL normal saline). After the second event, the subject will be re-challenged at 50% of the original dose (5.0 mL GC4419 in 250 mL normal saline). Subjects who are unable to tolerate GC4419 infusions following 2 dose reductions must be discontinued from the study treatment but should continue with cisplatin/IMRT and other study assessments and procedures, with the concurrence of the treating Investigator, if the subject maintains informed consent to do so.

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

The Sponsor strongly recommends managing treatment modifications for cisplatin related toxicities 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.

OM will not be considered an AE requiring dose modification for the purposes of this study.

9.2. 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 8.9.1.

9.2.1. 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 5). Adult patients who are treated with cisplatin (considered a high-emetic-risk single agent for the purposes of these guidelines) should be offered a four-drug combination of a NK_1 receptor antagonist, a serotonin ($5\text{-}HT_3$) receptor antagonist, dexamethasone, and olanzapine. Dexamethasone and olanzapine should be continued on days 2 to 4. (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: strong.) (Hesketh, Kris et al. 2017).

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

10. ASSESSMENTS

The study procedures to be conducted for each subject enrolled in the study are described in the text that follows and summarized in the Schedule of Assessments in Appendix 1.

Adherence to the study design requirements, including those specified in the Schedule of Assessments, is required for study conduct.

Any deviation from protocol procedures should be explained in the source documents. The Sponsor (or designee) and the site's institutional review board (IRB/IEC/REB) – as required by the IRB/IEC/REB policies and procedures – should be notified as soon as possible of any deviations potentially affecting subject safety, GC4419 administration or the assessment of safety, efficacy and tolerability parameters.

All screening evaluations must be completed and reviewed to confirm that the potential participants meet eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, if applicable.

10.1. 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.

10.1.1. 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. Vital signs are required to be taken at Screening, Day 1 (Baseline), once during Week 4, once during Week 7 and any additional IMRT weeks, and on the Last Day of IMRT.
- Blood Pressure: On Day 1 (Baseline) and Day 22, blood pressure must be measured at the following times:
  - Within 30 minutes prior to the pre-GC4419 PK draw, and
  - After GC4419 infusion, prior to standing and prior to the End of GC4419 Infusion PK draw.
- Weight and Height: measured in kilograms (kg) and centimeters (cm), respectively
- Performance Status: ECOG assessment to be performed at Screening, Day 1 (Baseline), once during Week 4, once during Week 7 and any additional IMRT weeks, and on the Last Day of IMRT (see Appendix 3 for conversion criteria for Karnofsky to ECOG).

10.1.2. 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 11.2.

The following laboratory assessments are defined when referenced in the schedule of events (Table 5) 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, blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, albumin, total protein, direct bilirubin, total bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), chloride, phosphate, bicarbonate, magnesium.
- Serum Pregnancy Test: required for all women of childbearing potential. Lack of childbearing potential must be noted in the source documents, if applicable.
- Urine Pregnancy Test: required for women of childbearing potential. Lack of childbearing potential must be noted in the source documents, if applicable.

10.2. Symptom Related Questionnaires

Subjects will be asked to complete a brief questionnaire (Appendix 7) at Baseline and then once weekly before the second oral assessment of each week during treatment and 4 weeks after the end of treatment. On the days of the questionnaire completion, the study staff member should provide the questionnaire worksheet to the subject for completion prior to the OM assessment and should review the worksheet for completion.

The subjects' reported symptoms will support hypothesis generation surrounding the potential effects of GC4419 on long term OM related symptoms.

10.3. Oral Mucositis Assessments

OM assessments will be completed at the Screening Visit (within 28 days of IMRT start), Baseline Visit, twice weekly (no less than two days apart) within each five-day IMRT treatment period and once weekly for four weeks following end of treatment.

The extent of subjects' OM will be assessed by a trained evaluator and scored using the WHO OM toxicity scoring scale (Appendix 2). All subjects must have an oral assessment on the last day of IMRT treatment. If a subject withdraws for any reason prior to the end of IMRT, a complete oral assessment should be done on that day.

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 subject. 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 subject's ability to eat is critical for accurate scoring of the WHO scale. Therefore, standardization of the assessment is very important. A third-party vendor will perform data quality management for all OM scoring. This process will be outlined in a separate study document.

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 Appendix 2.

10.4. Radiation Therapy Quality Assurance

An independent radiation oncologist who is not an Investigator on the study will review the overall treatment plan, for summary and retrospective analysis at the end of the study. In addition to IMRT treatment, dosimetry and dose volume histograms will be collected after simulation. The 50-Gy isodose line should be clearly indicated, along with relevant imaging through the anatomic region for planned treatment.

10.5. Pharmacokinetic (PK) Measurements of GC4419

PK sampling for GC4419 will be sought from all subjects for GC4419. Plasma samples for GC4419 PK measurements will be collected during Cycle 1 and Cycle 4 on Study Days 1 and 2 (Cycle 1), and on Study Day 22 (Cycle 4).

On Study Days 1 and 22, four samples will be drawn as follows:

- The first sample will be drawn prior to GC4419 administration.
- The second sample will be drawn within 10 minutes after the end of GC4419 infusion.
- The third sample will be drawn within 10 minutes after the end of IMRT.
- The fourth and final sample will be drawn between 60 and 180 minutes after the end of
- GC4419 infusion.

On Study Day 2 only one PK sample will be drawn.

- This sample should be drawn prior to the GC4419 infusion on Day 2.

Table 3 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 discussed with the Sponsor or its representative ahead of time. 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 3: Pharmacokinetic Sampling Schedule to Assess GC4419

Timepoint	Day 1	Day 2	Day 22
Pre-GC4419	X	X	X
End of GC4419 (+10 min)	X		X
60-180 min Post End of GC4419 Infusion	X		X
Post-IMRT (+10min)	X		X

10.6. Tumor Status Assessment

10.6.1. Tumor Imaging

10.6.1.1. Pre-Treatment Tumor Imaging

Radiographic tumor imaging should occur within 60 days prior to the first day of IMRT (Baseline), and should be conducted according to local standard of care to ensure consistency with eligibility criteria. 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 subject has no evidence of disease at Baseline, it should be clearly indicated.

10.7. Schedule of Time and Events

A schedule of study assessments table is located in Appendix 1, Table 5. Minor changes to the assessment schedule may be made to accommodate holidays, administrative closures, etc., which if necessary, are not considered deviations by the Sponsor. Sites should contact the Sponsor (or its representative) prospectively to address rescheduling protocol assessments and data handling.

10.7.1. Screening

Screening assessments and procedures will be completed within 28 days of IMRT and GC4419 start.

- Obtain a signed IRB/IEC/REB-approved informed consent form (ICF)
- Confirm subject eligibility by reviewing inclusion/exclusion criteria
- 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 subjects, the subject must be cleared for IMRT per SOC (i.e., oral exam).

- Obtain medical history, tobacco use history, and alcohol use history
- Obtain HNC history; HNC history should include:
  - Tumor HPV status, for oropharyngeal cancers
  - Pre-treatment tumor imaging (See Section 10.6.2.1); may be completed within 60 days prior to the first day of IMRT)
  - Prior treatments
  - Confirmation of histopathological diagnosis of SCC
  - Tumor staging (AJCC 8th Edition) (pre-surgical staging for surgical subjects if available; otherwise, provide post-surgical staging)
- Conduct a complete physical examination, including height
- Measure vital signs, body weight, and ECOG Performance Status
- Confirm required Radiographic imaging performed within 60 days prior to first day of IMRT per Section 10.6.1.1.
- Conduct a 12-lead ECG.
- Conduct OM assessment per Appendix 2 and record the WHO score
- Draw blood for clinical laboratory measurements per Section 10.1.2 to include hematology profile, serum chemistry profile and serum pregnancy test for women of childbearing potential
- Record planned IMRT and chemotherapy parameters
- Record/update medical conditions and illnesses that have occurred since the subject signed the ICF and record in medical history
- All questions related to subject eligibility should be directed to Galera's Medical Monitor or designee.

10.7.2. Treatment Phase

10.7.2.1. Prior to GC4419 Infusion

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

- Confirm continued subject eligibility by reviewing inclusion/exclusion criteria (IMRT Week 1 Day 1 only)
- Record/update medical conditions and illnesses that have occurred since the subject signed the ICF and record in medical history including a review of tobacco and alcohol use (Week 1 Day 1 only)

- Complete Physical Exam (Last Day of IMRT regimen or Early Termination Visit Only)
- Body Weight (Week 1 Day 1, once weekly during Treatment Phase, and Last Day of IMRT or Early Termination Visit)
- Vital signs to be obtained at Week 1 Day 1, once during Week 4 and once during Week 7 and any additional IMRT weeks, and Last Day of IMRT or Early Termination Visit to include temperature, systolic and diastolic blood pressures, heart rate and respiration rate

  On Day 1 (Week 1) and Day 22 (Week 4), blood pressure must be measured at the following times: 1) within 30 minutes prior to the pre-GC4419 PK draw, and 2) after GC4419 infusion, prior to standing and prior to the End of GC4419 Infusion PK draw.
- ECOG Performance Status to be evaluated at Baseline Visit, once during Week 4 and once during Week 7
- Record BSA at Week 1 Day 1, and once during Weeks 4 and 7 for tri-weekly cisplatin dosing or once per week for subjects receiving weekly cisplatin.
- Conduct clinical tumor assessment per Section 10.6.1 Last Day of IMRT regimen or Early Termination Visit Only)
- Ensure concomitant medications have been recorded from date of enrollment
- Ensure AEs have been recorded from date of enrollment
- OM assessment using the WHO OM toxicity scale (Appendix 2) beginning on Week 1 Day 1 and then twice weekly thereafter (no less than two days apart) within each 5-day IMRT period, and Last Day of IMRT or Early Termination Visit.
- Draw blood for clinical laboratory measurements per Section 10.1.2 to include hematology profile and serum chemistry profile (Week 1 Day 1, Day 3, 4 or 5 and once per week thereafter through the last day of IMRT. *Note: If safety labs have not been drawn during the study week in which the last day of IMRT regimen/Early Termination Visit occur, then the clinical laboratory measurements should be collected at that time.*
- Urine Pregnancy Test on Week 1 Day 1 and Week 4 Day 1
- Draw blood for Pre-dose PK sampling per Section 10.1.1, Table 3 (Day 1, Day 2 and Day 22 only)
- Serum Pregnancy Test for women of childbearing potential on Last Day of IMRT or Early Termination Visit.

10.7.2.2. GC4419 Infusion

- Administer GC4419 dose by continuous intravenous infusion over 60 minutes weekly, Monday through Friday, beginning at Week 1 Day 1 and continuing through 35 doses. See Section 8.6, Table 2.

10.7.2.3. Following GC4419 Infusion

Following GC4419 administration the following observations and procedures will be conducted for all subjects:

- Measure Blood Pressure prior to standing (Week 1 Day 1 and Day 22 only)
- Draw blood for End of GC4419 Infusion (+10 minutes) PK sampling (Week 1 Day 1 and Day 22 only)
- Administer IMRT as soon as possible but no later than four hours following the end of GC4419 dosing. On days on which chemotherapy and GC4419 are administered, the following administration sequence should be used when possible to ensure that IMRT is initiated within four hours of the stop time of GC4419 infusion: GC4419, IMRT, prehydration, and cisplatin.
- Draw blood for Post IMRT (+10 minutes) PK sampling (Week 1 Day 1 and Day 22 only)
- Draw blood for 60-80 Minutes Post End of GC4419 Infusion PK sampling

10.7.3. Follow-up Phase

10.7.3.1. Post-IMRT OM Follow Up

All subjects will be evaluated weekly (± 2 calendar days) for the four weeks post-IMRT. At each visit, the following should be completed:

- Conduct OM assessment and record the severity using the WHO score
- Record AEs and concomitant medications through 30 days following the last dose of IMRT, cisplatin, or GC4419 (i.e., whichever occurs last)

11. 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. To avoid confusion, the AE should be recorded in standard medical terminology.

11.1. Definitions

The following definitions of terms are guided by the ICH and the US CFR and are included here verbatim.

11.1.1. 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.

11.1.2. 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.

11.2. Adverse Event Reporting Requirements

11.2.1. Serious Adverse Events

All events meeting the criteria for Serious Adverse Events (see Section 11.1.2) must be reported by investigational sites within 24-hours of becoming aware of the event. In order to determine the timeline for notifying the appropriate regulatory authorities and investigators, an event term, serious criteria, and causality is required at the time of the initial report. Specific SAE reporting instructions are provided in the SAE Report Completion Guidelines.

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.

11.2.2. Collection Period for AEs and SAEs

Any adverse medical condition or laboratory abnormality with an onset date prior to the date and time the subject received his/her first dose of study drug, GC4419, is considered pre-existing in nature and should be recorded as part of the subject's medical history. An adverse medical condition that begins on or after the first dose of study drug will be considered an adverse event, and will be considered an SAE if it meets serious criteria. AEs and SAEs will be followed for 30 days after the last dose of IMRT, cisplatin, or GC4419 (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 the 30-Day Follow-up Period. Increases in toxicity grade of pre-existing conditions that occur on or after the first study drug administration are also considered adverse events.

All adverse events must be recorded in the subject's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to therapy. Additionally, SAEs must be submitted to the Safety vendor within 24 hours of awareness.

11.2.3. 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 subject's condition, or that are present or detected at the time of enrollment and prior to study drug dosing that 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, IMRT, and/or cisplatin
- Treatment is initiated for the abnormality
- Investigational product was discontinued
- Grade 3 or Grade 4 per NCI CTCAE v5.0

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 11.1.

11.2.4. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Oral mucositis will not be reported as an AE as it is captured as a study endpoint in the CRF. Progressive disease found by scan or on clinical evaluation should be captured on the applicable CRF pages and not recorded as an AE.

11.2.5. Grading of Adverse Events

The severity of adverse events will be designated as mild, moderate, severe, life threatening, or fatal per NCI CTCAE version 5.0. If not specifically addressed in NCI CTCAE version 5.0, use Table 4 below:

Table 4: 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.

11.3. Relationship to Study Drug

All AEs will be categorized by the Investigator with respect to their relationship to GC4419. The Investigator should consult the current IB and/or product information in the determination of his/her assessment. The relationship between GC4419 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 caused or contributed to the cause of the adverse event or laboratory abnormality, when the temporal sequence from the time of GC4419 administration, the known consequences of the subject's clinical/state condition or study procedures, the effects of discontinuing or reintroducing GC4419 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, when the temporal sequence from the time of GC4419 administration, the known consequences of the subject'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 subject's clinical state/condition, study procedures, or other medically relevant factors other than treatment with GC4419 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.

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.

11.4. Recording Adverse Events

All AEs must be recorded on the appropriate CRF regardless of the severity or relationship to GC4419. 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 11.2.

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
- Subject verbal reports to the investigational staff and documented in the medical chart

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 use. AEs resulting from concurrent illnesses, reactions to concurrent medications or symptomatic progression of disease states, other than the disease under study, 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 as defined in Section 11.3
- Management of GC4419 administration and other action taken to alleviate the clinical events
- Clinical outcome of the AE

11.5. Follow-up of AEs and SAEs

If an adverse event changes in severity grade between the date it was initially recorded through the 30-Day Follow-up Period, the event should be recorded as a new AE; however, only one SAE should be reported to the Safety vendor for the event with the highest severity grade recorded.

After the initial AE/SAE report, the Investigator is required to proactively follow each subject and provide further information on the subject'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 within 30 days after last dose of GC4419 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 30 days after last dose of GC4419, IMRT, or cisplatin (i.e., whichever occurs last); however, collection of clinical data will continue on events of interest or as clinical circumstances warrant that exceed the 30 days after last dose of GC4419, per below and described in other sections of the Protocol:

- OM: 4 weeks post last IMRT dose (Section 10.7.3.1)
- 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 (Section 11.6 and Section 11.8). 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 the Sponsor, 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 subject dies during participation in the study or during a 30-Day Follow-Up Period, the Sponsor will be provided with a copy of any post-mortem findings, including histopathology.

11.6. Post-Study Reporting Requirements

Although such information may not be routinely sought or collected by the Sponsor, SAEs that occur after the subject has completed a clinical study may be reported. Such cases will be evaluated for expedited reporting.

11.7. Regulatory Reporting of Adverse Events

The Sponsor, or its designee, is responsible for submitting reports of suspected, unexpected, serious adverse reactions (SUSARs) to regulatory authorities on an expedited basis, according to the International Council on Harmonisation Guidelines and to other regulatory authorities according to national and local regulations as required.

The Investigator will report all SAEs that occur at his/her site to the IRB/IEC/REB per the IRB/IEC/REB regulations.

Investigators will also be notified of SUSARs that occur at other Sponsor sites and Sponsor trials using the study product. Each site is responsible for notifying its IRB/IEC/REB of these additional SUSARs 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 the Sponsor including documentation that the IRB/IEC/REB was notified of each safety report.

11.8. 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

highly effective method of contraception throughout the study and for 30 days (females) or 90 days (males) following the last dose of GC4419.

For the purpose of this document, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.

Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

A highly effective method of contraceptive is defined as any methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.

Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence

11.8.1. Time Period for Collecting Pregnancy Information

As permitted by IRB/EC/REB policies, any pregnancy that occurs from the first dose of GC4419 up to 30 days after last dose (30-Day Follow-Up Period) should be reported using the appropriate form within 24 hours of learning of the subject's pregnancy. The subject will be followed throughout the course of the pregnancy. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy should be reported. If a pregnancy is identified outside the 30-Day Follow-Up Period, the Investigator may report using clinical judgment.

11.8.2. Action to be Taken if Pregnancy Occurs in a Female Partner of a Male Subject

The Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while the male partner is participating in this study. In the case of paternal exposure, the investigator should obtain permission from the subject's partner in order to collect any pregnancy information. The Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours 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 the Sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported. If a pregnancy is identified outside the 30-Day Follow-Up Period, the Investigator may report using clinical judgment.

12. STATISTICS

12.1. 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.

12.1.1. Randomization and Stratification

Not applicable.

12.2. Sample Size

The sample size is selected with the intent that it will contribute to an overall safety database of 300 subjects with head and neck cancer who will, across all studies of GC4419, have received a full course of GC4419 at the intended dose (90 mg), schedule (1-hour infusion, 5 days/week, prior to IMRT), and duration (single course of 6-7 weeks) in combination with concurrent IMRT and cisplatin. Up to 70 such subjects are expected to be needed to reach the total safety database of 300. Enrolling up to 70 patients to the present study is expected to provide these subjects, assuming that approximately 10-20% will discontinue GC4419 before receiving it for at least 6 weeks.

The overall safety database size of 300 will allow for detection with 95% probability of adverse events of 1% true incidence in at least 1 subject.

Enrollment may be adjusted to ensure an overall safety database size of 300 across the development program.

12.3. Analysis Populations

Safety and efficacy analyses will be conducted on an “intent to treat” (ITT) population, consisting of all enrolled subjects who receive at least one dose of GC4419, and on a "per protocol" population consisting of subjects who receive at least 60 Gy of IMRT and at least 5 weeks (25 doses) of GC4419.

Subjects who withdraw prior to any dosing will have their reasons for withdrawal noted.

12.4. Safety Analysis

AEs 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 and vital signs will be summarized by treatment group at each of the protocol-specified time points.

Safety parameters will be summarized with descriptive statistics on the safety population, defined as the ITT population; viz., all subjects who received at least one dose of GC4419.

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

12.5. Efficacy Analysis

Overall rates of SOM/Grade 4 OM incidence and number of SOM/Grade 4 days will be summarized descriptively.

12.5.1. Multiplicity

Not applicable.

12.5.2. Handling of Missing Data

Subjects who withdraw consent for GC4419 administration should be encouraged to continue and complete standard IMRT/cisplatin, and protocol assessments.

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

12.5.3. Covariate Adjustment

Not applicable.

12.6. Exploratory Analyses

Any exploratory analyses will be described in the Statistical Analysis Plan.

12.7. ETHICS

12.7.1. 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), ICH guidelines, in particular ICH-GCP, or with the laws and regulations of the country in which the research is conducted, whichever affords the greatest protection to the study subject. 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 are adhered to.

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

This protocol and any accompanying material to be provided to the subject (such as advertisements, 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 the Sponsor or its representatives before initiating the conduct of any study procedures including screening or enrolling any patients into the study.

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 the Sponsor. Significant protocol deviations will be reported to the Sponsor 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.

12.8. 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 Informed Consent Form (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.

12.9. Data Monitoring Committee (DMC)

Not applicable.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

In accordance with 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 subject 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.

13.2. Audits and Inspections

Authorized representatives of the Sponsor, 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 Sponsor 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, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

13.3. Protocol Compliance

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

13.4. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the Sponsor 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.

13.5. Information Disclosure

13.5.1. Ownership

All information provided by the Sponsor 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 the Sponsor.

13.5.2. Confidentiality

All information provided by the Sponsor 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 the Sponsor.

13.5.3. 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 the Sponsor.

14. QUALITY CONTROL AND QUALITY ASSURANCE

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

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor 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.

15. DATA HANDLING AND RECORDKEEPING

15.1. Case Report Forms

All required study data must be recorded on the electronic CRF provided by the Sponsor 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-GCP 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 subject, 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 subject withdraws from the study, the electronic CRFs should be promptly completed and the reason for withdrawal must be noted. If a subject is withdrawn from the study because of a drug-related toxicity, thorough efforts should be made to clearly document the outcome.

15.2. 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 25 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 25 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 25 years after notification by the Sponsor of the FDA or other applicable regulatory agency decision. The records must be available for copying and inspection if requested by regulatory authorities.

The Sponsor 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.

16. LIST OF REFERENCES

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Table 5: Schedule of Assessments

Assessments	Screening	Treatment Period									OM Follow-Up
	≤28 days of IMRT Day 1	Wk 1		Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Last Day of IMRT or Early Term[1]	Wks 1, 2, 3 and 4 (±2 D)[2]
		Day 1	Days 2-7	Days 8-14	Days 15-21	Days 22-28	Days 29-35	Days 36-42	Days 43-49		
Informed consent	X										
Inclusion/exclusion criteria[3]	X	X									
Dental exam/IMRT clearance	X										
Medical and HNC histories[4]	X										
Complete physical exam[5]	X									X	
Height	X										
Weight	X	X		X	X	X	X	X	X	X	
Vital signs, ECOG[6]	X	X				X			X	X	
Record BSA[7]		X		X	X	X	X	X	X		
Tumor imaging[8]	X										
Concomitant medications[9]		X	Weekdays							X	X
Adverse Events[10]		X	Weekdays							X	X
ECG (12-lead)[11]	X										
OM assessment[12]	X	X	Twice-weekly							X	X
Symptom Related Questionnaire [13]	X	X	X	X	X	X	X	X	X		X
Blood draw: Serum pregnancy[14]	X									X	
Blood draw: Lab safety tests[15]	X	X	X	X	X	X	X	X	X	X[16]	
Blood draw: PK[17]		X	X			X					
Urine Pregnancy Test[18]		X				X					
Dosing GC4419[19]		X	Weekdays when IMRT is given							X	

BSA = body surface area; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HNC = head and neck cancer, IMRT = intensity-modulated radiation therapy; OM = oral mucositis; PE = physical examination; PK = pharmacokinetics

Table footnotes

[1] If a subject ends study participation early and/or withdraws consent after Baseline (Day 1), all last day of IMRT procedures should be completed.
[2] The Post-IMRT OM and Safety Follow-up Visits will be scheduled based on the last day of IMRT. All subjects will be seen at Days 7, 14, 21 and 28 (± 2 calendar days) from the last day of IMRT.
[3] See protocol Sections 7.1 and 7.2.
[4] The HNC history should include tumor HPV status, staging (AJCC 8th Edition) information, prior treatments, and confirmation of histopathological diagnosis of SCC. Medical conditions and illnesses that have occurred since the subject signed the ICF up until the date of enrollment 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), 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. On Day 1 (Baseline) and Day 22, blood pressure must be measured at the following times: 1) within 30 minutes prior to the pre-GC4419 PK draw, and 2) after GC4419 infusion, prior to standing and prior to the End of GC4419 Infusion PK draw.
[7] For subjects 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 subjects receiving weekly cisplatin, BSA will be recorded to confirm cisplatin dosing at the Baseline Visit and once per week until chemotherapy is completed.
[8] Radiographic imaging must be performed within 60 days prior to the first day of IMRT for all subjects.
[9] All concomitant therapies (e.g., prescription and over-the-counter medications) taken by subjects on or after the date of enrollment through 30 days following the last dose of GC4419, IMRT or cisplatin (i.e. whichever occurs last) will be collected in the CRF. Any concomitant therapies used to treat any serious or related adverse event will be recorded in the CRF.
[10] AEs and SAEs with onset dates on or after the date of enrollment through 30 days following the last dose of GC4419, IMRT or cisplatin (i.e. whichever occurs last) will be recorded on the CRF. All subjects with SAEs will be followed until the events resolve, stabilize, become chronic, the subject completes the study, or the subject is lost to follow-up.
[11] Ventricular rate and P-R, QRS, QT, and QTc intervals will be assessed and recorded at Screening.
[12] All OM assessments must be performed by trained evaluators. The extent of the subject's OM will be scored using the WHO OM toxicity scale. OM assessments will be completed at the Screening Visit, at the Baseline Visit, twice weekly (no less than two days apart) within each 5-day IMRT period and on the last day of IMRT or Early Termination Visit. For Week 1, the first OM assessment will occur at the Baseline Visit and one additional OM assessment must occur at least two days later during the week. The extent of the subject's OM will be scored using the WHO OM toxicity scale. OM assessments should continue weekly for four weeks following the last day of IMRT (Day 7, Day 14, Day 21 and Day 28 ± 2 calendar days).
[13] Symptom Related Questionnaires to be completed by subjects prior to the OM assessment at W1D1, and then prior to the second OM assessment each week and 28 days (± 2 calendar days) post end of treatment (EOT).
[14] For a woman of childbearing potential, serum pregnancy test must be performed at the Screening Visit and at the Last Day of IMRT or Early Termination Visit.
[15] 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, magnesium).
[16] 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.

[17]Blood samples will be collected for GC4419 pharmacokinetic (PK) measurements at Baseline (Day 1), Day 2, and Day 22. See Section 10.5 for details.
[18] For women of childbearing potential, urine pregnancy tests should be administered at Baseline (Day 1) and Q4 weeks from enrollment.
[19]GC4419 will be administered up to 35 times: weekly, Monday through Friday, beginning at Baseline (IMRT Day 1) and continuing through the 35th dose. IMRT must begin no longer than four hours 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. Subjects should resume GC4419 administration when IMRT resumes. If GC4419 was already administered on a given day and IMRT is not administered due to unforeseen circumstances, that day's GC4419 dose will still count as one of the 35 doses.

APPENDIX 2. WORLD HEALTH ORGANIZATION (WHO) SCORE OF ORAL MUCOSIT`IS

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

APPENDIX 3. 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

APPENDIX 4. NATIONAL CANCER INSTITUTE-COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS, VERSION 5.0

See the following website link for the complete NCI-CTCAE Version 5.0:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

APPENDIX 5. 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://ascopubs.org/doi/pdf/10.1200/JCO.2017.74.4789

Table 6: Antiemetic Dosing for Adults – High Risk (Cisplatin)

Drug Class	**Agent**	**Dose on Day of Chemotherapy**	**Dose(s) on Subsequent Days**
NK_1 Receptor Antagonist	Aprepitant	125 mg oral	80 mg oral; days 2 and 3
	Fosaprepitant	150 mg IV	Day 1 only
	Netupitant-palonosetron	300 mg netupitant/0.5 mg palonosetron oral in single capsule (NEPA)	Day 1 only
	Rolapitant	180 mg oral	Day 1 only
5-HT_3 Receptor Antagonist	Granisetron	2 mg oral OR 1 mg OR 0.01 mg/kg IV OR 1 transdermal patch OR 10 mg SC	Day 1 only
	Ondansetron	8 mg oral twice daily OR 8 mg oral dissolving tablet twice daily OR three 8 mg oral soluble films 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	
Corticosteroid if aprepitant is used*	Dexamethasone	12 mg oral OR IV	8 mg oral OR IV; once daily on 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*
Corticosteroid if netupitant-palonosetron is used*	Dexamethasone	12 mg oral OR IV	8 mg oral OR IV; once daily on days 2-4*

Corticosteroid if rolapitant is used	Dexamethasone	20 mg oral OR IV	8 mg oral OR IV; once daily on days 2-4
Olanzapine	Olanzapine	10 mg oral	10 mg oral on days 2-4

*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.

MASCC: full updated guidelines may be found at: http://www.mascc.org/antiemetic-guidelines (2016)

For the prevention of non-AC highly emetogenic chemotherapy, a three-drug regimen including single doses of a 5-HT3 RA, dexamethasone and an NK1 RA (aprepitant, fosaprepitant, netupitant or rolapitant), given before chemotherapy is recommended. In patients receiving non-AC highly emetogenic chemotherapy treated with a combination of an NK1 RA, a 5-HT3 RA and dexamethasone to prevent acute nausea and vomiting, dexamethasone on days 2–4 is suggested to prevent delayed nausea and vomiting. If aprepitant 125 mg is used in day 1, then dexamethasone 8 mg x 1 (days 2-4) + aprepitant 80 mg x 1 (days 2-3) OR dexamethasone 8 mg x 2 (days 2-4) + metoclopramide 20 mg x 4 (days 2-4). Please note that this dosage of metoclopramide derives from a phase III study and some regulatory authorities like EMA now recommend a maximum 0.5 mg/kg total daily dose.

APPENDIX 6. DAILY ORAL CARE RECOMMENDATIONS

The following protocol is strongly recommended for all dentulous or partially dentulous study participants to optimize oral health during radiation therapy and minimize the risk of post-radiation dental sequelae.

1. Diet – Minimize foods that contain refined sugars such as cookies, cakes, candy, sugar-containing drinks, etc. Favor fruits and vegetables.
2. Avoid alcohol, tobacco products, and carbonated beverages.
3. Practice scrupulous oral hygiene:
    a. Use a soft toothbrush or an electric toothbrush at least twice daily.
    b. Use fluoride-containing toothpaste or fluoride gel. When mouth becomes sore from mucositis continue to use toothbrush dipped in bland oral rinse.
    c. Clean spaces between the teeth using dental floss or similar device.
    d. If mouth is too sore to carry this out, rinse with topical anesthetic rinse to ensure completion of daily oral care.
4. Chew sugarless chewing gum after meals. Avoid other forms of chewing gum.
5. Use bland oral rinse three times a day until mouth becomes sore, then increase to every hour when mucositis begins.

Recipe for bland oral rinse: 1 teaspoon salt and 1 teaspoon baking soda in 4 cups of water

APPENDIX 7. SYMPTOM RELATED QUESTIONNAIRE

GTI-4419-202 Symptom Related Questionnaire

Subject Identifier: _____ Visit Name: _____ Date: _____

	Easy				**Very Difficult**
1. During the last week, rate the difficulty you experience in speaking due to dryness*	0	1	2	3	4
2. During the last week, rate the difficulty you experience in swallowing due to dryness	0	1	2	3	4
	Not dry at all				**Very Dry**
3. During the last week, rate the dryness of your mouth	0	1	2	3	4
4. During the last week, rate the dryness of your throat	0	1	2	3	4
	Comfortable				**Extremely Uncomfortable**
5. During the last week, rate your mouth and throat discomfort.	0	1	2	3	4
6. During the last week, rate the mouth and tongue discomfort you have due to dryness	0	1	2	3	4
7. During the last week, describe your ability to move/open your jaw.	0	1	2	3	4
	Never				**A lot**
8. During the last week, how often does food choke you after swallowing?	0	1	2	3	4
9. During the last week, how often do you cough after you swallow?	0	1	2	3	4
10. During the last week, how often does excess mucus cause you to gag or choke?	0	1	2	3	4
11. During the last week, have you had less desire to eat due to taste change?	0	1	2	3	4
12. During the last week, has your sense of smell decreased?	0	1	2	3	4

For Study Coordinator Use Only:

Name of Staff reviewing worksheet: _____ **Date:** _____