CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2a Open-Label Trial of the Effects of Intravenous GC4419 on the Incidence and Severity of Esophagitis in Subjects Receiving Chemoradiotherapy for Lung Cancer
Sponsor:	Galera Therapeutics, Inc.
IND Number:	143,437
Protocol ID:	GTI-4419-203
Medical Monitor:	Jon T. Holmlund, MD Charlotte Moser, MD PhD
Protocol Version/Date:	Amendment 3: 24 February 2021

STUDY ACKNOWLEDGEMENT

A Phase 2a Open-Label Trial of the Effects of Intravenous GC4419 on the Incidence and Severity of Esophagitis in Subjects Receiving Chemoradiotherapy for Lung Cancer.

Amendment 3: 24 February 2021

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: February 24, 2021 | 1:27:00 PM EST
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Jon T. Holmlund, MD
Chief Medical Officer
Galera Therapeutics, Inc.

Investigator Statement

I have read the attached protocol and appendices dated 24 February 2021 and agree to abide by all provisions set forth therein. I will provide copies of the protocol and other pertinent information to all individuals responsible to me who will assist with the study.

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

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

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

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

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

_____ _____

Signature of Principal Investigator Date (DD Month YYYY)

_____

Printed Name of Principal Investigator

REVISION HISTORY

Revisions to Amendment 2 dated 27 January 2020

Summary of Change	Rationale	Affected Protocol Sections
Updated estimated enrollment period and studied period	To be accurate with current study status	• Synopsis
Revised Inclusion criteria 1 to include all stage 3 (AJCC version 8) NSCLC	All stage 3 NSCLC by AJCC 8th edition receive CTRT as standard of care and carry the same risk of radiation induced esophagitis	• Synopsis • Section 6.1 • Section 7.1
Added formula for Inclusion criteria 6a (creatinine clearance)	To provide sites with further guidance	• Synopsis • Section 7.1
Risk estimation based on historic controls: ≥ Grade 2 esophagitis incidence changed from 50 to 30%	Adapted on risk profile of ≥ Grade 2 esophagitis with 75% of plans done with modulated radiotherapy planning rather than 3D-conformal (Kwint 2012, Palma 2013)	• Synopsis • Section 4.1 • Section 12.2 • Section 12.6
Exclusion criteria #9 changed to "symptomatic pneumonitis (≥ Grade 2 CTCAE v 5.0)"	Asymptomatic changes are not systematically scored in daily practice. All changes in lung are relative to baseline.	• Synopsis • Section 7.2
Exclusion criteria #11 changed to "history of hepatitis"	Because of the risk of reactivation of hepatitis in subjects with a history of disease, these subjects will be excluded.	• Synopsis • Section 7.2
Larger visit window allowed for post-RT assessments (4 week and 90-day)	Due to limited flexibility during COVID pandemic	• Section 10.7.6 • Section 10.8.1 • Appendix 1
Other editorial changes have been made throughout	To correct administrative errors and ensure content accuracy and consistency.	• Throughout

Revisions to Amendment 1 dated 08 October 2019

Summary of Change	Rationale	Affected Protocol Sections
Updated number of study centers from 8-10 to 10-15	To be accurate with current study status	• Synopsis
Updated estimated date of first patient enrolled from September2019 to December2019	To be accurate with current study status	• Synopsis
Updated exploratory endpoint and assessments to include collection of parenteral or tube feeding	Parenteral/tube feeding is known objective way to evaluate esophagitis and secondary weight loss	• Synopsis • Section 5.3 • Section 10.7 • Section 12.4.3 • Appendix 1

Summary of Change	Rationale	Affected Protocol Sections
Updated Inclusion Criteria #2, methodology section in synopsis and treatment plan to include more refined requirements for pts planned with intensity-modulated radiation therapy (IMRT)/ volumetric modulated arc therapy (VMAT) and adaptive work flows.	Esophagitis risk depends on how high the dose exposure cumulatively gets, but also to what kind of volume this can be restricted. With introduction of IMRT/VMAT techniques dose exposure can be better streamlined around organs, however due to continuous movement the esophagus exposure stays still significant. To better guide planning with these modalities we introduced volume-based criteria (V38 and V60), referenced in literature as best predictor of esophagitis-risk	• Synopsis • Section 6.2 • Section 7.1
Clarifications made to pregnancy and contraception requirements	In order to stress the pregnancy risk and reduction need more	• Synopsis • Section 7.1 • Section 7.2 • Section 11.7
Removed Exclusion Criteria #3 - Chemotherapy before start of concurrent radio-chemotherapy is allowed	Because of logistics or advanced disease, sometimes chemotherapy is started before radiation therapy. The influence on risk of esophagitis is not expected to be important, therefore this exclusion has been removed.	• Synopsis • Section 7.2
Updated Exclusion Criteria #6 (EC#4 in Amendment 2) to specify the use of electronic symptom-reporting device	To provide clarity on protocol conduct	• Synopsis • Section 7.2
Updated duration of GC4419 treatment to cover total number of fractions prescribed per subject (vary from 30-35).	To allow for maximum duration of GC4419 administration up to 35 doses to cover all RT fractions prescribed.	• Synopsis • Section 6.2 • Section 8.3.4
Updated prohibited medication/treatment section to specify timeframes	Drug interactions are expected while GC4419 is actively given. .	• Synopsis • Section 8.2
Added Radiation Therapy section	To include more details on Radiation Therapy dose specifications and treatment planning.	• Section 6.3

Summary of Change	Rationale	Affected Protocol Sections
Updated collection time of information regarding concomitant medications from within 28 days of Day 1 to Baseline Day 1.	Concomitant Medication information prior to baseline is not needed.	• Section 8.1 • Section 10.6 • Appendix 1
Removed reference of pain medication diary	Analgesic/narcotic medication use will be captured along with other concomitant medications.	• Section 8.1
Updated timeframe for collection of narcotics to extend to 30 days post treatment	To obtain additional information on narcotic use	• Section 8.1
Updated details for GC4419 in regards to use of filter and packaging	For clarification and to be consistent with pharmacy manual	• Section 8.3
Updated instructions for dosing GC4419 relative to RT administration (eg. how to handle RT treatment breaks)	Clarification of administration instructions	• Section 8.3.4
Updated Radiotherapy Quality Assurance (RTQA) section to provide additional detail	To provide clarification on radiation therapy requirements for centers using VMAT/IMRT treatment delivery and what information in these plans is needed to assess treatment planning	• Section 10.2
Updated Patient Reported Outcomes (PRO) language to allow completion at the baseline visit prior to dosing if not done during the week prior.	Clarification to enhance data capture	• Section 10.4 • Section 10.6 • Section 10.7 • Appendix 1
Updated to only record height at the screening visit	Correction as height will not change over time	• Section 10.6 • Section 10.7 • Appendix 1
Broadened window for Spirometry, Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) and electrocardiogram (ECG) to 56 days	These functional tests are done in the diagnostic work-up which extends up until 2 months in general.	• Section 10.6 • Appendix 1
Updated to specify administration sequence of study drug and other treatments	Clarification	• Section 10.7
Added other important medical event SAE definition	Correction	• Section 11.1.2
Updated Schedule of Assessments to specify that medical history should include NSCLC or SCLC cancer history including prior	The TNM disease state will determinate the volumes that will need radiation and indirectly the esophagitis risk	• Appendix 1

Summary of Change	Rationale	Affected Protocol Sections
treatments and confirmation of histopathological diagnosis.		
Other editorial changes have been made throughout	To correct administrative errors and ensure content accuracy and consistency.	• Throughout

Revisions to Original Protocol dated 17 April 2019

Change	Rationale	Affected Protocol Sections
Clarifications made to specify gemcitabine is not an allowed chemotherapy	Clarification, in response to FDA request	• Synopsis • Section 6.2
Inclusion Criteria 6a revised to be based on creatinine clearance (Cl_{cr})	Per FDA request	• Synopsis • Section 7.1
Exclusion Criteria #7 and prohibited medications clarified	Clarification, in response to FDA request	• Synopsis • Section 7.2 • Section 8.2
Added PK sampling to determine GC4419 exposure in the study population	Per FDA request	• Synopsis • Section 6.2 • Section 10.3 • Section 10.7 • Appendix 1
Added "Grade 3 or greater nausea or vomiting" to the list of toxicities requiring 25% GC4419 dose reduction	Per FDA request to add dose reduction for GC4419-related nausea/vomiting	• Synopsis • Section 9.2
Updated instructions for other toxicities (including those attributable to chemotherapy and RT)	Clarification, in response to FDA request	• Synopsis • Section 9.2
Inserted a section for Anticipated toxicities of GC4419	Per FDA request	• Section 9.1
Added Tumor assessment	Per FDA request	• Section 10.1.4 • Section 10.6 • Section 10.7 • Appendix 1
Added interim safety analysis/rules for stopping study	Per FDA request	• Section 12.5.1

1. SYNOPSIS

Name of Sponsor/Company:
Galera Therapeutics, Inc.

Name of Investigational Product:
GC4419

Name of Active Ingredient:
GC4419 (avasopasem manganese) (Manganese (II), is a water soluble, highly stable, low molecular weight manganese-containing macrocyclic complex whose activity mimics that of naturally occurring Superoxide Dismutase (SOD) enzymes.)

Title of Study:
A Phase 2a Open-Label Trial of the Effects of Intravenous GC4419 on the Incidence and Severity of Esophagitis in Subjects Receiving Chemoradiotherapy for Lung Cancer

Number of Study Center(s): 10-15 centers in the United States

Estimated Enrollment Period: 15-18 months

Studied period (years):	**Phase of development:** 2a
Estimated date first patient enrolled: December 2019 Estimated date last patient completed assessment for primary endpoint: December 2021	

Objectives:

Primary:

- To evaluate the incidence of acute radiation esophagitis (≥ Grade 2; National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 5) through the end of chemoradiotherapy for non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) when GC4419 is added.

Secondary:

- To evaluate and compare the incidence of acute severe (Grade 3-4) radiation esophagitis by NCI-CTCAE scales (Grade 3-4) through the completion of chemoradiotherapy;
- To evaluate and compare the incidence of acute esophagitis ≥ Grade 2, 4 weeks after completion of chemoradiotherapy, using the NCI-CTCAE scale;
- To evaluate and compare the presence of acute severe radiation esophagitis 4 weeks after completion of chemoradiotherapy;
- To evaluate the incidence of acute (through 90 days after radiation therapy) radiation pneumonitis, ≥ Grade 2 using NCI-CTCAE scale;
- To evaluate the adverse events (AEs) associated with GC4419 by the NCI-CTCAE scale;
- To assess weight loss (percent weight change from baseline through the completion of chemoradiotherapy, and 4 weeks after treatment).

Exploratory objectives:

- To explore the trend of severity of radiation esophagitis-related pain, dysphagia, and dyspepsia during combined chemotherapy and radiation therapy (RT) using these fields of the National Cancer Institute- Common Terminology Criteria for Adverse Events-Patient Reported Outcome (NCI PRO-CTCAE) weekly during treatment, and 4 weeks after completion of chemoradiotherapy;
- To evaluate the incidence of acute radiation esophagitis (≥ Grade 2; radiation therapy oncology group [RTOG] scale) through the end of chemoradiotherapy;
- To evaluate and compare the incidence of acute esophagitis ≥ Grade 2, 4 weeks after completion of chemoradiotherapy, using the RTOG scale;
- To assess patient-reported dysphagia via a daily patient log and collect use of parenteral or tube feeding due to esophagitis;
- To assess opioid use by collecting the patient's narcotic use in the previous 24-hour period at each weekly evaluation.

Methodology:

GTI-4419-203 will be an open-label, multi-center study to evaluate GC4419 administered intravenous (IV) for the reduction of radiation induced esophagitis in subjects receiving chemoradiotherapy for unresectable Stage 3 or post-operative Stage 2B NSCLC, SCLC treatable with chemoradiotherapy (AJCC 8th edition).

Subjects will receive radiation therapy, delivered in once-daily fractions, 5 days/week to a total dose of at least 60 Gy combined with chemotherapy other than gemcitabine, per investigator choice.

Subjects can be enrolled when an estimated 5cm of the esophagus is expected to be near the 60 Gy treatment volume.

In all subjects, the final plan should show that at least one surface of the esophagus is included in the 60 Gy isodose volume. Making sure that the full esophagus is contoured, the dose volume histogram needs to confirm high dose exposure in the range of V38>30% and/or V60>20%.

Each subject will receive GC4419, 90 mg, by 60-minute IV infusion, prior to each fraction of RT. GC4419 should be administered so that RT is administered within 60 minutes of the end of the GC4419 infusion.

Toxicity by common terminology criteria for adverse events (CTCAE), and esophagitis by CTCAE criteria, will be assessed at each treatment visit and 4 weeks after completion of treatment. Opioid use, weight loss, common terminology criteria for adverse events- patient reported outcome (CTCAE-PRO) fields will be assessed weekly during treatment and 4 weeks after completion of treatment. Patient-reported swallowing diaries will be completed daily. To assess early pneumonitis, NCI-CTCAE scale, CT scan, spirometry, and diffusing capacity of the lungs for carbon monoxide (DLCO) will be assessed at the end of treatment and 90 days after completion of treatment.

PK sampling will be sought from all subjects.

Number of Subjects (planned):

Approximately 60 subjects with NSCLC and SCLC referred for chemoradiation

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

1. Subjects scheduled to be treated with (definitive or adjuvant) radiation therapy in combination with chemotherapy once daily for pathologically confirmed Stage 3 or post-operative Stage 2B NSCLC or limited stage SCLC.
2. Treatment plan for subjects show that 5 cm of the esophagus for at least one surface, is included in the 60 Gy isodose volume. Dose volume histograms show esophagus dose exposure meet V38>30% and/or V60>20%.

   Note: In case the final planning shows that the contoured esophagus is close to but the 60 Gy isodose does not cover completely 5 cm, this subject may be allowed on the trial at the discretion of the principal investigator after discussion with and review by the Medical Monitor.

3. Age ≥ 18 years or older
4. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
5. Adequate hematologic function as indicated by:
   a. Absolute neutrophil counts (ANC) ≥ 1,500/mm^3
   b. Hemoglobin (Hgb) ≥ 9.0 g/dL
   c. Platelet count ≥ 100,000/mm^3
6. Adequate renal and liver function as indicated by:
   a. Estimated baseline creatinine clearance >60 cc/min (CrCl = (140 – Age) x Mass (kg) x [0.85 if female] / 72 x [Serum Creatinine (mg/dL)])
   b. Total bilirubin ≤ 1.5 x upper normal limit (ULN)
   c. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN
   d. Alkaline phosphatase ≤ 2.5 x ULN
7. Males and females must agree to use a highly effective contraception starting at least one day prior to the first day of treatment and continuing for 30 days after the last dose of GC4419 (females) or 90 days (males)
8. Properly obtained written informed consent

Exclusion Criteria:

1. Metastatic disease
2. Prior radiation therapy 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. Subjects not receiving chemotherapy
4. Grade 2 or greater esophagitis at baseline

5. Inability to provide information in the electronic symptom-reporting device
6. Subjects receiving approved or investigational immunotherapy, targeted therapy, hormone therapy, or biologic therapy
7. Participation in another clinical trial or use of another investigational agent within 30 days of first dose of GC4419
8. Malignant tumors other than the current lung cancer within the last 5 years, unless treated definitively and with low risk of recurrence in the judgment of the treating investigator
9. Previous diagnosis of symptomatic pneumonitis (≥ Grade 2 CTCAE v 5.0 including immunotherapy induced pneumonitis)
10. Untreated, active infectious disease requiring systemic anti-infective therapy
11. Untreated HIV or history of hepatitis B/C (subjects who have been vaccinated for hepatitis B and do not have a history of infection are eligible)
12. Pregnant female subjects (including positive test for pregnancy); breastfeeding/lactating female subjects; female subjects of child-bearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol
13. Known allergies or intolerance to chemotherapy and similar platinum-containing compounds
14. Requirement for concurrent treatment with nitrates
15. Requirement for treatment with drugs other than nitrates that may, in the judgment of the treating investigator, create a risk for a precipitous decrease in blood pressure.
16. Clinically significant heart disease (eg, congestive heart failure of New York Heart Association Class 3 or 4, angina not well controlled by medication, or myocardial infarction within 6 months)

Investigational Product, Dosage and Mode of Administration:

GC4419 is formulated as a sterile solution at a concentration of 9 mg/mL in 26 mM sodium bicarbonate-buffered 0.9 wt. % sodium chloride for parenteral administration (drug product). GC4419 will be presented in single use vials. Vials will be filled with 11 mL ± 0.1 mL of GC4419, of which 10 mL be added into a 250 mL bag of normal saline, for daily IV administration over 60 minutes.

Duration of Treatment:

Approximately 30 doses, covering the total number of fractions of the prescribed radiation therapy (to a maximum of 35 doses) on days in which RT is administered, Monday-Friday, for approximately 6 weeks. GC4419 should be administered so that RT is administered within 60 minutes of the end of the GC4419 infusion.

Reference Therapy, Dosage and Mode of Administration:

Not applicable

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

Criteria for Evaluation:

- NCI-CTCAE, version 5.0, for Adverse Events and esophagitis
- NCI PRO-CTCAE fields for pain, dysphagia, and dyspepsia
- Numerical Pain Rating Scale for esophagitis pain
- For evaluation of pneumonitis:
  - NCI-CTCAE criteria version 5.0
  - Spirometry
  - DLCO
  - CT scanning

Safety Monitoring and Toxicity Management:

Adverse/Serious Adverse Event (SAE) assessments per CTCAE version 5.0 and GCP standards

Toxicity requiring 25% GC4419 dose reduction:

- Grade 2 or greater hypotension occurring within one hour of the end of GC4419 infusion
- Grade 3 or greater nausea or vomiting
- The dose of GC4419 may be reduced by 25% for Grade 3-4 AEs judged by the Investigator to be likely attributable to the study infusion.
- Subject to the judgment of the treating investigator, GC4419 dosing should be interrupted or reduced according to the provisions of this section as necessary for toxicities potentially attributable to either GC4419 or chemoradiotherapy.

Two dose reductions for toxicity will be permitted per patient. Subjects unable to tolerate GC4419 after two dose reductions must discontinue treatment with the study drug GC4419 but should continue with standard chemoradiotherapy at the discretion of the treating investigator.

Toxicities including those attributable to chemotherapy and RT) should also be managed per institutional and American Society of Clinical Oncology (ASCO) guidelines and investigator judgment.

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

Concomitant Medications/Treatments:

Investigators may prescribe any concomitant medication or supportive therapy deemed necessary to provide adequate supportive care. Supportive care includes antiemetic prophylaxis, hematopoietic growth factor used per ASCO guidelines, systemic antibiotics,

hydration to prevent renal damage etc., consistent with local standard of practice, with the following exceptions:

Prohibited medications/treatments:

- Gemcitabine
- Nitrates, phosphodiesterase type 5 (PDE 5) inhibitors (eg, 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
- Other biologic response modifiers – except systemic hematopoietic growth factors for the management of anemia or myelosuppression
- Concurrent approved or investigational immunotherapy, targeted therapy, hormone or biologic therapy.
- Concurrent investigational agents intended to reduce mucosal toxicity of radiation therapy
- Other investigational agents

All medication restrictions end after the 4-week post RT follow-up visit is completed unless otherwise noted.

Concomitant use of GC4419 increases the concentration of drugs that are CYP2D6 substrates, which may increase the risk of toxicities of these drugs. Avoid concomitant use of GC4419 with CYP2D6 substrates where minimal increases in concentration of the CYP2D6 substrate may lead to serious or life-threatening toxicities (substrates with a narrow therapeutic range).

Statistical Considerations:

The incidence of ≥ Grade 2 esophagitis will be summarized and compared descriptively with historical controls based incidence rate of 30% incidence (Fogh 2017, Kwint 2012, Palma 2013) for chemoradiotherapy alone (range in literature since 2010; 18-42%). Percentages and 95% confidence intervals will be calculated and a binomial test performed.

A dropout/in evaluable rate of 10% is assumed, leading to an overall target enrollment of approximately 60 subjects to yield 55 who either complete treatment or are known to have had esophagitis before discontinuation.

For illustration, if the true incidence of ≥ Grade 2 esophagitis in GC4419-treated subjects is 13%, the trial will have roughly 80% power with 55 subjects in the analysis to demonstrate incidence lower than 30% with a one-sided Type I error rate of 2.5%.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

LIST OF TABLES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1. Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Definition
4DCT	Four-dimensional computed tomography
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BED	biologically equivalent dose
BID	twice a day
BUN	blood urea nitrogen
BSA	body surface area
CAT	computerized axial tomography
CINV	chemotherapy-induced nausea and vomiting
CRF	case report form
CRT	chemoradiation therapy
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	clinical target volume (consisting of gross tumor volume plus margin for microscopic disease presence)
DLCO	diffusing capacity of the lungs for carbon monoxide
Dmax	maximum dose
Dmean	mean dose
DVH	dose-volume histogram
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GTV	gross tumor volume
iGTV	interpolated gross tumor volume (representing the extension of geographies of this tumor volume during a respiratory cycle)

Abbreviation or Specialist Term	Definition
Hgb	hemoglobin
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMRT	intensity-modulated radiation therapy
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
ITV	Internal target volume (consists of an internal margin added to the CTV to compensate for internal physiologic movement and variations in size, shape, and position of the CTV)
LD50	median lethal dose
MASCC	Multinational Association of Supportive Care in Cancer
NSCLC	non-small cell lung cancer
NCI	National Cancer Institute
NPRS	numeric pain rating scale
OM	oral mucositis
PDE	phosphodiesterase type 5
PK	Pharmacokinetic
PRO	Patient Reported Outcome
PTV	planning target volume
REB	Research Ethics Board
ROS	Reactive Oxygen Species
RT	radiation therapy
RTOG	Radiation Therapy Oncology Group
SAE	serious adverse event
SCLC	small cell lung cancer
SOD	superoxide dismutase
SOM	severe oral mucositis
TPN	total parenteral nutrition
ULN	upper limit of normal
VMAT	volumetric modulated arc therapy (rotational IMRT)
WHO	World Health Organization

4. INTRODUCTION

4.1. Background

4.1.1. Mechanisms of Mucositis and the Role of Superoxide in its Initiation

Mucositis is the inflammatory disruption of an area of the normal surface epithelium of an organ. Terms for mucositis in individual organs include dermatitis, head and neck mucositis, esophagitis, enteritis, proctitis, and cystitis. Mucositis in all of these sites has a common pathway, allowing information from one area of study, such as mucositis of the head and neck, to be translatable to another area, such as esophagitis.

Mucositis can be modeled on a tissue scale and on a sub-cellular scale. The commonly accepted model of mucositis on the tissue scale is that of (Sonis 1998). This model functions best to highlight the temporal effects, rather than the mechanistic effects, involved in tissue damage and healing. The model has 5 phases: Initiation, Damage, Inflammation, Ulceration, and Healing. Mucositis modifiers can be classified by where they intervene in the model. Radioprotectors work by decreasing the damage from the ionizing radiation. Anti-inflammatory agents such as non-steroidal anti-inflammatory drugs would inhibit inflammation, and antifungal agents would intervene in the ulceration phase, by preventing superinfection. A growth factor such as keratinocyte growth factor-alpha (palifermin) would stimulate epithelial regrowth during Phase 5. However, many of the cytokines and growth factors, like palifermin, involved in the normal mucosal healing response are the same compounds that induce growth and spread of tumors.

The tissue-scale model, although enlightening on a macroscopic level, gives no insight into the complexities of the cellular/subcellular mechanisms involved in the induction and resolution of mucositis. Superoxide (O_2•-) plays a central role in initiation of the process (Murphy 2008). Under normal circumstances O_2•- is a by-product of mitochondrial cellular respiration and is also produced by activated phagocytes. Since O_2•- is extremely reactive with biological molecules, it is quite toxic to cells. In all studied species, this potentially toxic O_2•- burden is normally contained by a complement of superoxide dismutase (SOD) enzymes. In vertebrates, SOD enzymes are present in the cytoplasm (SOD1 Cu/Zn based), mitochondria (SOD2, Mn based) and extracellular spaces (SOD3, Cu/Zn based). Superoxide dismutase are a class of oxidoreductase enzymes that convert superoxide into molecular oxygen and hydrogen peroxide.

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

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

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

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

Taken as a whole, this suggests that an agent that efficiently and rapidly removes superoxide offers a treatment paradigm for or controlling oral mucositis (OM). Numerous published studies indicate that mucositis, esophagitis, pneumonitis, fibrosis, or other normal-tissue radiation damage may be reduced by treatment with liposomally encapsulated exogenous MnSOD or a MnSOD transgene, exogenous Cu/Zn SOD, or a dismutase mimetic enantiomerically related to GC4419.

4.1.2. Radiation Esophagitis

4.1.2.1. Assessment of Esophagitis and Esophagitis-related Pain

Radiation esophagitis is the most common dose-limiting toxicity associated with the treatment of lung cancer with chemoradiation therapy (CRT) (Baker 2016). Chemoradiation therapy-induced esophagitis may affect an individual's ability to eat/swallow and in some instances may require hospitalization or parenteral feeding (National Cancer Institute 2017). More severe cases of acute CRT-induced esophagitis may include life-threatening complications such as stricture, ulceration, perforation, or fistula (Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer [RTOG/EORTC] 2019) (Table 2).

Table 2. Esophagitis Grading Scales NCI-CTCAE & RTOG

Grade	NCI-CTCAE	RTOG
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Mild dysphagia/odynophagia Topical anesthetics, non-narcotic agents, or soft diet might be needed
2	Symptomatic; altered eating/swallowing; oral supplements indicated	Intermediate dysphagia/odynophagia Narcotic agents or pure liquid diet might be needed
3	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated	Severe dysphagia/odynophagia Dehydration or weight loss > 15% Nasogastric tube might be required for nutrition
4	Life-threatening consequences; urgent operative intervention indicated	Complete obstruction, ulceration, perforation/fistula
5	Death	Death

NCI-CTCAE = National Cancer Institute- Common Terminology Criteria for Adverse Events, RTOG/EORTC = Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer, TPN = total parenteral nutrition.
Sources: NCI-CTCAE 5.0 (2017); RTOG/EORTC (2019).

4.1.2.2. Incidence of Radiation Esophagitis in Lung Cancer

The incidence of severe acute esophagitis in subjects treated for lung cancer with standard RT alone depends on esophageal RT dose and is markedly higher when radiation and chemotherapy are combined, when chemotherapy is concurrent with RT, and when RT is given twice daily (hyper fractionated) or by an accelerated fractionation (eg, 6 days/week) regimen:

- Vokes 2002 reported 49% rate of grade 3 or higher esophagitis with concurrent gemcitabine and thoracic RT.
- In a Phase 3 study conducted by Ball 1995, which examined 100 subjects with non-small cell lung cancer (NSCLC), the duration of symptomatic esophagitis was 1.4 months (mos.) in the conventional RT arm, 1.6 months. In the conventional RT arm with concurrent carboplatin, 3.2 months. In the accelerated arm, and 2.4 months. In the accelerated RT plus carboplatin arm.
- Byhardt 1998 looked at toxicity in 5 RTOG trials using sequential and or concurrent chemotherapy with RT for advanced NSCLC. They found that hyperfractionated RT to a total dose of 69.6 Gy was associated with a 24%-34% incidence of severe esophagitis.
- The CHART regimen (Continuous Hyperfractionated Accelerated Radiation Therapy), given without chemotherapy for locally advanced NSCLC, resulted in a 19% rate of severe esophagitis (Emami 1996).
- Concomitant boost technique with concurrent chemotherapy also resulted in a dose-limiting incidence of esophagitis of 33% (Xiao 2004).
- The Eastern Cooperative Oncology Group (ECOG) trial of once-a-day versus twice-a-day RT with concurrent cisplatin and etoposide for small cell lung cancer (SCLC) showed a survival advantage for twice-a- day radiation but at the expense of increased esophagitis. Specifically, 56% of subjects in the once-daily arm did not experience esophagitis vs. only 37% of subjects in the twice-daily arm. Moreover, the rates of Grade 3 esophagitis

(defined as an inability to swallow solids, requiring narcotic analgesics, or the use of a feeding tube) were 11% the once-daily arm versus 27% in the twice-daily arm (Turrisi 1999).

- In the Locally Advanced Multimodality Protocol (LAMP) study (Belani 2005), esophagitis was > National Cancer Institute (NCI) Grade 3 in 19% to 28% of subjects receiving 63 Gy of RT by standard fractionation plus concurrent carboplatin and paclitaxel.
- In RTOG 9801, the rate of > Grade 3 esophagitis was 30% to 34% with hyperfractionated RT (69.6 Gy in 1.2 Gy fractions twice a day [BID]) plus concurrent carboplatin and paclitaxel (Movsas 2005).
- In RTOG 9410, the rate of > Grade 3 esophagitis for RT plus concurrent cisplatin-based chemotherapy was 23% with standard fractionation RT (63 Gy in 34 fractions) and 45% with hyperfractionated RT (69.6 Gy in 1.2 Gy fractions BID) (Curran 2011).
- In RTOG 1012, a randomized, placebo-controlled, double blind trial in subjects receiving CRT that included standard fractionation RT of least 60 Gy delivered to at least 5 cm of the esophagitis, 12.5% of subjects in the placebo arm developed NCI/RTOG Grade 3 esophagitis (Fogh 2017). (The trial failed to demonstrate a beneficial effect for Manuka honey to reduce esophagitis.)

However, more recently, the RTOG 0617 trial of carboplatin/paclitaxel +/- cetuximab with standard fractionation RT to either 60 Gy or 74 Gy reported 7% esophagitis > Grade 3 for the 60 Gy arm vs 21% for the higher RT dose (Bradley 2015). While cross study-comparisons are challenging, this raises the possibility that contemporary refinements to RT technique for NSCLC may be substantially reducing the incidence of the most severe radiation esophagitis. However, in the same studies, the rate of ≥ Grade 2 esophagitis was approximately 30% (Kwint 2012, Palma 2013).

4.1.2.3. Prevention of Radiation Esophagitis

The classical, two-dimensional fields used in RT for lung cancer include the primary lesion, ipsilateral hilum, bilateral mediastinum, and often ipsilateral supraclavicular region, establishing elective nodal irradiation as a standard approach. The current trend is for smaller, tighter fields frequently encompassing only the grossly visible tumor or positron emission tomography -positive tumor with a small margin (such an approach was used in RTOG 0617). The benefits include less irradiated lung volume and a shorter length of irradiated esophagus, which is assumed to decrease the probability of esophageal toxicity. This concept stems from reports that doubling the length of irradiated portion of the esophagus leads to a decrease of the LD50 dose, or dose causing the death of 50% of irradiated animals (Michalowski 1986).

However, the evidence that esophageal toxicity is minimized with shorter esophageal length irradiated is contradictory (Werner-Wasik 2000; Choy 1999; Langer 1999; Ball 1995).

In animal models, amifostine had been demonstrated to increase the amount of radiation that can be delivered before reaching mean lethal doses (LD50) from approximately 38.0 Gy to 60.0 Gy, achieving an overall Protection Factor of 1.5-1.6 for both acute and chronic esophageal damage (Ito 1986). Improved esophagitis with amifostine in Phase 2 and 3 trials have been noted in subjects with NSCLC receiving thoracic RT, with or without concurrent chemotherapy (Werner-Wasik 2001; Werner-Wasik 2002; Koukourakis 1996; Antonadou 2001;

Antonadou 2002). In a randomized Phase 3 trial, Antonadou 2001 examined 146 subjects with lung cancer treated with thoracic RT who received daily infusion of amifostine (340 mg/m^2) or no amifostine. They noted grade 2 or higher acute esophagitis in 32/72 RT subjects vs. 6/72 in amifostine/RT subjects ($p < 0.001$). In the subsequent study of chemoradiotherapy for lung cancer, a similarly significant decrease in esophagitis was observed (88% vs. 47%) (Antonadou 2002).

In contrast to these previous findings, RTOG 98-01 (Movsas 2005), a Phase 3 randomized study of amifostine for esophagitis prevention examined 243 subjects with locally advanced NSCLC who received 2 courses of induction chemotherapy (carboplatin and paclitaxel) followed by concurrent twice-daily thoracic RT and weekly low-dose carboplatin and paclitaxel. Subjects were randomized to receive amifostine or no amifostine. Amifostine did not demonstrate a reduction in severe esophagitis (30% rate with amifostine vs. 34% without); however, based on patient diaries, the swallowing dysfunction measured over time was significantly lower with amifostine ($p = 0.03$). In this trial, only 40% of all RT fractions were "protected" by amifostine infusion in that study and only 29% of subjects received amifostine according to protocol requirements. It is unwise to conclude that poor patient compliance was necessarily why the amifostine failed to show efficacy; it is equally likely that the poor compliance was because the amifostine was not sufficiently beneficial.

The use of non-steroidal compounds to prevent radiation esophagitis also has been studied. Neither indomethacin nor naproxen showed significant efficacy in small randomized trials (Milas1992; Nicolopoulos 1985). Non-randomized trials have shown an apparent efficacy of granulocyte-macrophage colony-stimulating factor and glutamine, and preclinical studies suggest that administration of manganese superoxidedismutase-plasmid/liposome prior to radiation inhibits esophagitis (Algara 2007; Epperly 2004; Koukourakis 1999).

The NRG Oncology RTOG group conducted a trial (RTOG 1012) of Manuka honey to reduce the pain experienced by subjects receiving concurrent RT to at least 60 Gy plus chemotherapy. Manuka honey failed to demonstrate a significant improvement in that trial (Fogh 2017). One third of patients experienced ≥ Grade 2 esophagitis, which was taken in this study as our estimated incidence expected without GC4419.

In this trial, we follow the same inclusion criteria as in RTOG 1012, selecting those subjects with the highest esophagitis risk, according to the dose-volume exposure of the esophagus as described in this trial. We know that in RTOG 1012 only half of the patients were planned with modulated (rotational) techniques, whereas we expect more than 75% of subjects treated in this more restrictive manner. Dose-volume parameters are collected with care to address esophagitis risk directly to esophagus exposure, rather than general treatment.

The impact of radiation planning (IMRT vs. 3D) on incidence of esophagitis depends on the total volume of disease that needs to be treated and the proximity to the esophagus. Kwint et al described dose volume relations being of impact, rather than the technique used in stage 3 disease (Kwint 2012). In series scoring esophagitis, while using modulated planning incidence of radiotherapy combined with platin-based chemotherapy, still an incidence of grade 3 of approximately 20% and grade 2 of 38% was reported (Palma 2013, Kwint 2012).

4.2. GC4419

GC4419 is a novel, highly stable manganese-containing macrocyclic complex with a molecular weight of 483, whose activity mimics that of naturally occurring SOD enzymes. It is therefore a prototype of a new class of drugs termed selective SOD mimetics.

The mechanism of action and nonclinical pharmacology of GC4419 suggest that it has the potential to be a radiation protectant for a variety of normal tissues, including the oral mucosa, esophageal mucosa, and lung.

GC4419 selectively removes superoxide without reacting with other ROS, including nitric oxide, hydrogen peroxide, and peroxynitrite. Preclinical data identify GC4419 as a promising new radiomodulatory agent. GC4419 demonstrated a dose-related reduction in the number of days of severe mucositis in a hamster cheek-pouch model of OM, and protected other normal tissues (gastrointestinal mucosa, lung) from the toxicity of radiation in animal models, while also demonstrating mechanism-related synergy with high-dose fraction RT.

GC4419 is being developed for the initial indication of "Reduction of the incidence and severity of SOM induced by RT, with or without systemic therapy" under Investigational New Drug 111,539 with the Division of Dermatology and Dental Products, United States Food and Drug Administration (FDA).

In a Phase 1b/2a trial, GC4419 demonstrated an acceptable safety profile at doses up to 112 mg, administered on weekdays prior to scheduled standard-fractionation RT plus concurrent cisplatin for the treatment of 46 subjects with locally advanced, squamous cell carcinoma of the oral cavity or oropharynx. Separate cohorts of subjects received GC4419 to cover 3 weeks to the full 7 weeks of RT. The maximum tolerated dose of GC4419 was not reached in that trial. Dose limiting toxicities in 2 of 18 subjects receiving the top dose of 112 mg were NCI Grade 3 gastroenteritis and Grade 3 vomiting in one patient each. Forty-three of the subjects were evaluable for OM. The OM evaluations indicated that, compared with historical expectations:

- The overall incidence of severe (World Health Organization [WHO] Grade 3 or 4) OM appeared reduced;
- Severity of OM (specifically, Grade 4 OM) appeared to be lowered;
- Onset of SOM appeared delayed;
- Duration of SOM appeared reduced.

In general, efficacy to reduce the incidence and severity of OM appeared greatest when GC4419 was administered throughout the full RT dosing period. However, there was not a clear relationship between absolute daily dose and OM results.

In a 223-patient 3-arm, dose-randomized, placebo-controlled, double-blind Phase 2 trial of GC4419 in a similarly-defined and treated patient population, a 90 mg dose of GC4419 demonstrated a significant and clinically meaningful reduction in SOM duration, as assessed on the entire randomized population, and also reduced the incidence of SOM during the study treatment period by approximately one-third, compared with placebo. The safety profile in the active GC4419 arms was similar to that in the placebo arm, indicating that GC4419 does not

increase the known toxicity of the background, standard intensity-modulated radiation therapy/cisplatin treatment. A confirmatory Phase 3 trial is planned with the 90 mg dose of GC4419.

The mechanism of mucosal injury induced by chemoradiotherapy, and of GC4419 to protect normal mucosa from that injury, is the same regardless of anatomic location in the gastrointestinal tract, supporting the hypothesis that GC4419 may be able to reduce the incidence and/or severity of radiation-induced esophagitis in subjects with cancer.

4.3. Rationale for the Present Trial

The goals of this Phase 2a trial are to obtain an initial estimate of the efficacy of GC4419 to reduce esophagitis in subjects receiving CRT for NSCLC and NSCLC. This Phase 2 trial will provide important data on the prevalence and degree of esophagitis during modern chemoradiotherapy for lung cancer, using the standard NCI and RTOG toxicity grading scales. Additional explorations will include descriptive assessment of radiation pneumonitis, patient-reported aspects of esophagitis using the National Cancer Institute- Common Terminology Criteria for Adverse Events-Patient Reported Outcome (NCI PRO-CTCAE), and incidence of narcotic use.

This will be a single-arm, open-label study that will compare the frequency of ≥ Grade 2 esophagitis in the study population to historical expectations.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Primary Objective

The primary objective of this study is to evaluate the incidence of acute radiation esophagitis (≥ Grade 2; NCI-CTCAE version 5) through the end of chemoradiotherapy for non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) when GC4419 is added.

5.1.1. Rationale for Primary Endpoint

Radiation esophagitis is commonly reported according to the NCI grading scale. For this initial study, this scale is appropriate to make an initial estimate of whether a clinically meaningful reduction in radiation esophagitis may be possible when GC4419 is administered concurrent with standard chemoradiotherapy of subjects with lung cancer. Secondary and exploratory observations will further inform the efficacy results of the present trial.

5.2. Secondary Objectives

- To evaluate and compare the incidence of acute severe (Grade 3-4) radiation esophagitis by the NCI-CTCAE scale (Grade 3-4) through the completion of chemoradiotherapy;
- To evaluate and compare the incidence of acute esophagitis ≥ Grade 2, 4 weeks after completion of chemoradiotherapy, using the NCI-CTCAE scale;
- To evaluate and compare the presence of acute severe radiation esophagitis 4 weeks after completion of chemoradiotherapy;
- To evaluate the incidence of acute (through 90 days after radiation therapy) radiation pneumonitis, ≥ Grade 2 by the NCI-CTCAE scale;
- To evaluate the adverse events (AEs) associated with GC4419 by the NCI-CTCAE scale;
- To assess weight loss (percent weight change from baseline through the completion of chemoradiotherapy, and 4 weeks after treatment).

5.3. Exploratory Objectives

- To explore the trend of severity of radiation esophagitis-related pain, dysphagia, and dyspepsia during combined chemotherapy and RT using these fields of the NCI PRO-CTCAE weekly during treatment, and 4 weeks after completion of chemoradiotherapy;
- To evaluate the incidence of acute radiation esophagitis (≥ Grade 2; radiation therapy oncology group [RTOG] scale) through the end of chemoradiotherapy
- To evaluate and compare the incidence of acute esophagitis ≥ Grade 2, 4 weeks after completion of chemoradiotherapy, using the RTOG scale
- To assess patient-reported dysphagia via a daily patient log and collect use of parenteral or tube feeding due to esophagitis;
- To assess opioid use by collecting the patient's narcotic use in the previous 24-hour period at each weekly evaluation.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

GTI-4419-203 will be an open-label, multi-center study to evaluate GC4419 administered IV for the reduction of radiation induced esophagitis in subjects receiving chemoradiotherapy for unresectable Stage 3 or post-operative Stage 2B NSCLC or SCLC.

6.2. Treatment Plan and Duration of Therapy

Aiming to include patients with expected significant risk of developing esophagitis, selected are those who will receive at least 60 Gy to the esophagus and are scheduled to receive RT combined with chemotherapy, delivered in once-daily fractions, 5 days/week, to a total dose of at least 60 Gy in fractions of 1.8-2.0 Gy, following the RTOG 1012 (Fogh 2017) trial design.

Dose exposure to the esophagus, while using modern rotational techniques translates to a prescription based on the dose-volume exposure and histogram (DVH) relating an over 15% grade >2 esophagitis risk with V60>20% and/or V38> 30% (Verma 2017).

In eligible subjects, at least an estimated 5 cm of the esophagus is exposed for at least 60 Gy (V60). Final RT planning should show that, at least one surface of the esophagus is included in the 60 Gy isodose volume. The volume exposure of the entire esophagus of 60 Gy (V60) should be at least in the 20% range and/or volume exposure of 38 Gy (V38) at least in the range of 30%. Subjects will receive concurrent chemotherapy other than gemcitabine, per investigator choice.

Each subject will receive GC4419, 90 mg, by 60-minute IV infusion, prior to each fraction of RT. GC4419 should be administered so that RT is administered within 60 minutes of 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 RT, to a cumulative radiation dose of at least 60 Gy.

If RT 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 RT will be determined by the subject's treating physician in accordance with standard of care, but in general should not exceed 5 days without compensation by additional fractions. Subjects should resume GC4419 administration when RT resumes. On days when planned doses of both GC4419 and RT are not administered (eg, due to a holiday site closure, etc.), GC4419 dosing may be extended along with RT to make up the missed dose(s). If a fraction of RT is not administered for any reason after GC4419 has been administered, that day's GC4419 will count as one of the total doses.

Antiemetic prophylaxis and hematopoietic growth factor use should be administered per ASCO guidelines. On days in which chemotherapy and GC4419 are administered, the administration sequence should be GC4419, RT, prehydration, and chemotherapy, when possible. Subjects treated with induction chemotherapy prior to concomitant chemoradiotherapy are not eligible for this study.

PK sampling to assess GC4419 will be sought from all subjects.

6.2.1. Rationale for GC4419 Dose and Schedule Selection

Data from the randomized Phase 2b study (GT-201) of GC4419 to reduce OM indicate that the acute toxicity of GC4419 at the 90 mg dose, and the overall AE profile, in combination with chemoradiotherapy will be acceptable. In addition, the efficacy results with the 90 mg dose of GC4419 in GT-201 support its use by a similar schedule and the same route and duration of IV administration in GTI-4419-203.

6.3. Radiation Therapy

6.3.1. Radiation Therapy Dose Specifications

1. Subjects will be scheduled to receive treatment 5 days per week, in once daily fractions, 1.8-2.0 Gy per fraction in combination with chemotherapy. Total biological equivalent dose of 120 Gy is prescribed to (PET+) gross tumor areas combined with BED>100 Gy elective target coverage where indicated.
2. All fields and the entire PTV must be treated daily. In case of machine problems or national holidays, a maximum 5-day gap and/or treatment over the weekend is permitted, additional compensating fractions are allowed per investigator discretion.
3. The assigned drug needs to be given daily **prior** to the radiation treatment for all fractions.
4. For simulation/planning GTV-PTV margins, we strongly advise 4D guidance and any form of motion management. In case 4D is not available, at least 7 mm margins are advised. Motion monitoring can reduce margins, however a minimum of 3mm CTV-PTV is recommended. Normalization of the treatment plan will cover 95% of the PTV with the prescription dose.
5. All radiation doses will be calculated with inhomogeneity corrections that consider the density differences within the irradiated volume (i.e., air in the lung and bone). Beam Energy: photons 6-18 MV are to be used. No electrons or protons are permitted. For Beam Shaping: Multi-leaf collimation (MLC) or individually-shaped custom blocks should be used to protect normal tissues outside of the target volume.
6. Re-planning and adaptive workflows are permitted, although eligibility and analyses are based on the starting treatment plan. Changes or stops in both chemotherapy and radiotherapy need to be documented.
7. The mean total dose (MTD) will be quoted as the PTV minimum target dose. This dose will be for a point that is at least 0.03 cc (approximately 3x3x3 mm) in size. The maximum and minimum point doses (within the PTV) will be reported for points that have a volume of 0.03 cc. The maximum dose must not exceed a value that is 120% of the prescribed dose. A 95% PTV coverage is aimed for.

6.3.2. Localization, Simulation, and Immobilization

A volumetric treatment planning CT study will be required to define gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV), see definitions below. Each

patient will be positioned in an immobilization device in the treatment position on a flat table, arms up if possible. Contiguous CT slices, having 3 mm thickness through the regions harboring gross tumor and grossly enlarged lymph nodes and 8-10 mm thickness of the remaining regions are to be obtained starting from the level of the vocal cords and extending inferiorly through the entire liver volume. The GTV, CTV, and PTV and normal organs will be outlined on all appropriate CT slices. For correct planning all CTs need to cover both entire lungs, delineation of the entire esophagus, both lungs, heart and a reconstructed Lung volume with PTV subtracted to estimate Dmean (lungs-PTV). With 4DCT based simulation, the iGTV can be constructed expressing all CT slices where GTV is present during the respiratory cycle. Extrapolation to ITV is recommended before translating to PTV.

A treatment planning FDG PET/CT with 4D acquisition scan (or FDG-PET alone) with the patient in the treatment position is optional but strongly encouraged for treatment planning. In the case where the PET/CT is obtained in the treatment position, the CT from this study may be used as the planning CT scan.

Intravenous (i.v.) contrast during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the major blood vessels. If not, i.v. contrast should be given during the planning CT. If contrast is used, the densities can be overridden, or the contrast scan must be registered to a non-contrast scan for planning purposes. Optimal immobilization is critical for this protocol. Immobilization to assure reproducibility of the set-up is necessary.

6.3.3. Target Volumes

The definitions of target volumes will be in accordance with the 1993 ICRU Report #62.37.

Definition of the GTV: The primary tumor and clinically positive lymph nodes seen either on the planning CT (> 1 cm short axis diameter) or pretreatment PET scan (SUV > 3) will constitute the GTV. This volume(s) may be disjointed. In the event of a collapsed lobe or lung segment, the use of PET to distinguish tumor from fluid/atelectasis is encouraged.

Definition of the CTV: The CTV is defined to be the GTV plus a 0.5 cm to 1 cm margin as appropriate to account for microscopic tumor extension.

Internal target volume (ITV) consists of an internal margin added to the CTV to compensate for internal physiologic movement and variations in size, shape, and position of the CTV and includes here the envelope that encompasses the tumor motion for a complete respiratory cycle. Elective treatment of nodal areas is left up to the treating physician.

Definition of the PTV: Free-breathing non-ITV approach (i.e. standard CT simulation without 4DCT or fusion of inhalation and exhalation scans).

There are two components to the PTV expansion: the internal motion (IM margin) which should be at least 1 cm in the inferior-superior direction, 0.5 cm in the axial plane and an additional set-up margin (SU margin) of 0.5 cm. Thus, the total PTV includes the CTV plus a total margin of at least 1.5 cm to the superior-inferior dimensions and at least 1.0 cm in the axial plane.

For institutions not using 4DCT, the use of fluoroscopy to determine the margin for motion in the inferior superior direction is encouraged. For institutions with gating technology, the use of respiratory gating is encouraged. For breath-hold or gating approaches, the PTV margin should be at least 1 cm in the inferior-superior direction and 0.5 cm in the axial plane. It is expected that daily imaging will be used for both breath-hold and gating techniques.

Definition of the PTV: Free-breathing ITV approach:

If the ITV approach is used, then the PTV margin should account for setup uncertainties and may be individualized but should not be less than 1.0 cm. If daily imaging is used in combination with motion management tools, then the margins for setup margins (iGTV to PTV) may be reduced to 0.5 cm.

In summary, there are 2 components to the PTV expansion: the internal motion (IM margin) which should be at least 1 cm in the inferior-superior direction, 0.5 cm in the axial plane and an additional set-up margin (SU margin) of 0.5 cm. Thus, the total PTV includes the CTV plus a total margin of at least 1.5 cm to the superior-inferior dimensions and at least 1.0 cm in the axial plane. In cases in which the PTV expansion extends outside of the skin, towards the spinal cord, or into the spinal canal, it can be assumed that tumor motion will not occur in this direction, and the PTV margin in this direction can be limited. PTV margin can be limited to 0.5 cm towards this dimension (skin or spinal canal).

Normal anatomy to be identified: The normal anatomy to be outlined on each CT image will include the lungs (right and left done separately), heart, skin, esophagus and spinal cord. The heart should be contoured from its base to apex, beginning at the CT slice where the ascending aorta originates. The esophagus should be contoured from the bottom of the cricoid to the gastroesophageal junction. The skin and spinal cord should be contoured on each CT slice.

6.3.4. Treatment Planning

3D Conformal Therapy: The PTV is to be treated with any combination of coplanar or noncoplanar 3-dimensional conformal fields shaped to deliver the specified dose while restricting the dose to the normal tissues. Field arrangements will be determined by 3D planning to produce the optimal conformal plan in accordance with volume definitions. The treatment plan used for each patient will be based on an analysis of the volumetric dose including DVH analyses of the PTV and critical normal structures. Each field is to be treated daily. In case of machine failure, the rest of fields can be treated the following day, any compensation in extra fractions is judged by the treating physician.

Intensity Modulated Radiation Therapy (IMRT): IMRT, as well as rotational arc planning (RapidArc/VMAT) are allowed. The NCI Guidelines for the Use of IMRT can be found on the RTOG home page, http://www.rtog.org/. Acceptable approaches include the use of abdominal compression devices, breath hold techniques or other motion management technologies.

6.3.5. Critical Structures

Normal tissue constraints shall be prioritized in the following order for treatment planning: 1=spinal cord, 2=lungs, 3=esophagus, and 4=heart.

1. Spinal Cord: The spinal cord dose limitation is the highest priority dose constraint and thus must be met irrespective of other constraints. Total "direct" plus "scatter" dose to the spinal cord must not exceed 50.5 in 2 Gy fractions (BED 100).

2. Lungs: The dose-volume constraint to the lungs is the second highest priority and must be met, except if it conflicts with the cord dose constraints. The volume of both lungs that receive more than 20 in 2 Gy fractions (the V20) should not exceed 37% of the total. Alternatively, the mean lung dose should optimally be 20 Gy. (By total lung volume we mean the total lung minus the PTV.) If either of these constraints is exceeded, several solutions can be entertained. First, one might increase the weighting of AP / PA treatments by one and reduce the obliques. This can be done if the cord dose (above), which takes precedence, is not exceeded. Second, one can reduce the CTV to the minimum range suggested above. Third, one can try to reduce the PTV by using respiratory gating techniques. If after all attempts to decrease the V20 to below 37%, the V20 value still exceeds this limit, the patient should be treated to the dose on the arm to which they were randomized.

3. Esophagus: Esophagus must be contoured from the cricoid/vocal cords to GE junction/pylorus. The mean dose (Dmean) to the esophagus is optimally kept below 30 Gy (Martel 1999). This is not an absolute requirement, but is strongly recommended unless other, more critical constraints force the situation. The V60 and V38 (% volume of esophagus exceeding 38 and 60 Gy, respectively) should be calculated for each patient.

** For this trial, V60 must be > 20% and/or V38 >30% to be enrolled, and remain on this trial OR at least 5 cm of one surface of the esophagus must be in the 60 Gy isodose volume (to ensure that there is a similar, significant risk for esophagitis among the subjects).

OR

*** A patient in whom the final planning shows that the esophagus is close but less than 5 cm is covered in the 60 Gy isodose volume may be allowed on the trial while V60>20% or V38>30% at the discretion of the principal investigator after discussion with the Medical Monitor.

4. Heart: The following limits are recommended: 60 Gy to <1/3, 45 Gy to <2/3, and 40 Gy to <100% of the heart.

6.3.6. Documentation Requirements

1. Portal image of each field of 3-D radiation therapy or orthogonal images that localize the isocenter placement of IMRT must be obtained on the first day of therapy but should not be submitted.

2. Weekly verification or orthogonal images are required to be taken, but not submitted. This verification information also can be gathered with cone-beam CT or other CT devices that are present in the treatment room.

3. Isodose plans and DVH in at least one axial, sagittal and frontal slice for each isocenter and DVHs of GTV, CTVs, and critical normal structures. All replanning needs to be documented in the same way.

4. Full QA report of planning (see section 10.2) needs a package of PDF or JPG documents including justification of contouring the whole esophagus (vocal cords to pylorus) pictured in 1cm CT slices, indicating the 60 Gy and 38 Gy isodose in clear colors, while subtracting other isodose-lines. Including a color coded to indicate DVH including PTV and GTV coverage, Lung: Dmax, Dmean, V20; Esophagus: V20, V38, V60 and Dmean, as well as spine and heart: Dmax and Dmean is essential. At least one transverse, coronal and longitudinal image with the 38 Gy and 60 Gy isodose lines in relation with the esophagus contour need to be provided in PDF or JPG files.

6.3.7. Compliance Criteria

1. Variation Acceptable: Deviations of this magnitude are not desirable but are acceptable for treatment situations in which the target to critical structure geometry is challenging. The prescribed dose can cover as little as 90% of the PTV and still be a Variation Acceptable. The minimum dose within the PTV can fall to 93% of the prescribed dose. The max dose can exceed 120% of the prescribed dose, but it cannot go above 125% of that dose. The 5 cm esophageal exposure up to 60 Gy is a pre-planning estimate for risk, final planning acceptation is judged upon V60, V38.

2. Deviation Unacceptable: Dose distributions falling in this region are not acceptable, and plan modifications should be attempted to improve results. A Deviation Unacceptable occurs if any of the Variation Acceptable dose limits stated above are exceeded. Additionally, a Deviation Unacceptable is assigned if more than 1 cm of tissue outside the PTV receives ≥ 120% of the prescribed dose.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

Approximately 60 total subjects from investigational sites in US will be enrolled to achieve approximately 55 subjects who receive a full course of GC4419 with standard chemoradiotherapy, assuming a dropout rate of 10%. Subjects appropriate for this trial will be identified by the institutional Principal Investigator (or designee) who will make a preliminary determination of the patient's eligibility for the trial in accordance with the provisions of the study protocol. Once a patient is enrolled to the study, the Sponsor or designee will assign a unique patient identification number that does not contain any Personal Health Information that will be used to reference the patient and corresponding data that is collected.

7.1. Subject Inclusion Criteria

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

1. Subjects scheduled to be treated with (definitive or adjuvant) radiation therapy in combination with chemotherapy once daily for pathologically-confirmed Stage 3 or post-operative Stage 2B NSCLC or limited stage SCLC
2. Treatment plan for subjects show that 5 cm of the esophagus for at least one surface, is included in the 60 Gy isodose volume. Dose volume histograms show esophagus dose exposure meet V38>30% and/or V60>20% (to ensure that there is a similar, significant risk for esophagitis among the subjects).

   Note: In case the final planning shows that the contoured esophagus is close to but the 60 Gy isodose does not cover completely 5 cm, this subject may be allowed on the trial at the discretion of the principal investigator after discussion with and review by the Medical Monitor.

3. Age ≥ 18 years or older
4. ECOG performance status ≤ 2
5. Adequate hematologic function as indicated by:
   a Absolute neutrophil counts (ANC) ≥ 1,500/mm^3
   b Hemoglobin (Hgb) ≥ 9.0 g/dL
   c Platelet count ≥ 100,000/mm^3
6. Adequate renal and liver function as indicated by:
   a Estimated baseline creatinine clearance >60 cc/min (CrCl = (140 – Age) x Mass (kg) x [0.85 if female] / 72 x [Serum Creatinine (mg/dL)])
   b Total bilirubin ≤ 1.5 x upper normal limit (ULN)
   c Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN
   d Alkaline phosphatase ≤ 2.5 x ULN
7. Males and females must agree to use a highly effective contraception starting at least one day prior to the first day of treatment and continuing for 30 days after the last dose of GC4419 (females) or 90 days (males)
8. Properly obtained written informed consent

7.2. Subject Exclusion Criteria

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

1. Metastatic disease
2. Prior radiation therapy 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. Subjects not receiving chemotherapy
4. Grade 2 or greater esophagitis at baseline
5. Inability to provide information in the electronic symptom-reporting device
6. Subjects receiving approved or investigational immunotherapy, targeted therapy, hormone therapy, or biologic therapy
7. Participation in another clinical trial or use of another investigational agent within 30 days of first dose of GC4419.
8. Malignant tumors other than the current lung cancer within the last 5 years, unless treated definitively and with low risk of recurrence in the judgment of the treating investigator
9. Previous diagnosis of symptomatic pneumonitis (≥ Grade 2 CTCAE v 5.0 including immunotherapy induced pneumonitis)
10. Untreated, active infectious disease requiring systemic anti-infective therapy
11. Untreated HIV or history of hepatitis B/C (subjects who have been vaccinated for hepatitis B and do not have a history of infection are eligible)
12. Pregnant female subjects (including positive test for pregnancy); breastfeeding/lactating female subjects; female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol
13. Known allergies or intolerance to chemotherapy and similar platinum-containing compounds
14. Requirement for concurrent treatment with nitrates
15. Requirement for treatment with drugs other than nitrates that may, in the judgment of the treating investigator, create a risk for a precipitous decrease in blood pressure.
16. Clinically significant heart disease (eg, congestive heart failure of New York Heart Association Class 3 or 4, angina not well controlled by medication, or myocardial infarction within 6 months)

7.3. Rationale for Patient Population

As noted in the background sections, the lung cancer patient population to be included in this study is expected to have a significant rate of radiation esophagitis to afford an opportunity to observe a clinically meaningful reduction in esophagitis when GC4419 is added to the regimen.

7.4. Screen Failures

A subject is considered a screen failure if the subject signs the informed consent form (ICF) but withdraws consent or is deemed ineligible prior to Day 1 investigational product administration. The reason why the subject was precluded from the clinical study will be collected. All subjects who sign the ICF for this study, including screening failures, will be entered in the case report form (CRF).

7.5. 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:

- 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 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 study drug because 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 RT/chemotherapy and should be encouraged to continue with other study procedures, notably with esophagitis assessments as scheduled.

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

7.6. 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 Institutional Review Board (IRB)/Independent Ethics Committee (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. INVESTIGATIONAL PRODUCT AND TREATMENT OF SUBJECTS

8.1. Concomitant Medications

All concomitant therapies (eg, prescription and over-the-counter medications) taken by subjects from Baseline of Day 1 GC4419 until 30 days following the last GC4419 dose, RT or chemotherapy dose (ie, whichever occurs last) will be collected in the CRF. Additionally, any concomitant therapies if used to treat any serious or related AE will be recorded in the CRF.

Analgesic/narcotic medications will be captured and recorded along with other concomitant medications in the CRF. Narcotic use will be recorded from the baseline visit until 30 days following the last GC4419 dose, RT or chemotherapy dose (ie, whichever occurs last).

Antiemetic prophylaxis and hematopoietic growth factors use should be administered per ASCO guidelines.

Subjects who withdraw consent for further administration of GC4419 should be encouraged to continue and complete standard RT/chemotherapy treatment and other study procedures.

However, if a subject withdraws consent for the study or is removed from the study completely (ie, 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.

8.1.1. Drug Interactions

GC4419 is a strong inhibitor of CYP2D6.

Concomitant use of GC4419 increases the concentration of drugs that are CYP2D6 substrates, which may increase the risk of toxicities of these drugs. Avoid concomitant use of GC4419 with CYP2D6 substrates where minimal increases in concentration of the CYP2D6 substrate may lead to serious or life-threatening toxicities (substrates with a narrow therapeutic range). Such CYP2D6 substrates (Appendix 7) include certain beta blockers (eg, propranolol and metoprolol), antidepressants (eg, tricyclics), antipsychotics (eg, phenothiazines and most atypicals), and antiarrhythmics (eg, propafenone, flecainide).

In addition, concomitant use of GC4419 may decrease the concentration of active metabolites of prodrugs that require CYP2D6 for activation. Concomitant use of GC4419 with CYP2D6 prodrug substrates requiring functional CYP2D6 activity for their clinical benefit (eg, codeine, tramadol, tamoxifen) may decrease their effectiveness.

Concomitant administration of a CYP2D6-substrate drug concurrent with administration of GC4419 should be limited to cases in which the treating investigator has determined that the use of the specific CYP2D6-substrate drug is medically necessary. In such cases, the subject should be carefully observed for clinical adverse events of the CYP2D6-substrate drug, the dose of which may require reduction.

See the Investigator's Brochure for additional information.

8.2. Prohibited Medications

Investigators may prescribe any concomitant medication or supportive therapy deemed necessary to provide adequate supportive care. Supportive care includes anti-emetic prophylaxis, hematopoietic growth factor use is per ASCO guidelines, systemic antibiotics, hydration to prevent renal damage etc., consistent with local standard of practice, with the following exceptions:

Prohibited medications/treatments:

- Gemcitabine
- Nitrates, phosphodiesterase type 5 (PDE 5) inhibitors (eg, 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
- Other biologic response modifiers – except systemic hematopoietic growth factors for the management of anemia or myelosuppression
- Concurrent approved or investigational immunotherapy, targeted therapy, hormone or biologic therapy.
- Concurrent investigational agents intended to reduce mucosal toxicity of radiation therapy
- Other investigational agents

All medication restrictions end after the 4-week post-RT follow-up visit 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.

Antiemetic prophylaxis and hematopoietic growth factor use are permitted per ASCO guidelines. Following ASCO (and multinational association of supportive care in cancer [MASCC]) guidelines for the prevention and management of chemotherapy-induced nausea and vomiting (CINV) is strongly encouraged.

8.3. Description of Study Drug (GC4419)

GC4419 is formulated as a sterile solution at a concentration of 9 mg/mL in 26 mM sodium bicarbonate-buffer and 0.9 wt. percentage sodium chloride in a stoppered glass vial.

8.3.1. GC4419 Drug Packaging and Labeling

Open-label GC4419 will be provided as single-use vials for daily doses to be administered IV concurrent with RT.

GC4419 is packaged as a 9 mg/mL solution in a 10 mL glass vial. Each vial will be labeled with the appropriate language, including information required by local heath authority regulations.

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

8.3.2. Study Drug Storage

GC4419 9 mg/mL drug product in 26 mM sodium bicarbonate buffered 0.9 wt % sodium chloride solution for parenteral administration should be stored refrigerated at 2°C-8°C in a secured and controlled area with restricted access. Temperature excursions above freezing and 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 also be stored at 2°C to 8°C until use and must be administered to subjects within 24 hours of preparation. GC4419 dosing solutions must not be frozen at any time. If freezing of the material is evident, that supply must be quarantined per institutional guidelines and Galera Therapeutics, Inc. or its designee must be notified immediately.

8.3.3. Study Drug 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.

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 (ie, the infusion solution volume will be 250 mL normal 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. Infusions must be prepared using a sterile 0.2- or 0.22-micron syringe filter prior to introduction into the infusion bag **or** a sterile 0.2 or 0.22 micron inline filter must be used during IV administration. NOTE: Filtration is mandatory, either during preparation with syringe filters or at IV administration with inline filters. Unfiltered GC4419 solution or infusion solution must not be administered to patients.

Further information and preparation details will be provided in a separate Pharmacy Manual.

8.3.4. 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 (ie, 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.

Radiation therapy should be administered as soon as possible after the end of the GC4419 infusion. While detailed data to dictate a maximum permissible interval between the end of GC4419 infusion and administration of RT, the latter should be administered within 60 minutes of 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 RT, up to the last prescribed fraction and the prescribed total cumulative radiation dose of at least 60 Gy.

If RT is not administered on any given day due to a treatment break or unforeseen circumstances, GC4419 should not be administered on that day. Duration of treatment breaks need to be determined by the subject's treating physician in accordance with standard of care. When GC4419 is administered, but RT could not be given that day, that dose is counted. All following RT retake days will need to be accompanied by GC4419 dosing before each fraction; resulting in a total number of drug dosing one greater than the RT fractions given in total. GC4419 dosing must be extended along with RT until the end (to a maximum of 35).

8.3.5. Accountability and Compliance

Compliance with GC4419 dosing, including administration details (eg, 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, subject initials, 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. All GC4419 and used containers are to be retained by the site until notified by the study monitor, who will instruct the site in the disposal and/or destruction of all used GC4419 supplies. 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.

8.3.6. Study Drug Handling and Disposal

After completion of the study, all unused study drug will be inventoried and if possible, destroyed locally at the site. GC4419 should not be returned directly to Galera Therapeutics, Inc. unless specifically requested by Galera Therapeutics, Inc.. The study monitor will instruct the

site in the disposal and/or destruction of all used and unused GC4419 supplies. Destruction of any GC4419 should be documented appropriately.

9. TOXICITY MANAGEMENT

9.1. Anticipated toxicities of GC4419

Based on the drug's mechanism of action, adverse effects anticipated with GC4419 are attributable to transient potentiation of nitric oxide. Clinical results with GC4419 to date are consistent with this. These effects have been IV infusion related and transient, typically with onset during or at the end of infusion, resolving within 1-2 hours of cessation of GC4419 administration. At the dose and schedule planned in this trial, these effects may include mild hypotension, postural lightheadedness/presyncope, and perioral/facial tingling or paresthesia. Mild nausea and vomiting have also been observed in human subjects receiving GC4419.

Safety results from the randomized Phase 2b trial of GC4419 in combination with IMRT and concurrent cisplatin to reduce severe oral mucositis experienced by patients with head and neck cancer do not suggest that GC4419 increases the frequency or severity of the known adverse effects of IMRT/platinum. This finding includes an absence of increase in severe nausea or vomiting when GC4419 was added to the standard chemoradiotherapy. Accordingly, routine antiemetic prophylaxis is not considered required for GC4419, and antiemetic prophylaxis should follow guidelines for concurrently administered chemotherapy.

Per the investigator's brochure, individual adverse events commonly occurring with chemoradiotherapy administered concurrently with GC4419 are considered "expected" for purposes of ongoing safety analysis. See the investigator's brochure for additional details.

Interference with the anti-tumor efficacy of chemoradiotherapy by GC4419 is a potential risk, although nonclinical studies and clinical observations to date suggest that such interference is unlikely, and nonclinical studies have demonstrated mechanism-related anti-tumor synergy of GC4419 with radiotherapy. However, patients must be informed of the potential risk before receiving GC4419.

9.2. Dose Delays and Dose Modifications for Toxicity

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

- Grade 2 or greater hypotension occurring within one hour of the end of GC4419 infusion
- Grade 3 or greater nausea or vomiting
- The dose of GC4419 may be reduced by 25% for Grade 3-4 AEs judged by the Investigator to be likely attributable to the study infusion.

Subject to the judgment of the treating investigator, GC4419 dosing should be interrupted or reduced according to the provisions of this section as necessary for toxicities potentially attributable to either GC4419 or chemoradiotherapy.

Two dose reductions for toxicity will be permitted per patient. After the first event, the patient will be re-challenged at 75% of the original dose (7.5 mL GC4419 in 250 mL normal saline).

After the second event, the patient will be re-challenged at 50% of the original dose (5.0 mL GC4419 in 250 mL normal saline). Subjects who are unable to tolerate GC4419 infusions following two dose reductions must be discontinued from the study treatment but may continue with chemotherapy/RT at the discretion of the treating investigator.

Dose re-escalation of GC4419 may be considered ONLY after consultation with the Sponsor's Medical Monitor.

Toxicities (including those attributable to chemotherapy and RT) should also be, managed per institutional and ASCO guidelines and investigator judgment.

9.3. 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 subjected to the exclusions listed in Section 8.2.

9.3.1. Supportive Care for Chemotherapy-induced Nausea and Vomiting

Medication to prevent or manage CINV should follow recent guidelines from ASCO and MASCC.

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 patient enrolled in the study are described in the text that follows and presented in Appendix 1.

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

10.1. Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all CTCAE grades (for both increasing and decreasing severity). Safety will be assessed based on 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 (Appendix 1) for this study:

- 12-Lead ECG: ventricular rate, P-R interval, QRS interval, QT interval, and QTc
- Vital signs: measured following two minutes of rest in the sitting position – temperature, systolic and diastolic blood pressures, heart rate, and respiration rate
- Weight and Height: measured in kilograms (kg) and centimeters (cm), respectively
- Performance Status: ECOG (see Appendix 3 for conversion criteria for Karnofsky to ECOG).

10.1.2. Laboratory Assessments

Clinical laboratory tests during the study will be performed by a central lab. All protocol-required blood samples will be collected and sent to the central laboratory as specified in the laboratory manual.

Local laboratories may be used for treatment decisions, safety evaluation, and for management of chemotherapy-related toxicity, as appropriate; however, local laboratory results will not be collected. All local hematology and blood chemistry samples are to be obtained prior to study drug administration and results reviewed prior to administration/dispensing of study drug at the beginning of each treatment cycle.

A laboratory abnormality reported by either the central laboratory or local laboratory may meet the criteria to qualify as an AE or SAE as described in this protocol. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event electronic CRF.

For laboratory abnormalities meeting the criteria of SAEs, the site must fax or email the SAE report including the laboratory report (as regionally required) to the sponsor using the SAE form.

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 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.

The following laboratory assessments are defined when referenced in the schedule of events (Appendix 1) for this study:

- Hematology Profile: Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count. Differential to include total neutrophils, lymphocytes, monocytes, eosinophils, and basophils.
- Serum Chemistry Profile: glucose, BUN, creatinine, sodium, potassium, calcium, albumin, total protein, direct bilirubin, total bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), chloride, phosphate, bicarbonate.
- Serum Pregnancy Test: required for all females of childbearing potential. Lack of childbearing potential must be noted in the source documents, if applicable.

10.1.3. Pneumonitis Assessment

The following will be completed for the pneumonitis assessment:

- NCI-CTCAE scale (version 5.0)
- CT of chest with IV contrast, unless contrast is medically contraindicated.
- FDG positron emission tomography/CT, and mediastinal staging if appropriate (investigator's discretion); and
- Spirometry including forced expiratory volume measurement and diffusing capacity of the lungs for carbon monoxide (DLCO).

10.1.4. Tumor Assessment

Tumor recurrence is common after SCLC and NSCLC treatment. Therefore, surveillance with history and physical (H &P) and chest CT (with or without contrast) is recommended in the NCCN guidelines Version 7.2019. Data from 3 randomized phase 3 trials are not available to clarify surveillance recommendations; therefore, the most appropriate schedules are controversial. An analysis suggests that patients who survive lung cancer have a high symptom burden and are most likely to endure an event 1 year after diagnosis and treatment. In this study, patients will undergo H&P and chest CT with or without contrast, consistent with institutional guidelines, at screening and every 3 months for one year after treatment, to assess progression-free and overall survival. This is considered consistent with standard of care.

10.2. Radiation Therapy Quality Assurance

Quality assurance for RT (RTQA) will be conducted by a prospective review of the overall treatment plan, at the time of subject screening, by a radiation oncologist who is not an Investigator on the study. For validation, RT treatment details, dosimetry, and dose volume histograms will be collected after simulation. Table position, slice thickness should be displayed on treatment plan images. For each subject, each sites' dosimetrist will calculate and document numeric information on the RTQA worksheet which will be sent for review. Recommendations, including key points for Radiation Oncologist when completing RT planning can be found in Section 6.3.

It is important that CT simulation imaging is done from vocal cords (superiorly) to mid liver (inferiorly) for scan completeness covering whole esophagus and both entire lungs. 4D and/or PET fusion and acquisition is recommended for ITV, iGTV definition. For contouring, the lower border of the cricoid defines as superior extent of cervical esophagus and the GE junction/pylorus as the lower extent of esophagus.

The following data is required:

- For the esophagus: V60, V20, V38, Dmean, Dmax
- For the lung: Mean lung dose, V20 and V30

Available information should be collected regarding PTV coverage, prescribed doses for elective and gross tumor volumes, fractionation and type of chemotherapy.

This review is to confirm that the RT plan meets the eligibility requirements for the study.

10.3. Pharmacokinetic (PK) Measurements

10.3.1. Pharmacokinetic (PK) Measurements of GC4419

PK sampling will be sought from all subjects for GC4419.

Plasma samples for GC4419 PK measurements will be collected in two cycles: Study Days 1 and 2, and on Study Day 22. 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 RT.

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 Infusion (+10min)	X		X
Post-RT (+10min)	X		X
60-180 min Post End of GC4419 Infusion	X		X

10.4. Patient Reported Outcomes (PRO) and Diaries

10.4.1. Patient Reported Outcomes (PROs)

Subjects will be required to personally complete the following PROs once prior to treatment (may be done at the baseline visit prior to dosing), weekly during treatment and at the 4-week post-RT follow-up visit.

- NCI PRO-CTCAE pain, dysphagia, and dyspepsia; and
- Numeric Pain Rating Scale (NPRS).

10.4.2. PRO-swallowing Diary

Subjects will be required to personally complete a daily swallowing diary. The diary will be completed once prior to treatment (may be done at the baseline visit prior to dosing), daily during treatment and daily until the 4-week post-RT follow-up visit.

10.4.3. Pain Medication

Information regarding analgesic / narcotic use will be obtained weekly during the radiation treatment period through 4 weeks post completion of chemoradiotherapy (Baseline Visit through 4-week post-RT). In addition, general concomitant medications will be recorded by study personnel on weekdays during RT treatment.

10.5. Schedule of Time and Events

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

10.6. Screening Phase

The following screening observations and procedures will be completed within 28 days prior to the start of RT and GC4419 unless otherwise noted below:

- Obtain a signed IRB/IEC/REB-approved informed consent
- Confirm patient eligibility by reviewing inclusion/exclusion criteria
- Obtain medical history, smoking and alcohol use
- Obtain NSCLC or SCLC cancer history; history should include:
  - Prior treatments
  - Confirmation of histopathological diagnosis
- Conduct a complete physical examination, including height (record body surface area). Height will only be collected at screening.
- Conduct Esophagitis assessment and record the CTCAE and the RTOG score (Appendix 2)
- Conduct Pneumonitis Assessment: NCI-CTCAE scale, CT scan, spirometry, and DLCO – Spirometry and DLCO tests can be used if completed within 56 days prior to start of treatment as standard of care.
- Conduct Tumor Assessment: Chest CT (with or without contrast)
- Patient to complete the NCI PRO-CTCAE and NPRS within 1 week prior to treatment. This may be completed at the baseline visit prior to dosing.
- Patient to complete swallowing diary once within 1 week prior to treatment. This may be completed at the baseline visit prior to dosing.
- Record planned RT and chemotherapy parameters
- Measure vital signs, body weight and ECOG Performance Status
- Conduct a 12-lead ECG – performed at screening or within 56 days prior to start of treatment as standard of care.
- Record/update medical conditions and illnesses that have occurred since the patient signed the ICF
- Draw blood for laboratory measurements:
  - Chemistry profile
  - Hematology profile
  - Serum pregnancy test for women of childbearing potential

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

10.7. Active Phase

10.7.1. Baseline/Day 1 (First Day of RT and GC4419)

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

- Confirm continued patient eligibility by reviewing inclusion/exclusion criteria
- Measure vital signs, body weight, and ECOG Performance Status
- Provide and review instructions for completion of the daily swallowing diary if not done prior to this visit
- Provide the daily swallowing diary if not done prior to this visit
- Have the patient complete the PROs and NPRS and review completion if not done prior to this visit
- Conduct Esophagitis assessment and record the severity using the CTCAE and RTOG score
- Ensure concomitant medications, including analgesic / narcotic use, have been recorded from date of baseline
- Record/document AEs starting from date of baseline
- Record/update medical history with conditions and illnesses that have occurred since the patient signed the ICF
- Draw blood for laboratory measurements:
  - Chemistry profile
  - Hematology profile
  - PK sampling (See Section 10.3)

Administer the first GC4419 dose by continuous IV infusion over 60 minutes. GC4419 should be administered so that RT is administered within 60 minutes of the end of the GC4419 infusion. The following administration sequence should be used when possible: GC4419, RT, prehydration then chemotherapy.

10.7.2. Week 1 of RT and GC4419

Prior to GC4419 administration, the following observations and procedures will be conducted for all subjects on all RT Days:

- Record concomitant medications
- Record AEs
- Conduct esophagitis assessment daily and record the severity using both the CTCAE and RTOG grading scales.
- Ensure the daily swallowing diary is completed

- Administer GC4419 dose by continuous IV infusion. GC4419 should be administered so that RT is administered within 60 minutes of the end of the GC4419 infusion.

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

- Draw blood for laboratory measurements:
  - Chemistry profile
  - Hematology profile
  - PK sampling (See Section 10.3) – Day 2 only

10.7.3. Weeks 2, 3, 5, and 6 (and additional RT weeks if needed)

Prior to RT administration, the following observations and procedures will be conducted for all subjects on all RT days:

- Record concomitant medications and need for parenteral or tube feeding
- Record AEs
- Conduct esophagitis assessment daily and record the severity using both the CTCAE and RTOG grading scales.
- Ensure the daily swallowing diary is completed.

Prior to GC4419 administration, the following observations and procedures will be conducted for all subjects once each week:

- Record analgesic / narcotic use
- Have the patient complete the PROs and NPRS and review completion.
- Draw blood for laboratory measurements:
  - Chemistry profile
  - Hematology profile

Administer GC4419 doses by continuous IV infusion. GC4419 should be administered so that RT is administered within 60 minutes of the end of the GC4419 infusion.

10.7.4. Week 4

Prior to RT administration, the following observations and procedures will be conducted for all subjects on **all RT days**:

- Record concomitant medications and need for parenteral or tube feeding
- Record AEs
- Conduct esophagitis assessment daily and record the severity using both the CTCAE and RTOG grading scales.
- Ensure the daily swallowing diary is completed.

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

- Record analgesic / narcotic use
- Perform symptom-directed PE
- Have the patient complete the PROs and NPRS and review completion.
- Measure vital signs, body weight and ECOG Performance Status
- Draw blood for laboratory measurements:
  - Chemistry profile
  - Hematology profile
  - PK sampling (See Section 10.3) – Day 22 only

Administer GC4419 doses by continuous IV infusion. GC4419 should be administered so that RT is administered within 60 minutes of the end of the GC4419 infusion.

10.7.5. Last Day of RT or Early Termination Visit

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

- Conduct a complete physical examination
- Measure vital signs, body weight, and ECOG status
- Pneumonitis Assessment: NCI-CTCAE scale, CT scan, spirometry, and DLCO
- Ensure the daily swallowing diary is completed
- Conduct Esophagitis assessment for the week and record the severity using both the CTCAE and RTOG scales
- Have the patient complete the PROs and NPRS and review completion
- Record any concomitant medications including analgesic/narcotic use and need for parenteral or tube feeding
- Record AEs
- Draw blood for laboratory measurements:
  - Chemistry profile
  - Hematology profile

10.7.6. 4 Weeks Post-RT

All subjects will be evaluated at 28 ± 15 calendar days from the last day of RT. The following should be completed at this visit:

- Conduct a complete physical examination
- Measure vital signs, body weight, and ECOG status

- Record any concomitant medications including analgesic/narcotic use and need for parenteral or tube feeding
- Record AEs through 30 days after the last dose of RT
- Conduct Esophagitis assessment for the week and record the severity using both the CTCAE and RTOG scales
- Have the patient complete the PROs and NPRS review completion.
- Collect swallowing diary and ensure it was completed daily through 4 Weeks post-RT
- Draw blood for laboratory measurements:
  - Chemistry profile
  - Hematology profile

10.8 Post Active Phase

10.8.1 90 Days Post-RT

All subjects will be evaluated at 90 ± 15 calendar days from the last day of RT. The following should be completed at this visit.

- Conduct a complete physical examination
- Pneumonitis Assessment: CT scan, spirometry, and DLCO. Evaluate for acute RT pneumonitis, ≥ Grade 2 by the NCI-CTCAE scale
- Record any updates to SAEs which were ongoing at the 4 weeks post-RT visit
- Tumor Assessment: Chest CT (with or without contrast) to be performed based on standard of care CT follow up

10.8.2 6 months, 9 months and 1-year post-RT (±30 days)

Subjects will undergo a physical exam and Chest CT (with or without contrast) based on standard of care CT follow-up

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 International Conference on Harmonization and the US Code of Federal Regulations 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 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, ie, 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.
- Is a other important medical event

11.2. Adverse Event Reporting Requirements

11.2.1. Serious Adverse Events

All events meeting the criteria for SAEs (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 sponsor's timeline for notifying regulatory authorities and investigators per Federal Regulations, an event term, serious criteria, and causality is required at the time of the initial report. Specific SAE reporting instructions are provided in a separate manual.

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

11.2.2. All Adverse Events (AEs) Regardless of Seriousness

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

All AEs must be recorded in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to study drug.

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

A laboratory abnormality reported by either the central laboratory or local laboratory may meet the criteria to qualify as an AE or SAE as described in this protocol. Laboratory abnormalities should only be recorded in the AE 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, RT, and/or chemotherapy
- Treatment is initiated for the abnormality
- Investigational product was discontinued
- Grade 3 or Grade 4 per (NCI-CTCAE version 5.0)

For laboratory abnormalities meeting the criteria of SAEs, the site must complete and send the SAE report including the laboratory report (as regionally required) to the sponsor using the SAE form. Abnormal assessments (eg, 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 SAEs

Esophagitis will not be reported as AEs 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 as an AE.

11.2.5. Grading of Adverse Events

The severity of AEs 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 non-invasive 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

ADL = Activities of Daily Living.

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 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 AE or laboratory abnormality, when the temporal sequence from the time of GC4419 administration, the known consequences of the patient's clinical/state condition or study procedures, the effects of discontinuing or re-introducing GC4419 on the AE, and other medically relevant factors are considered.
- **Possibly Related:** There is a reasonable possibility that the AE or laboratory abnormality was caused by GC4419, when the temporal sequence from the time of GC4419 administration, the known consequences of the patient's clinical state/condition or study procedures, and other medically relevant factors are considered.
- **Unrelated:** The investigator has a high level of certainty that the patient's clinical state/condition, study procedures, or other medically relevant factors other than treatment with GC4419 caused the AE 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 as 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 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, RT and chemotherapy 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

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

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

Routine collection of AEs will stop at the end of the 30-Day Follow-up Period.

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 patient dies during participation in the study or during a recognized follow-up period, Galera Therapeutics, Inc. will be provided with a copy of any post-mortem findings, including histopathology.

11.6. Post-Study Reporting Requirements

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

11.7. Pregnancy

The risks of treatment with GC4419 during pregnancy have not been evaluated. Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse should use a highly effective method of contraception starting at least on day prior to the first day of treatment and throughout the study and for 30 days (females) or 90 days (males) following the last dose of GC4419.

All females will be considered as of childbearing potential unless they are postmenopausal (eg, amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing). Subjects with a vasectomy or a vasectomized partner with confirmed azoospermia are eligible.

If a subject of childbearing potential is neither surgically sterile nor postmenopausal, a highly effective contraceptive method (ie, a method that can achieve a failure rate of less than 1% per year when used consistently and correctly) must start either before and throughout the entire study period and for 30 days after the last dose of Test Article is administered. Highly effective methods of contraception include any of the following:

- total abstinence from heterosexual intercourse (if it is their preferred and usual lifestyle)
- an intrauterine device or intrauterine hormone-releasing system (IUS)
- a contraceptive implant
- an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation)

Pregnant and/or lactating females are excluded.

Pregnancies or exposure to study drug through breastfeeding must be reported as soon as possible but no later than 24 hours from the date the investigator becomes aware of the event. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The outcome of the pregnancy must be reported as soon as possible but no later than 24 hours from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

11.7.1. 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 should be reported using the appropriate form within 2 weeks of learning of the patient's pregnancy. The patient will be followed throughout the course of the pregnancy. Generally, follow-up will be no longer than six to eight weeks following the estimated delivery date. Any premature termination of the pregnancy should be reported. If a pregnancy is identified outside the 30 days after last dose, the investigator may report using clinical judgment.

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

The investigator will attempt to collect pregnancy information on any female partner of a male study patient who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to Galera Therapeutics, Inc. within 2 weeks of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Galera Therapeutics, Inc.. Generally, follow-up will be no longer than six to eight weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported. If a pregnancy is identified outside the 30 days after last dose, the investigator may report using clinical judgment.

11.8. Regulatory Reporting of Adverse Events

Galera Therapeutics, Inc. will have final determination of reportability and is responsible for notifying the relevant regulatory authorities of certain events. The investigator will report all SAEs that occur at his/her site to the IRB per the site's IRB regulations. AEs will be reported to regulatory authorities in compliance with 21 Code of Federal Regulations (CFR) 312.32, local and regional law and established guidance by the Sponsor or its designee. The format of the reports will be dictated by the local and regional requirements.

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

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.

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

12.2. Sample Size

Approximately 60 subjects will be enrolled to ensure that 55 subjects are evaluable for the primary analysis, with an assumed proportion of early discontinuations without previous ≥ Grade 2 esophagitis of approximately 10%.

The incidence of ≥ Grade 2 esophagitis will be summarized and compared descriptively with historical controls based incidence rate of 30% for chemoradiotherapy alone (Palma 2013, Kwint 2012, Fogh 2016).

For illustration, with 55 patients in the primary analysis, the 95% Clopper-Pearson confidence interval around an observed incidence of ≥ Grade 2 esophagitis (NCI-CTCAE) of 16% (9/55) would be 8% to 29%.

Assuming that the true incidence of ≥ Grade 2 esophagitis in GC4419-treated subjects is 13%, the trial will have roughly 80% power with 55 subjects in the analysis to demonstrate incidence lower than 30% with a one-sided Type I error rate of 2.5%.

12.3. Analysis Populations

The primary efficacy population will include all subjects who receive at least one dose of GC4419 and either a) complete their RT course or b) discontinue their RT course early but are known to have had acute radiation esophagitis. Sensitivity analyses will also be performed to assess the effect on estimated incidence when including GC4419-treated subjects who did not complete their RT course and did not have observed acute radiation esophagitis before discontinuing. Safety analyses will include all subjects who receive at least one dose of GC4419. Efficacy and safety may also be summarized for a "per protocol" population of subjects completing RT/chemotherapy and at least 5 weeks of GC4419.

12.4. Definition of Endpoints

12.4.1. Primary Endpoint

Incidence of acute radiation esophagitis (≥ Grade 2; NCI-CTCAE version 5 through the end of chemoradiotherapy for NSCLC or SCLC when GC4419 is added.

12.4.2. Secondary Efficacy Endpoints

- Incidence of acute severe (Grade 3-4) radiation esophagitis by the NCI-CTCAE scale (Grade 3-4) through the completion of chemoradiotherapy;

- Incidence of acute esophagitis ≥ Grade 2 through 4 weeks after completion of chemoradiotherapy, using the NCI-CTCAE scale;
- Incidence of acute severe (Grade 3-4) radiation esophagitis through 4 weeks after completion of chemoradiotherapy;
- Presence of acute (≥ Grade 2) and acute severe (Grade 3-4) radiation esophagitis at evaluation 4 weeks after completion of chemoradiotherapy;
- Incidence of acute (through 90 days after radiation therapy) radiation pneumonitis, ≥ Grade 2 by the NCI-CTCAE scale;
- Percentage weight change from baseline through the completion of chemoradiotherapy and 4 weeks after treatment.

12.4.3. Exploratory Endpoints

- Severity of radiation esophagitis-related pain, dysphagia, and dyspepsia during combined chemotherapy and RT using these fields of the NCI PRO-CTCAE weekly during treatment, and 4 weeks after completion of chemoradiotherapy;
- Incidence of acute esophagitis > Grade 2 through 4 weeks after completion of chemoradiotherapy, using the RTOG scale;
- Incidence of acute severe (Grade 3-4) radiation esophagitis through 4 weeks after completion of chemoradiotherapy, using the RTOG scale;
- Patient-reported dysphagia via a daily patient log and need for parenteral or tube feeding;
- Opioid use by collecting the patient's analgesic/narcotic use in the previous 24-hour period at each weekly evaluation.

12.5. Safety Analysis

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

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

Further details will be provided in the trial's statistical analysis plan.

12.5.1. Interim Safety Analysis/Study Stopping Rules

An interim assessment of safety will be made by a study review group consisting of the Principal Investigator, the Galera Medical monitor, the CRO medical monitor, and other attendees as deemed appropriate. For this assessment, descriptive safety data will be reviewed after 15 patients have completed study treatment. In the event that any of the following occur, enrollment to the study will be suspended pending full review of all safety data to determine next steps:

- Radiation delay of $\geq$ 7 days in > 20 % of patients
- Chemotherapy delays of $\geq$ 7 days for non-hematologic toxicity, or discontinuation of chemotherapy for hematologic toxicities in >20% of patients.
- Progression of malignancy within 3 months of enrollment in > 20% of patients
- Discontinuation of treatment due to treatment-related AEs (GC4419 or chemoradiotherapy) within 3 months of enrollment $\geq$ 33% of patients.

Safety will be assessed on an on-going basis by the CRO Medical Monitor and Galera MM, who may call for an unscheduled safety review by the study review group at any time.

12.6. Primary Efficacy Analysis

Incidence of acute radiation esophagitis (≥ Grade 2) will be presented descriptively along with 95% Clopper-Pearson exact confidence intervals. The incidence will be formally tested against 30% by a binomial test using the "exact binomial;" statement in SAS's Frequency procedure (PROC FREQ).

12.6.1. Multiplicity

Because the trial has only one primary endpoint and because the secondary endpoints are only descriptively presented, no accounting for multiple comparisons is planned.

12.6.2. Handling of Missing Data

Investigators should make reasonable attempts to continue to collect Esophagitis RTOG and CTCAE scores for inclusion in the study database for subjects who discontinue from study drug but continue to receive further RT fractions.

The trial's statistical analysis plan will discuss the imputation strategy for subjects who lack Esophagitis scores, who discontinue from the trial without complete follow-up of Esophagitis scores, and whose resolution date of severe Esophagitis is unknown.

12.7. Secondary Efficacy Analyses

12.7.1. Incidence Endpoints

Secondary incidence endpoints will be presented descriptively along with 95% Clopper-Pearson exact confidence intervals. Each incidence endpoint will have an analysis population that includes all subjects who receive at least one dose of GC4419 and either a) complete the follow-up period for the endpoint or b) discontinue follow-up early but are known to have had the endpoint.

12.7.2. Percentage Weight Change from Baseline Through the End of Treatment and 4 Weeks After Treatment

Percentage weight change through both periods will be descriptively summarized with univariate statistics.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

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

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

During site visits, the monitor will:

- Check the progress of the study;
- Review study data collected;
- Conduct source document verification;
- Identify any issues and address their resolution;
- This will be done in order to verify that the:
    - Data are authentic, consistent, 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 Galera Therapeutics, Inc., a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Galera Therapeutics, Inc. audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The investigator should contact Galera Therapeutics, Inc. 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.

In general, major protocol deviations include deviations from inclusion/exclusion criteria, from concomitant medication restrictions, and from any other protocol requirement that could, at least hypothetically, result in significant risk to the subject and/or affect the outcome of the clinical trial. Major protocol deviations will be noted in the final Clinical Summary Report.

A minor deviation is defined as non-adherence to the protocol procedures or schedule as defined by the protocol or the primary endpoint that does not place the subject at any added or significant risk or affect the data quality or the outcome of the clinical trial (eg, a missed procedure, an out-of-window site visit).

Only subjects who meet protocol-defined eligibility criteria may be enrolled in this clinical trial. If any protocol eligibility criteria or procedures are unclear, the investigator or investigational site personnel should contact the Clinical Research Associate. If the question requires medical interpretation, the sponsor's medical monitor should be consulted. All protocol deviations should be reported to the IRB/IEC according to the standard practices of the investigational site and applicable regulatory requirements.

13.4. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Galera Therapeutics, Inc. or its representatives. All protocol modifications must be submitted to the IRB/IEC/REB and regulatory authorities 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 Galera Therapeutics, Inc. or its representatives, and all data and information generated by the site as part of the study (other than a subject's medical records), are the sole property of Galera Therapeutics, Inc.

13.5.2. Confidentiality

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

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 Galera Therapeutics, Inc.

14. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

15. ETHICS

15.1. 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 E6, or with the laws and regulations of the country in which the research is conducted, whichever affords the greatest protection to the study patient. The investigator will also assure that the basic principles outlined in "ICH Guideline for Good Clinical Practice" as published in the Federal Register May 9, 1997, and all applicable Federal regulations including 21 CFR parts 50, 54, 56, and 312 are adhered to.

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

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

No modifications or deviations from this protocol other than those that are deemed medically necessary by the Principal Investigator or designated sub-investigator are to be made. Any protocol deviations will be reported to Galera Therapeutics, Inc. and to the IRB/IEC/REB in accordance with its reporting policy.

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

15.3. Written Informed Consent

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

16. DATA HANDLING AND RECORDKEEPING

16.1. Case Report Forms

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

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

The sponsor will ensure that the electronic CRF selected meets the requirements per ICH E6 R2 regarding data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning.

16.2. Retention/Inspection of Records

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

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

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

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessments	Screening Phase	Active Phase									Post Active Phase	
	Within 28 days of RT start	Baseline RT Day 1	Wk 1 Days 2-7	Wk 2 Days 8-14	Wk 3 Days 15-21	Wk 4 Days 22-28	Wk 5 Days 29-35	Wk 6 Days 36-42	Last Day of RT or Early Term[1]	4 weeks from Last Day of RT (± 15 Days)	90 Days Post-RT (± 15 Days)	6, 9, 12 months post treatment (+ 30 days)
Informed consent	X											
Inclusion/exclusion criteria	X	X										
Medical history[2]	X	X										
Complete Physical Exam	X								X	X	X	X
Height/Record BSA	X											
Symptom-directed Physical Exam						X						
Vital signs, ECOG and weight	X	X				X			X	X		
Serum pregnancy test	X											
Concomitant medications[3]		X	Weekdays						X	X		
Adverse Events[4]		X	Weekdays						X	X	X[3]	
Pneumonitis Assessment[5]: NCI-CTCAE scale, CT Scan, spirometry, and DLCO	X								X		X	
Tumor assessment (Chest CT with or without contrast)	X										X	X
ECG (12-lead) [6]	X											
Esophagitis assessment—CTCAE[7]	X	X	Weekdays						X	X		
Esophagitis assessment—RTOG[7]	X	X	Weekdays						X	X		
Patient reported outcomes: NCI-PRO-CTCAE, NPRS[8]	X	X		X	X	X	X	X	X	X		
Patient-reported swallowing diary[9]	X	X	Daily including weekends						X	X		
Analgesic/narcotic use reporting		X	X	Weekly					X	X		
Parenteral/tube feeding use reporting			X	Weekly					X	X		
Blood draw: Lab safety tests[10]	X	X	X	X	X	X	X	X	X[11]	X		
Blood draw: PK[12]		X	X			X						
RT + chemotherapy parameters recorded	X	Per protocol schedule/standard regimen										
Dosing GC4419[13]		X	Days 2-5	Days 8-12	Days 15-19	Days 22-26	Days 29-33	Days 36-40				

BSA = Body Surface Area, CTCAE = Common Terminology Criteria for Adverse Events, DLCO = diffusing capacity of the lungs for carbon monoxide, ECG = Electrocardiogram, ECOG = Eastern Cooperative Oncology Group, NCI-PRO-CTCAE = National Cancer Institute-Patient Reported Outcome- Common Terminology Criteria for Adverse Events, NPRS = Numeric Pain Rating Scale, RT = Radiation Therapy, RTOG = Radiation Therapy Oncology Group.

1 If a subject ends study participation early and/or withdraws consent after first dose of GC4419, all last day of RT procedures should be completed.

2 Medical History should include NSCLC or SCLC cancer history including prior treatments and confirmation of histopathological diagnosis

3 All concomitant therapies (eg, prescription and over-the-counter medications) taken by subjects on or after the date of baseline through 30 days following the last GC4419, RT or chemotherapy (ie, whichever occurs last) dose will be collected in the CRF. Additionally, any concomitant therapies if used to treat any serious or related adverse event will be recorded in the CRF.

4 All AEs and SAEs with onset dates on or after baseline through 30 days following the last GC4419, RT or chemotherapy (ie, whichever occurs last) dose will be recorded on the CRF. All subjects with SAEs will be followed until the events resolve or a new baseline is established. All subjects will be evaluated for acute RT pneumonitis, ≥ Grade 2 through 90 days after radiation therapy. Any adverse medical condition or laboratory abnormality with an onset date before the date of the baseline visit is pre-existing in nature, and part of the subject's medical history.

5 If Spirometry and DLCO have been performed as standard of care prior to screening and within 56 days of RT start, these tests can be used for inclusion.

6 If an ECG has been performed as standard of care prior to screening and within 56 days of RT start, this test can be used for inclusion

7 Toxicity by CTCAE for AEs, and esophagitis by CTCAE criteria, will be assessed at each treatment visit and 4 weeks after completion of treatment.

8 Patient Reported Outcome questionnaires (PROs), NCI-PRO-CTCAE and NPRS will be completed once within one week of baseline or during the baseline visit prior to dosing. PROs will subsequently be completed once weekly during all RT weeks. PROs are to be completed prior to esophagitis assessment.

9 Patient reported swallowing diary will be completed once within one week of baseline or during the baseline visit prior to dosing. The swallowing diary will be completed daily (including weekends) during treatment, and daily until the 4 weeks RT follow-up visit.

10 Clinical laboratory measurements will be conducted at the Screening Visit, twice during Week 1 (once at the Baseline Visit and again on Days 3, 4, or 5), and once weekly from Week 2 through the last day of RT. 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 serum chemistry profile (glucose, BUN, creatinine, sodium, potassium, calcium, albumin, total protein, total bilirubin, direct bilirubin, alkaline phosphatase, ALT [SGPT], AST [SGOT], chloride, phosphate, bicarbonate).

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

12 Blood samples will be collected for GC4419 pharmacokinetic (PK) measurements at Baseline (Day 1), Day 2, and Day 22. See Table 3 for additional information.

13 GC4419 will be administered Monday through Friday, beginning at Baseline (RT Day 1) and through Study Day 42 (end of RT). RT should begin no longer than 60 min following the end of the GC4419 infusion. If RT 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 RT resumes.

APPENDIX 2. ESOPHAGITIS NCI-CTCAE & RTOG SCORING

Grade	NCI-CTCAE	RTOG
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Mild dysphagia or odynophagia, may require topical anesthetic, non-narcotic agents or soft diet
2	Symptomatic; altered eating/swallowing; oral supplements indicated	Moderate dysphagia or odynophagia, may require narcotic agents or liquid diet
3	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated	Severe dysphagia or odynophagia with dehydration or weight loss (> 15% of pretreatment baseline), requiring nasogastric feeding, IV fluids, or hyperalimentation
4	Life-threatening consequences; urgent operative intervention indicated	Complete stricture, ulceration, perforation, or fistula
5	Death	Death

IV = intravenous, NCI-CTCAE = National Cancer Institute -Common Terminology Criteria for Adverse Events, RTOG = Radiation Therapy Oncology Group, TPN = total parenteral nutrition.
Sources: NCI-CTCAE 5.0 (2017); Radiation Oncology Toolbox (2017).

APPENDIX 3. PERFORMANCE STATUS CONVERSION

Performance Status Conversion: Eastern Cooperative Oncology Group (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. NUMERIC PAIN RATING SCALE

Pain Numeric Rating Scale

1. On a scale of 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable, how would you rate your pain RIGHT NOW.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

2. On the same scale, how would you rate your USUAL level of pain during the last week.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

3. On the same scale, how would you rate your BEST level of pain during the last week.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

4. On the same scale, how would you rate your WORST level of pain during the last week.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

APPENDIX 6. PATIENT SWALLOWING DIARY

Patient Swallowing Diary

Instructions for the patient: This is a calendar on which you are to record your swallowing ability each day of the week.

Be sure to turn in the sheets at the end of each week during treatment, and at 12 weeks from the start of treatment to the contact person listed below.

You will **fill out a column** by **adding the date**, by **writing in one number** that reflects your swallowing, before treatment begins, each day during radiation treatment, at end of treatment, and at 12 weeks after radiation completion of radiation.

You will receive at least 9 pages, one for each week and some extras. It is very important that we know how you feel, especially concerning your swallowing. If you have comments, be sure to add them to the page.

Please sign your name and date at the bottom of each page turned in.

If you have any questions,

Contact: _____ Telephone:_____

HAVE YOU HAD ANY PROBLEMS WITH SWALLOWING TODAY?

DATE								
DAY OF WEEK	Pretreatment	Mon	Tues	Wed	Thur	Fri	Sat	Sun
1 = None								
2 = Mild soreness only								
3 = Can swallow solids with some difficulty								
4 = Cannot swallow solids								
5 = Cannot swallow liquids								

COMMENTS:

Patient Signature: _____ Date: _____

APPENDIX 7. EXAMPLES OF CYP2D6-SUBSTRATE DRUGS

Beta-Blockers	Antidepressants	Antipsychotics	Others
carvedilol	amitriptyline	haloperidol	aripiprazole
S-metoprolol	clomipramine	risperidone	atomoxetine
propafenone	desipramine	thioridazine	codeine
timolol	duloxetine		dextromethorphan
	fluoxetine		doxepine
	imipramine		flecainide
	paroxetine		mexiletine
			ondansetron
			oxycodone
			risperidone
			tamoxifen
			tramadol
			venlafaxine

Source: https://drug-interactions.medicine.iu.edu/Clinical-Table.aspx.