SGX942 (DUSQUETIDE)

IDR-OM-02-USA

A PIVOTAL, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTINATIONAL STUDY OF SGX942 (DUSQUETIDE) FOR THE TREATMENT OF ORAL MUCOSITIS IN PATIENTS BEING TREATED WITH CONCOMITANT CHEMORADIATION FOR THE TREATMENT OF SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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Medical Monitor	Richard Straube, MD [redacted]

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1. PROTOCOL SYNOPSIS

Name of Sponsor/Company:
Soligenix, Inc.

Name of Investigational Product:
SGX942 (dusquetide), [redacted] sterile solution for intravenous (IV) infusion

Name of Active Ingredient:
Dusquetide (research name SGX94), [redacted] fully synthetic novel pentapeptide

Title of Study:
A Pivotal, Double-Blind, Randomized, Placebo-Controlled, Multinational Study of SGX942 (Dusquetide) for the Treatment of Oral Mucositis in Patients Being Treated with Concomitant Chemoradiation for the Treatment of Squamous Cell Carcinoma of the Head and Neck

Study Center(s): A total of 50-60 centers in the USA and EU

Principal Investigator: [redacted]

Studied Period (years):	**Phase of Development:**
Estimated date first patient enrolled: November 2017 Estimated date last patient enrolled: March 2020	Phase 3

Objectives:

Primary Objective:

- To assess the efficacy of SGX942 compared to placebo in decreasing the duration of severe oral mucositis (SOM; defined as World Health Organization [WHO] Grade lesion ≥3) in patients receiving fractionated radiation treatments and concomitant cisplatin chemotherapy, given as 80-100 mg/m^2 every third week, for the treatment of squamous cell carcinoma of the oral cavity or oropharynx.

Secondary Objectives:

To assess the impact of SGX942 compared to placebo on the following clinically important secondary objectives:

1. To assess the impact that SGX942 has on the Area-Under-the-Curve (AUC) for SOM (WHO Grade ≥3) by time plot (severity-weighted duration)
2. To assess the impact that SGX942 has on the Area-Under-the-Curve (AUC) for ulcerative oral mucositis (UOM; defined as WHO Grade ≥2) by time plot (severity-weighted duration)
3. To assess the impact that SGX942 has on the incidence of SOM
4. To assess the impact that SGX942 has on the quality of life assessment using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Question for Head and Neck Cancer 43 question (QLQH& N43) instrument
5. To assess the impact that SGX942 has on the amount of opioids used

To assess the impact of SGX942 compared to placebo on the following additional secondary objectives:

- To assess the impact that SGX942 has on the cumulative number of days of RT breaks
- To assess the impact that SGX942 has on the duration of SOM; in all randomized patients receiving fractionated RT and concomitant cisplatin chemotherapy, given as 80-100 mg/m^2

every third week (ITT population)

- To assess the impact that SGX942 has on the duration of UOM
- To assess the impact that SGX942 has on the cumulative amount of pain reported by patients
- The duration of SOM using an alternative definition calculated as the number of days from the first oral examination with WHO grade ≥3 through the last assessment with a WHO score ≥3 (and not to the first assessment with a WHO grade <3) with no further reports of a WHO grade ≥3.
- The duration of SOM in the Per-Protocol Population defined as patients receiving a cumulative radiation dose of at least 55 Gy and having received all study drug scheduled.

Safety Objective:

Safety objectives will include the following:

- To assess the impact that SGX942 has on the Adverse Events (AE) and serious Adverse Events (SAE)
- To assess the impact that SGX942 has on changes in safety laboratory values
- To assess the impact that SGX942 has on the Response Evaluation Criteria in Solid Tumors (RECIST) categorization of the primary tumor at 12 weeks and 12 months post-CRT
- To assess the impact of SGX942 on the incidence of reported presumed bacterial infections between Baseline and 6 weeks after completion of radiation therapy (RT) by total number and by severity of infection, graded using the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE)
- To assess the impact of SGX942 on 12 month all-cause mortality
- To assess the impact of SGX942 on progression free survival through 12 months

Methodology:

Approximately 260 patients with squamous cell carcinoma of the oral cavity and oropharynx scheduled to receive a minimum total cumulative radiation dose of 55 Gy fractionated as 2.0-2.2 Gy per day and concomitant cisplatin chemotherapy given as a dose of 80-100 mg/m^2 (every third week) will be enrolled. Subjects will be randomized to receive either 1.5 mg/kg SGX942 or placebo given as a 4-minute IV infusion using an infusion or syringe pump. Blinded study drug will be started within 3 days after starting RT and continued twice a week (2-4 calendar days apart) through 2 weeks after completion of the RT. Efficacy will be assessed by oral examination at each treatment visit and then at the 3 through 6 weeks post-RT completion visits. OM will be evaluated using the WHO Grade system and performed by observers trained on these measurements. SOM is defined as a WHO Grade of ≥3. The duration of SOM is defined as the first time the patient has a WHO Grade ≥3 until the first time the patient has a WHO Grade of <3 with no subsequent readings ≥3. Patients will be randomized (1:1; 1.5 mg/kg SGX942:placebo) using an interactive web response system (IWRS). Randomization will be stratified by site, presence of prophylactic gastrostomy feeding tube, and tumor human papillomavirus (HPV) status.

Routine clinical chemistry and hematology will be obtained at Screening/Baseline, then at 3, 6, and 9 weeks while receiving study drug, and then at the 4 and 6 week post-RT completion visit. The same type of scan initially used to stage the tumor (i.e., computed tomography [CT], magnetic resonance imaging [MRI] or positron emission tomography [PET]) will be repeated at 12 weeks and 12 months after completion of the radiation therapy and compared to the initial scan using the RECIST 1.1 criteria.

Number of Patients (planned):

260 patients (130 SGX942 treated and 130 placebo treated patients) will be enrolled.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

Patients must meet ***all*** of the following criteria in order to be eligible for enrollment:

1. Willing and able to understand and sign an informed consent
2. Males or females age greater than or equal to 18 years
3. Biopsy-proven squamous cell carcinoma of the oral cavity or oropharynx without distant organ metastases that has been evaluated for human papillomavirus (HPV)
4. Scheduled to receive cisplatin chemotherapy of 80-100 mg/m^2 given every third week
5. Scheduled to receive a continuous course of conventional external beam irradiation delivered by intensity-modulated radiotherapy (IMRT) as single daily fractions of 2.0 to 2.2 Gy, with a cumulative radiation dose between 55 and 72 Gy at each site
6. Planned radiation treatment fields must include at least 2 oral sites (retromolar trigone, buccal mucosa, floor of mouth, tongue, or soft palate), with each site receiving ≥55 Gy
7. All women of childbearing potential (WOCBP) and males with female partners who are WOCBP must agree to the use of effective contraception during the trial.
    - Women are considered to be WOCBP following menarche and until becoming post-menopausal unless permanently sterile (hysterectomy, bilateral salpingectomy and bilateral oophorectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
      Effective contraception methods for WOCBP should be started prior to randomization and continued for a minimum of 35 days following completion of study drug administration.
    - Acceptable contraceptive methods for WOCBP are those that achieve a failure rate of less than 1% per year and include:
        - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
            - Oral
            - Intravaginal
            - Transdermal
        - Progestogen-only hormonal contraception associated with inhibition of ovulation:
            - Oral
            - Injectable
            - Implantable
        - Intrauterine device (IUD)
        - Intrauterine hormone-releasing system (IUS)
        - Bilateral tubal occlusion
        - Vasectomized partner
        - Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments
- Male subjects should use condoms during treatment and for 98 days following the last study drug administration period.

Exclusion Criteria

Patients with any of the following criteria are **NOT** eligible for enrollment:

1. Current mucositis

2. Current, clinically significant, active infection that in the opinion of the Investigator would make them an unfit participant in the trial
3. Planned to receive Erbitux™ (Cetuximab) or similar targeted therapy between Baseline and 6 weeks post-RT
4. Current use of prohibited therapies listed in Section 8.2
5. Prior radiation to the head and neck
6. Chemotherapy treatment within the previous 12 months
7. Tumors of the lips, sinuses, salivary glands, nasopharynx, hypopharynx, or larynx
8. Evidence of significant renal, hepatic, hematologic, or immunologic disease determined by any one of the following: (the below are examples of evidence of significant disease, not required tests)
    A. Estimated creatinine clearance <30 mL/min
    B. ALT or AST level greater than 10-fold the upper limit of normal or total bilirubin greater than 3-fold the upper limit of normal
    C. Manifestations of end-stage liver disease, such as ascites or hepatic encephalopathy
    D. Thrombocytopenia (less than 60,000 cells/mm^3)
    E. CD4+ T cell count below 200 cells per µL (verification only required if there is a clinical diagnosis of HIV infection)
9. Evidence of immediate life-threatening disease or a life expectancy of less than 3 months
10. Women who are pregnant or breast-feeding
11. Participation in any study involving administration of an investigational agent within 30 days of randomization into this study
12. Any condition that, in the opinion of the Investigator, would compromise the safety of the subject or quality of the data

Investigational Product, Dosage, and Mode of Administration:

Dusquetide is a pentapeptide that is a first in class Innate Defense Regulator (IDR). SGX942 is dusquetide formulated for IV infusion. [redacted] The diluted solution will be administered as a 4-minute IV infusion using an infusion or syringe pump. Patients will be treated twice a week (2-4 calendar days apart) starting within 3 days after initiating RT and continuing through 2 weeks after completion of the RT. Patients missing more than 5 sequential scheduled RT sessions will be withdrawn from the trial.

Duration of Treatment:

Patients will start study drug infusions within 3 days after starting RT and continue through 2 weeks after completion of RT. RT is typically scheduled to continue for 5 to 7 weeks, if there are no breaks in treatment. Since distinct treatment breaks of up to 1 week may be encountered, the expected study drug treatment duration will be from 6 to 11 weeks.

Reference Therapy, Dosage, and Mode of Administration:

Placebo will consist of 0.9% sodium chloride (normal saline) that is identical in appearance to active drug. Blinded vials of placebo will be diluted identically to that of active drug to a final volume of 25 mL and infused using an infusion or syringe pump over 4 minutes. The frequency and duration of therapy will be identical to the active drug.

Criteria for Evaluation:

Efficacy:

Efficacy will be determined in patients who have received enough radiation exposure to put them at significant risk of developing SOM (defined as a cumulative radiation dose of at least 55 Gy).

Primary Endpoint:

The primary efficacy outcome for this study is the duration of SOM, defined as the number of days from the first oral examination with a WHO Grade assessment of ≥3 until the first time the patient has a WHO Grade of <3 with no subsequent readings ≥3.

Secondary endpoints will be analyzed in hierarchical order:

1. The Area-Under-the-Curve (AUC) for SOM (WHO Grade ≥3) by time plot (severity-weighted duration)
2. The Area-Under-the-Curve (AUC) for ulcerative oral mucositis (UOM; defined as WHO Grade ≥2) by time plot (severity-weighted duration)
3. The incidence of SOM
4. The quality of life assessment using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire 30 question module (EORTC QLQ-C30 (version 3)) and the EORTC Head and Neck Cancer latest 43 question module (QLQ-H&N43) instrument
5. The amount of opioids used

The following secondary endpoints will also be examined:

- The cumulative number of days of radiation treatment breaks
- The duration of SOM in all randomized patients receiving fractionated RT and concomitant cisplatin chemotherapy, given as 80-100 mg/m^2 every third week (ITT population)
- The duration of UOM
- The cumulative amount of pain reported by patients
- The duration of SOM using an alternative definition calculated as the number of days from the first oral examination with WHO grade ≥3 through the last assessment with a WHO score ≥3 (and not to the first assessment with a WHO grade <3) with no further reports of a WHO grade ≥3.
- The duration of SOM in the Per-Protocol Population defined as patients receiving a cumulative radiation dose of at least 55 Gy and all scheduled study drug.

Safety:

- The incidence, type, and body system categorization of AEs
- The incidence, type, and body system categorization of SAEs
- The changes from Baseline for hematology parameters, clinical chemistry parameters, and vital signs
- Tumor status at 12 weeks and 12 months following completion of RT categorized using the RECIST criteria
- The incidence and severity of reported infections assessed by CTCAE grading
- The 12 month post-RT survival

Statistical Methods:

The primary analysis will be a log-rank test of the differences in the duration of SOM between the 1.5 mg/kg SGX942 and placebo treated groups. A log-rank test will be used to compare the AUC of the WHO Grade-time curve and the number of days to onset of OM. The incidence of SOM and UOM, percent of RECIST complete responders, percent of patients with presumed bacterial infections and severity of infections will be compared using chi-squared tests. The primary analysis population will be all patients receiving drug who have received enough radiation exposure to put them at significant risk of developing SOM (defined as a cumulative radiation dose of at least 55 Gy).

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2.4. Appendices

Appendix 1: Common Terminology Criteria for Adverse Events (CTCAE) Version 4 - Quick Reference

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: Abbreviations and specialist terms

Abbreviation or specialist term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BAL	Bronchoalveolar lavage
BMI	Body mass index
BUN	Blood urea nitrogen
CFR	Code of federal regulations
Cmax	Maximum concentration
CNS	Central nervous system
CO_2	Carbon dioxide
CP	Conditional power
CR	Complete response
CRT	Chemoradiation therapy
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
DLT	Dose limiting toxicity
DMC	Data monitoring committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
GCP	Good clinical practices
GLP	Good laboratory practices
HED	Human equivalent dose
HCG	Human chorionic gonadotropin
HPV	Human papillomavirus
IB	Investigator's brochure
ICF	Informed consent form

Abbreviation or specialist term	Explanation
ICH	International Conference on Harmonisation
IDR	Innate Defense Regulator
IMRT	Intensity modulated radiation therapy
IRB	Institutional Review Board
ITT	Intent to treat
IV	Intravenous
IWRS	Interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
N	Number
NCI	National Cancer Institute
NDA	New drug application
NHP	Non-human primate
NOAEL	No observed adverse effect level
OM	Oral mucositis
PEG	Percutaneous endoscopic gastronomy
PET	Positron emission tomography
PD	Pharmacodynamics
PI	Principal investigator
PK	Pharmacokinetic
PP	Per protocol
PR	Partial response
RBC	Red blood cell
RT	Radiation therapy
SAE	Serious adverse event
SD	Stable disease
SOM	Severe oral mucositis
T_{max}	Time at which the maximum blood concentration was achieved
UOM	Ulcerative oral mucositis
WBC	White blood cell
WHO	World Health Organization

4. INTRODUCTION

This section contains a brief description of the rationale and available information concerning the chemistry, non-clinical pharmacology and toxicology, pharmacokinetics (PK), pharmacodynamics (PD), and previous clinical experience with SGX942. Please refer to the Investigator's Brochure (IB) for additional details and information.

4.1. SGX942 (Dusquetide)

Dusquetide is a five amino-acid peptide that binds to the intracellular p62 protein [1] resulting in modulation of the innate immune response to both infection and tissue damage by reducing induction of inflammation and increasing macrophage activation/recruitment, resulting in increased bacterial clearance and tissue healing [2-4]. The drug is formulated as an aqueous, sterile solution for injection containing 60 mg/mL of dusquetide. The formulation contains no preservatives and no excipients. The drug will be given at a dose of 1.5 mg/kg. Drug will be diluted into an infused volume of 25 mL and administered as a 4-minute infusion using either an infusion or syringe pump.

4.2. Toxicology

Non-GLP and GLP preclinical toxicology and safety pharmacology studies were conducted in mice and non-human primates (NHPs). Transient, high-dose acute toxicity was observed in both mouse and NHP. Resolution occurred within minutes in surviving animals with no long-term sequelae.

Pilot toxicology studies indicated that the maximum tolerated dose (MTD) of a single administration of dusquetide, administered as an IV injection over 30 to 60 seconds, is 88 mg/kg in mice. In NHP, mild clinical signs (i.e., shallow/labored respiration, decreased activity, partially closed eyes, and muscle twitches) were noted in 1 or both animals after administration of 90 (1 animal), 180 (both animals), and 220 (1 animal) mg/kg dusquetide during and shortly after dosing. These resolved within a few minutes without detectable residual effects.

The safety of multiple daily injections of dusquetide has also been evaluated in GLP studies in mice and NHPs. In mice, doses of 20, 60, or 90 mg/kg/day were given IV for 14 days. Deaths were observed at the high dose, preceded mainly by labored respiration and recumbency. Lethality was also observed in 1 animal given 60 mg/kg but no other animals exhibited clinical signs at this dose. No test article-related mortality or clinical signs were observed at 20 mg/kg. In survivors of all groups, there was no evidence of toxicity in any organ or abnormal biochemistry or hematology. No AEs were observed at 20 mg/kg administered daily for 14 days.

Dusquetide at 20, 80, or 160 mg/kg/day was given IV to cynomolgus monkeys for 14 days. Transient decreased activity and partially closed eyes continued to be observed during and shortly after dosing at 160 mg/kg for the first 3 days in most animals, then sporadically throughout the remaining dosing period. In all cases, these clinical signs resolved within a few minutes. No AEs were observed on any other measured parameter or microscopically in any tissue. The administration of dusquetide at doses of 20 and 80 mg/kg/day did not result in any

evidence of toxicity. A dose level of 80 mg/kg/day was considered the No-Observed-Adverse-Effect-Level (NOAEL) for this study.

No effects of dusquetide have been observed on the central nervous system (CNS) in any study at any dose level and little or no radiolabelled dusquetide was found in the mouse CNS at dose levels of either 20 or 90 mg/kg. No interaction was detected between dusquetide and a battery of CNS receptors and ion channels *in vitro*.

A cardiovascular (CV)/pulmonary study in cynomolgus monkeys using single IV doses of 20 or 80 mg/kg revealed no CV effects or changes in electrocardiogram (ECG) parameters. No respiratory effects were observed at doses of 20 or 80 mg/kg. At a dose of 80 mg/kg in this study, dusquetide was associated with transient drooping eyelids and prostration during dosing.

Overall, the NOAEL is considered to be 80 mg/kg/day for cynomolgus monkeys since transient clinical signs were limited to a single study and occurred in only 2 instances of the 98 administrations of the drug at this dose level.

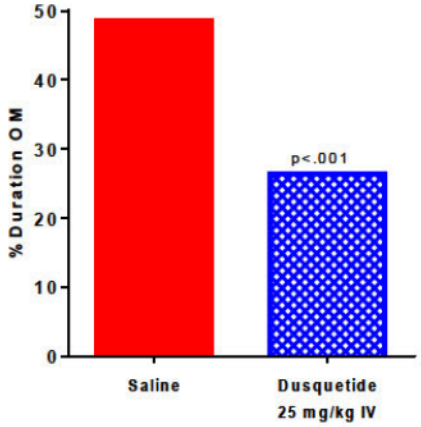
No carcinogenicity, mutagenicity or reproductive toxicity studies have been conducted with dusquetide.

The effect of dusquetide on the innate defense system is highly selective. Consistent with these findings, no changes were observed in immune-related organ weights, histopathology, hematology, and clinical chemistry during mouse and NHP 14-day toxicity studies. In the latter study, no effect on T-cell, B-cell or NK-cell counts was observed after 14 days of IV dusquetide dosing in NHPs. Collectively, there is no indication of a potential for dusquetide to cause immunotoxicity or non-specific immune activation. No hyperactivation or suppression of adaptive immune responses, or other impact on the phenotypes of cells associated with adaptive immunity, has been detected following dusquetide administration.

4.3. Preclinical Pharmacology

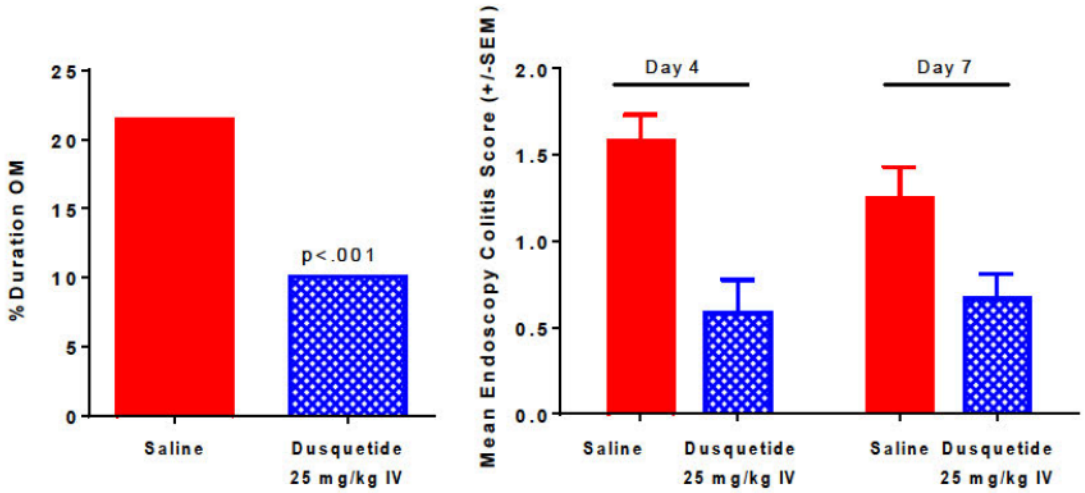
Preclinical studies with dusquetide revealed a significant reduction in both duration and peak intensity of OM in a fractionated radiation-induced hamster model of OM as seen in Figure 1 [3]. Efficacy was dose responsive and effective at 25 mg/kg (allometric equivalent for humans 1-2 mg/kg) dosed every third day during fractionated RT.

Figure 1: Duration of Severe Radiation-induced Oral Mucositis



Similar results were seen in the mucosa of the mouth and colon in a chemically induced model of mucositis in mice as seen in Figure 2.

Figure 2: Duration of Severe Chemo-induced Mucositis in Mice



Dusquetide has been studied in a variety of infection models. Because it works by enhancing the host reaction to the infection rather than interacting with the pathogen, dusquetide is effective in both gram-positive and gram-negative, intra- and extra-cellular infection, and antibiotic sensitive and antibiotic-resistant bacterial infections [2, 4,]. Interestingly, the drug appears to have an effect both prophylactically and when used following establishment of infection [2].

Antibiotic combination studies to assess any potential for interference with representative drugs of various antibiotic classes in an *in vivo* setting show no reduction in antibiotic effectiveness in the presence of dusquetide, co-administered at 20 or 50 mg/kg in mice.

Dusquetide did not promote the proliferation of either mouse or human normal blood cells *in vitro*, nor of primary human leukemia cells *in vitro*. Dusquetide did not enhance tumor growth or interfere with chemotherapy (paclitaxel) or radiation treatment of MCF-7 (breast cancer cell line) tumors in an MCF-7 tumor xenograft model in nude mice [3]. There was evidence of decreases in tumor volumes over time and prolonged survival of the animals.

4.4. Phase 1 Trial

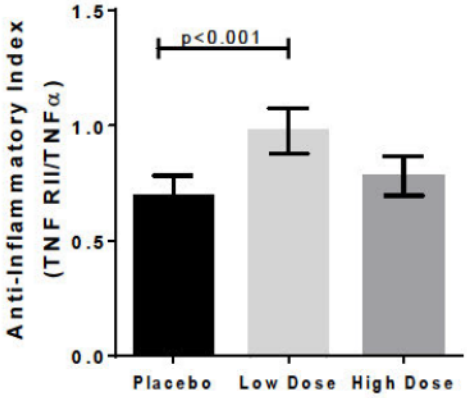
A placebo-controlled, Phase 1 study in healthy volunteers has been completed demonstrating that single IV doses of SGX942 are well tolerated up to the maximum tested (8 mg/kg) and daily IV doses are well tolerated up to the maximum tested (6.5 mg/kg for 7 days). There were no dose limiting toxicities (DLTs) and the MTD was not reached in either phase of the trial. There were no deaths and no clinically significant, severe, or serious AEs reported during the study. No safety concerns or significant differences in mean values or changes from baseline were observed for vital sign measurements, clinical laboratory, or ECG results between drug-treated and placebo control subjects.

Following IV administration in human subjects, dusquetide is cleared within minutes from the circulation. In the single-dose phase of the Phase 1 trial, dusquetide was rapidly eliminated, with plasma levels decreasing to less than 10% of the maximum concentration (C_{max}) within 9

minutes after the start of the 4-minute IV infusion. Following the rapid decline, a slower elimination phase was observed. The mean time of maximum concentration (T_{max}) ranged between approximately 4 to 4.8 minutes after the start of infusion for the dose range of 0.15 - 8 mg/kg. Maximum plasma concentrations and total exposure levels were dose-proportional and clearance of dusquetide from the circulation was rapid, consistent with the mouse and NHP experience. Considering the high clearance and short elimination half-life, accumulation following daily injection was not expected to occur. In the multiple-dose Phase 1 study, dusquetide was administered daily for 7 days and the pre-dose concentrations measured on Days 5, 6, 7, as well as on Day 8 (24 hours after the start of infusion on Day 7) were below the lower limit of quantitation for all of the subjects.

Pharmacodynamics of SGX942 were explored by stimulating blood from the subjects receiving study drug with lipopolysaccharide (LPS) and measuring the inflammatory cytokines released [2]. Compared to the subjects that received placebo, subjects receiving low dose (≤2 mg/kg) SGX942 had decreased pro-inflammatory and increased anti-inflammatory cytokine levels over time. High dose (≥3.0 mg/kg) subjects did not show a similar shift to a more anti-inflammatory profile (Figure 3).

Figure 3: Anti-Inflammatory Status in Subjects Receiving Placebo, Low Dose (0.15-2.0 mg/kg) or High Dose (3.0-8.0 mg/kg) Dusquetide



4.5. Phase 2 Trial in Head and Neck Cancer Patients

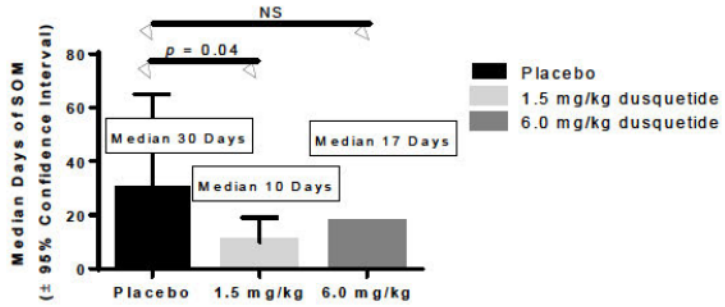
In this multicenter, double-blind, placebo-controlled trial, 111 patients with squamous cell carcinomas of the oral cavity or oropharynx scheduled to receive daily fractions of 2.0 Gy to 2.2 Gy with concomitant cisplatin were enrolled. Patients were randomized to receive placebo, 1.5, 3.0, or 6.0 mg/kg SGX942 given as a 4-minute IV infusion twice weekly during RT [3]. OM was assessed twice weekly using WHO criteria [6]. The prospectively defined primary analysis of effectiveness of SGX942 was the duration of SOM in those patients receiving at least 10 doses of study drug and at least 55 Gy of cumulative RT (mITT population).

Patients receiving 1.5 mg/kg of SGX942 had a 50% reduction in their median duration of SOM compared to the placebo group (9 days versus 18 days for the SGX942 1.5 mg/kg and placebo groups, respectively). This finding is supported by a 39% reduction in the median AUC for the WHO Grade-time calculation and a 7% relative reduction in the incidence of SOM when

compared to placebo. This is very consistent with the preclinical studies showing 46-53% (Figure 1, Figure 2) reductions in the duration of OM in both radiation and chemotherapy animal models [3].

SGX942 appeared to have the highest effectiveness in subpopulations expected to have the longest duration of SOM. In the subpopulation of patients receiving every third week cisplatin (i.e., the most aggressive cisplatin therapy of 80-100 mg/m^2 of cisplatin) there was a 67% decrease in the median duration of SOM (i.e., from 30 to 10 days in the placebo and SGX942 1.5 mg/kg dose groups, respectively) (Figure 4). This reduction was associated with a 51% reduction in the median AUC WHO Grade-time calculation and an 18% relative reduction in incidence of SOM compared to placebo.

Figure 4: Median Duration of Severe Oral Mucositis (SOM) in Patients Receiving Every Third Week Cisplatin



In placebo patients whose tumors were human papillomavirus negative (HPV-), the median duration of SOM was 33 days compared to 11 days in those patients whose tumors were human papillomavirus positive (HPV+). In patients with HPV- tumors, SGX942 reduced the median duration of SOM in both the 1.5 and 6.0 mg/kg SGX942 dose groups by 76%. This was associated with a 73% reduction in the median AUC for the WHO Grade-time measurement in the 1.5 mg/kg SGX942 dose group and a 76% decrease in the 6.0 mg/kg SGX942 dose group. Similarly, relative incidence decreased by 22% in the 1.5 mg/kg dose group and 10% in the 6.0 mg/kg group.

The lowest dose tested, 1.5 mg/kg, was effective in reducing the duration of oral mucositis (OM) in head and neck cancer patients. At the request of the USA Food and Drug Agency (FDA) during study design, the 3.0 mg/kg dose of dusquetide was included primarily as a safety step in the dose escalation. Only 3 patients received this dose, hence, no effectiveness conclusions are possible for this dose. The results in the 6.0 mg/kg SGX942 dose group compared to the placebo group are inconsistent across the various measures of SOM and across the various subpopulations, suggesting that it is not as effective in ameliorating OM as the 1.5 mg/kg SGX942 dose. Decreased effectiveness at the 6.0 mg/kg dose level is consistent with findings in the Phase 1 study with SGX942, where anti-inflammatory activity was more prevalent at the lower dose level (Figure 3) [3].

In addition to the improvement in OM, a decrease in the rate of infections, particularly non-fungal (bacterial) infections was also observed (Table 3).

Table 3: Reported Infections

Treatment Group	Placebo n = 38	1.5 mg/kg n = 36	6.0 mg/kg n = 19
All Infections: n (%) *p-value compared to placebo*	29 (76%) —	23 (64%) *0.311*	8 (42%) *0.018*
Non-fungal Infection: n (%) *p-value compared to placebo*	17 (45%) —	10 (28%) *0.153*	4 (21%) *0.144*
Serious Infection: n (%) *p-value compared to placebo*	8 (21%) —	7 (19%) *>0.999*	3 (16%) *0.735*

In the mITT population, the number of patients with RECIST evaluations categorized as complete responses to therapy was increased from 15/38 (39%) in the placebo group to 17/36 (47%) in the 1.5 mg/kg SGX942 dose group, a 21% increase. Disregarding those patients with missing or not assessed tumor status, this increase was 34% in the SGX942 1.5 mg/kg group. This is consistent with preclinical studies showing improved survival and decreased tumor volume size (3). Over the longer term, the overall resolution rate in the placebo population was high, making further improvement difficult to demonstrate. However, SGX942 definitely did not decrease the effectiveness of CRT therapy (Table 4). Similarly, the overall 1-year survival rate was similar between groups and more favorable for the SGX942 treated groups (Table 5).

Table 4: Incidence of Tumor Complete Response as a Function of Treatment Group and Timepoint (Safety Population)*

RECIST Response	Placebo n = 41	1.5 mg/kg n = 42	3.0 mg/kg n = 3	6.0 mg/kg n = 23
1-month follow-up	15/32 (47%)	17/27 (63%)	1/3 (33%)	4/16 (25%)
3-month follow-up	17/27 (63%)	18/27 (67%)	1/1 (100%)	9/17 (53%)
6-month follow-up	19/24 (79%)	19/28 (68%)	1/1 (100%)	10/14 (71%)
9-month follow-up	6/8 (75%)	14/16 (88%)	2/2/ (100%)	1/3 (33%)
12-month follow-up	22/23 (96%)	19/23 (83%)	1/2 (50%)	10/12 (83%)
LOCF** through 12-month follow-up	26/35 (74%)	28/35 (80%)	1/3 (33%)	13/22 (59%)

*Percentage calculation excludes missing/not assessed evaluations
** Last Observation Carried Forward

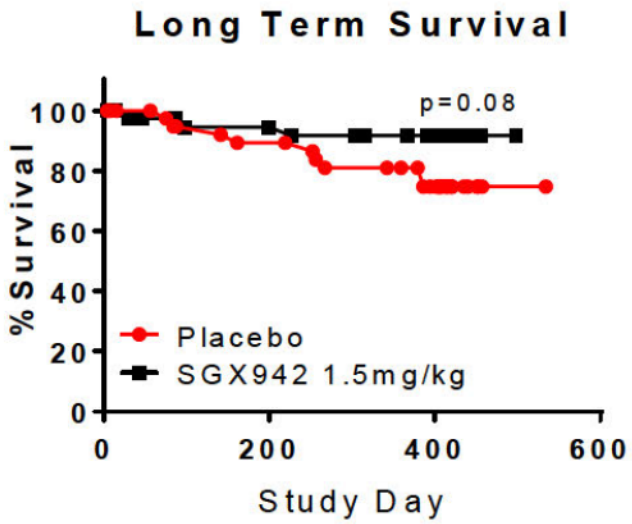
Table 5: Mortality (ITT Population[1])

Mortality	Placebo n = 43	1.5 mg/kg n = 41	3.0 mg/kg n = 3	6.0 mg/kg n = 24
Through 12-month follow-up	9 (21%)	3 (7%)	0	4 (17%)

[1] Includes one patient dying 373 days after receiving their last study drug dose

The survival curves for the 1.5 mg/kg SGX942 and placebo groups are shown in Figure 5.

Figure 5: Survival Curve



In this Phase 2 trial, confidence in the benefit of SGX942 is based not only on the magnitude of reduction in the duration of SOM and the concordance of the patient results with both qualitative and quantitative animal model data, but also in the internal consistency of the trial data. The duration data, AUC data, and incidence data consistently trend in the same direction and are similar across analysis populations (i.e., per protocol [PP], mITT, and ITT populations) as well as across subpopulations of groups defined by baseline characteristics (i.e., cisplatin treatment, HPV tumor status, age, sex, race, and prior tumor surgery). The additional findings of an increase in the number of patients with RECIST defined "complete response" and a reduction in the number of infections in the SGX942 dose groups are consistent with the animal model studies and strongly support the evidence for biologic activity of the drug in this patient population.

With its rapid degradation yet extended PD impact, the PK profile of SGX942 is of limited utility. Nonetheless, evaluating PK in a subset of patients demonstrated a roughly or greater than dose proportional response in C_{max} and area under the concentration time curve (AUC) of SGX942 in blood in response to increased dose levels (i.e., 1.5 vs. 6.0 mg/kg). There was no evidence of accumulation over multiple doses. These results were consistent with the nonclinical and Phase 1 clinical PK results.

Comparison of the AEs and SAEs across the dose groups (i.e., 1.5, 3.0, and 6.0 mg/kg) did not reveal any substantive differences in the incidence, severity, PI judgments as to relatedness or severity of the AEs, or specific AEs. The infusion procedures themselves were well tolerated. Complete resolution of tumor burden was similar or improved in the SGX942 1.5 mg/kg treatment group and all-cause mortality was also similar across treatment groups, with the best outcome in the 1.5 mg/kg SGX942 treatment group. SGX942 administration at all dose levels appeared to be safe and well tolerated.

[redacted]

[redacted]

[redacted]

[redacted]

4.7. Patient Population

This trial will enroll patients with biopsy proven squamous cell carcinoma of the oral cavity or oropharynx without distant organ metastases who are scheduled to receive a standard course of CRT consisting of at least 55 Gy of cumulative fractionated RT and chemotherapy using 80-100 mg/m^2 of cisplatin given every 3 weeks (21 days). Patients will be adults (≥18 years of age) and women must not be pregnant or breastfeeding. Patients scheduled to receive cetuximab, those with clinically significant organ dysfunction, those with a life expectancy of <3 months, and those participating in other investigational agent trials are excluded.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Primary Objective

To assess the efficacy of SGX942 compared to placebo in decreasing the duration of SOM (defined as WHO Grade lesion ≥3) in patients receiving fractionated radiation treatments and concomitant cisplatin chemotherapy, given as 80-100 mg/m^2 every third week, for the treatment of squamous cell carcinoma of the oral cavity or oropharynx.

5.2. Secondary Objectives

To assess the impact of SGX942 compared to placebo on the following clinically important secondary objectives:

1. To assess the impact that SGX942 has on the Area-Under-the-Curve (AUC) for SOM (WHO Grade ≥3) by time plot (severity-weighted duration)
2. To assess the impact that SGX942 has on the Area-Under-the-Curve (AUC) for ulcerative oral mucositis (UOM; defined as WHO Grade ≥2) by time plot (severity-weighted duration)
3. To assess the impact that SGX942 has on the incidence of SOM
4. To assess the impact that SGX942 has on the quality of life assessment using the EORTC QLQ-C30 (version 3) and QLQ-H&N43 instrument
5. To assess the impact that SGX942 has on the amount of opioids used

To assess the impact of SGX942 compared to placebo on the following additional secondary objectives:

- To assess the impact that SGX942 has on the cumulative number of days of RT breaks
- To assess the impact that SGX942 has on the duration of SOM; in all randomized patients receiving fractionated RT and concomitant cisplatin chemotherapy, given as 80-100 mg/m^2 (ITT population)
- To assess the impact that SGX942 has on the duration of UOM
- To assess the impact that SGX942 has on the cumulative amount of pain reported by patients
- The duration of SOM using an alternative definition calculated as the number of days from the first oral examination with WHO grade ≥3 through the last assessment with a WHO score ≥3 (and not to the first assessment with a WHO grade <3) with no further reports of a WHO grade ≥3
- The duration of SOM in the Per-Protocol Population defined as patients receiving a cumulative radiation dose of at least 55 Gy and study drug twice per week during and for 2 weeks after radiation therapy

5.3. Safety Objectives

Safety objectives will include the following:

- To assess the impact that SGX942 has on the Adverse Events (AE) and serious Adverse Events (SAE)
- To assess the impact that SGX942 has on changes in safety laboratory values
- To assess the impact that SGX942 has on the Response Evaluation Criteria in Solid Tumors (RECIST) categorization of the primary tumor at 12 weeks and 12 months CRT
- To assess the impact of SGX942 on the incidence of reported presumed bacterial infections between Baseline and 6 weeks after completion of radiation therapy (RT) by total number and by severity of infection, graded using the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE)
- To assess the impact of SGX942 on 12 month all-cause mortality
- To assess the impact of SGX942 on progression free survival through 12 months

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design and Plan: Description

Approximately 260 patients will be enrolled into this Phase 3, placebo-controlled, double-blind, multinational study to evaluate the efficacy of SGX942 compared to placebo in treating the duration of SOM in patients receiving CRT for the treatment of head and neck cancer. Patients will be randomized into one of two groups (1.5 mg/kg SGX942:Placebo) at a 1:1 ratio. They will be stratified by site, presence of gastrostomy tube, and HPV status. Patients will receive their initial blinded IV study drug (1.5 mg/kg SGX942 or placebo) within 3 days of starting radiation.

The primary efficacy outcome for this study is the duration of SOM, defined as the number of days from the first oral examination with a WHO Grade assessment of 3 or 4 through the first day that a WHO Grade of <3 is recorded with no subsequent assessments ≥3. OM will be evaluated using the WHO scoring for OM.

Patients will be screened to assess their eligibility prior to randomization. After randomization, subjects will begin treatment with study drug within 3 days of initiating RT.

Patients will receive study drug while undergoing CRT and continue to receive study drug for 2 weeks after the completion of their RT. Study visit days will be every third day (± 1 day). On study visit days, patients will receive the 4-minute infusion of study drug. Study drug will not be given on the same day as chemotherapy. Study drug can be given at any time during the visit day, but must occur on the same calendar day that is the study visit day. The study visit calendar extends to 2 weeks post-completion of RT.

Efficacy will be further assessed at the 3 through 6 weeks post-RT completion visits. Follow-up visits will be conducted at 12 weeks and 12 months after the last radiation dose to continue to evaluate safety and secondary endpoints.

Below is a table outlining the study schedule of procedures and assessments. The study week designations assume a 7-week CRT schedule. These times may require adjustment (as described below) if the treatment course is shorter or if treatment breaks prolong the CRT for more than 7 weeks.

Table 7: Schedule of Events by Week

Study week	Screen	Base[2]	1w[3]	2w	3w	4w	5w	6w	7 w	8w	9w	10w	11w	12w	13w	15- 55 w	19w	59w
Post-RT[1]										1w	2w	3w	4w	5w[4]	6w	2m-11 m[5]	12w	12m
Medical History	X	X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X	X	X	X	X	X
Informed Consent	X																	
Randomization		X																
History of Pain and Opioid Use		X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X	X	X		X	X
Assessment of Infections		X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X	X	X			
Radiation[6]			5X	5X	5X	5X	5X	5X	5X									
Cisplatin[6]			X			X			X									
Administer Drug			2X	2X	2X	2X	2X	2X	2X	2X	2X							
WHO OM[7]		X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X	X	X			
PEG Tube Use		X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X	X	X			
VS[8]	X	X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X	X	X			
Physical Exam	X	X									X[13]				X			
Safety Labs[9]	X	X[12]			X			X			X[13]		X		X			
AEs		X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X	X	X			
Tumor Scan[10]	X[11]																X	X
Serum Pregnancy	X	X[12]													X			
HPV Status	X[11]																	
Quality of Life		X				X					X[13]							

[1] Post-RT = time from the last radiation therapy treatment
[2] Baseline information needs to be obtained prior to (0 to 96 hours before) the first dose of study drug
[3] w = weeks
[4] Only to be done if WHO score is ≥2 at Week 4 Post-RT visit
[5] m = months; patient contact (clinic visit, telephone, or email) required monthly through the 12-month clinic visit
[6] Timing of radiation and chemotherapy at discretion of primary care physicians
[7] WHO OM = oral mucositis grading with WHO Oral Mucositis Grading system
[8] Vital signs to include temperature, weight, pulse, respirations, and seated blood pressure; Height will be obtained at Baseline only
[9] Safety labs = hematology and clinical chemistry panels
[10] Scan = obtain initial staging CT/PET/MRI scans (screening scan must be within 6 weeks prior to Baseline)
[11] Need to confirm that the initial diagnostic scans were CT, PET, or MRI and the tumor was tested for HPV status
[12] Repeat test required if Baseline sample >7 days from Screening
[13] To be done only on the second visit in week 2 post-RT

It is assumed that patients will receive 7 weeks of RT. In practice, some patients will have a shorter course (lower planned radiation dose) or stop treatment early. Similarly, patients with RT breaks who complete 7 weeks of RT may require treatment for more than 7 weeks. All post-RT visits will be scheduled from the last RT so that if the RT is completed after 6 weeks, study drug will be continued for the 2 weeks following (Weeks 7 and 8) and the 12 weeks post-radiation scan will be obtained in Week 18. Similarly, if there are treatment breaks such that RT completes in study Week 8, the study drug will continue for 2 weeks (Weeks 9 and 10) and the 12 weeks post-radiation scan will be obtained at Week 20.

6.2. Specific Assessments

6.2.1 Oral Mucositis (OM) Grading

OM will be evaluated by personnel trained in the use of the WHO Oral Mucositis Grading system which includes both physical and functional information. This grading system is widely utilized in OM clinical research trials including the Phase 2 trial and is shown in Table 8.

Table 8: WHO Oral Mucositis Grading System

Score	Findings
0	No findings OR Pain or erythema (not both)
1	Pain and erythema AND No ulcer
2	Ulcer and/or pseudomembrane, AND Able to eat solid food AND Able to drink
3	Ulcer and/or pseudomembrane, AND Not able to eat solid food AND Able to drink
4	Ulcer and/or pseudomembrane, AND Not able to eat solid food AND Not able to drink

Only medical personnel at the site who have undergone training and certification in using the WHO Grading system will perform the OM assessments.

6.2.2 Tumor Status

The tumor response to treatment will be used as a safety endpoint. Results at 12 weeks and 12 months post-RT will be compared to the Screening results using the RECIST 1.1 system. The evaluation criteria for the target lesion (the primary head and neck carcinoma) are shown in Table 9; the criteria for non-target lesions are shown in Table 10; and the criteria for overall categorization of the tumor status are shown in Table 11. In addition, details pertaining to recurrence of disease, additional therapy, or surgery required after the active treatment phase of the trial is completed will be collected and recorded in the eCRF throughout all follow up visits until 12 months following the last RT treatment.

Table 9: RECIST Evaluation of the Target Lesion

Target Lesion Response	Measurement
Complete Response (CR)	All target lesions gone
Partial Response (PR)	>30% decrease from baseline
Progressive Disease	>20% increase from smallest sum of longest diameter recorded since treatment started (best response)
Stable Disease (SD)	Neither Progressive Disease nor Partial Response

Table 10: RECIST Evaluation of the Non-target Lesion

Target Lesion Response	Measurement
Complete Response (CR)	All non-target lesions gone Tumor markers gone
Stable Disease (SD)	Persistence of ≥1 non-target lesion Tumor marker level elevated
Progressive Disease	Enlargement of non-target lesions

Table 11: Overall RECIST Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	Complete Response
CR	SD	No	Partial Response
PR	Non-Progressive Disease	No	Partial Response
SD	Non-Progressive Disease	No	Stable Disease
Progressive Disease	Any	Yes or No	Progressive Disease
Any	Progressive Disease	Yes or No	Progressive Disease
Any	Any	Yes	Progressive Disease

6.2.3 Infection

Infections will be reported at each clinic visit through to the 6-week post-RT visit. Any identified infection will be categorized as presumed fungal, presumed viral, or presumed bacterial. The severity of each reported infection will be graded 1 to 5 using the CTCAE.

6.2.4 History of Pain and Opioid Use

Except for the Screening visit, at every study visit, the study staff will review with the patient their current pain level as well as the cause of their pain. Efforts will be made to differentiate pain due to OM versus other causes of pain. The study staff will also review with the patient their current prescriptions for pain medication (opioids) with special care taken to review the as needed medications the patients have been given as well as the frequency with which they are taking them. Details for all of the above will be recorded in the eCRF.

In addition, site staff will review the study-specific oral hygiene requirements with the patient on a weekly basis.

6.2.5 Laboratory Assessments

6.2.5.1. Serum Pregnancy Test

Blood samples will be obtained at the Screening, Baseline (if Baseline **>7 days** from Screening), and 6 weeks post-RT visits for a serum pregnancy test (human chorionic gonadotropin [HCG]) for all women who are of childbearing potential.

6.2.5.2. Hematology Tests

The hematology panel will be performed at the Central Laboratory on samples collected at Screening, Baseline (if Screening tests were obtained **>7 days** from Baseline), Week 3, Week 6, and at the 2-week post-RT, the 4-week post-RT visit and the 6-week post-RT visits. The panel will consist of the following tests:

- Red blood cell count (RBC)
- Hematocrit
- Hemoglobin
- RBC indices
- Platelet count
- White blood cell count (WBC)
- WBC differential count

6.2.5.3. Clinical Chemistry Laboratory Tests

The clinical chemistry panel will be performed at the Central Laboratory on samples collected at Screening, Baseline (if Screening tests were obtained **>7 days** from Baseline), Week 3, Week 6, and at the 2-week post-RT, the 4-week post-RT and the 6-week post-RT visits. The panel will consist of the following tests:

- Serum sodium
- Serum potassium
- Serum chloride
- Serum bicarbonate (CO_2)

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Total bilirubin
- Alkaline phosphatase
- Total protein
- Serum creatinine
- Blood urea nitrogen (BUN)

6.2.6 Other Assessments

6.2.6.1. Medical History

Demographic information will be collected at Screening and include the following information that will be recorded in the Electronic Case Report Form (eCRF):

- Birth date
- Sex
- Race
- Ethnic group
- Smoking history
- Alcohol consumption

At each study visit, interim medical history will be obtained and recorded.

6.2.6.2. Physical Examination

A complete physical examination will be performed and all abnormalities noted in the eCRF at Screening, Baseline, the 2-week post-RT visit, and the 6-week post-RT visit.

6.2.6.3. Quality of Life Questionnaire

A Quality of Life Questionnaire will be completed by each patient at Baseline, 4 weeks and at the end of study drug treatment (2 weeks post-RT) and reviewed and entered by the site personnel into the eCRF. The EORTC QLQ-C30 (version 3) and the EORTC QLQ-H&N43 instrument will be used for these assessments.

6.2.6.4. Vital Signs

Vital signs will be collected at each study visit up to and including the 6-week post-RT visit. Vital signs will include the following measurements:

- Heart rate
- Respiratory rate
- Temperature

- Blood pressure (seated)
- Weight

6.2.6.5. Height and Body Mass Index (BMI)

Height will be collected at Baseline only and Body Mass Index (BMI) automatically calculated.

6.3. Visit Schedule

6.3.1 Screening

The Screening visit must be done within 4 weeks prior to the Baseline visit. Prior to starting the study medication, the results of all tests must be reviewed to assure that the patient meets all entry criteria. Procedures to be done at this visit are:

- Obtain Informed Consent Form (ICF) signature
- Assure that the initial tumor imaging is compatible with RECIST Criteria (CT, MRI, or PET scans)
- Assure that the tumor was evaluated for HPV status
- Assessment of entry criteria
- Complete Medical History
- Complete Physical Examination
- Vital Signs
- Serum HCG pregnancy test (women only)
- Hematology Panel
- Clinical Chemistry Panel

6.3.2 Baseline Day

Baseline assessment will be completed prior to radiation, chemotherapy, and study drug administration but within 96 hours of the initial study drug treatment. Patient will be seen on the first day of study drug treatment. The entry criteria will be reviewed and an interim medical history taken to assure that the patient meets all entry criteria. If the patient still qualifies, they will undergo the following procedures:

- Interim Medical History
- Randomization
- Vital signs
- Adverse events (begin collecting after randomization)
- Physical Exam
- Hematology Panel (if more than **7 days** from Screening sample)

- Clinical Chemistry Panel (if more than **7 days** from Screening sample)
- Clinical evaluation of mucositis (WHO Score)
- Quality of Life assessment
- Serum Pregnancy (if more than **7 days** from Screening sample)
- History of pain and opioid medication use
- Assessment of Infections

6.3.3 Study Drug Administration Visits During RT

Study visit days occur twice weekly (every 3 days +/-1 day) through the completion of RT. The first study visit must occur within 3 days of initiating RT. The study visit schedule should be adhered to and is independent of CRT administration. At study drug administration visits, the following will be performed:

- Interim Medical History
- Vital signs
- Adverse events
- Clinical evaluation of mucositis (WHO Score)
- Record details of percutaneous endoscopic gastrostomy (PEG) tube use (if applicable)
- Study Drug administration
- History of pain and opioid use
- Assessment of Infections
- Quality of Life assessment (Week 4 only)
- In addition to the above, routine safety laboratories will be obtained during Weeks 3 and 6 for:
    - Blood collection for hematology and clinical chemistry panel

6.3.4 Study Drug Administration Week 1 After RT

Study visit days occur twice weekly (every 3 days ±1 day) for the first week following completion of RT. At these study drug administration visits, the following will be performed:

- Interim Medical History
- Vital signs
- Adverse events
- Clinical evaluation of mucositis (WHO Score)
- Record details of gastrostomy tube use (if applicable)
- Study Drug administration

- History of pain and opioid use
- Assessment of Infections

6.3.5 Study Drug Administration Week 2 After RT

Study visit days occur twice weekly (every 3 days +/-1 day) for the second week following completion of RT. At these study drug administration visits, the following will be performed:

- Interim Medical History
- Vital signs
- Adverse events
- Clinical evaluation of mucositis (WHO Score)
- Record details of gastrostomy tube use (if applicable)
- Study Drug administration
- History of pain and opioid use
- Assessment of Infections
- In addition, the final day of study drug administration (last visit Week 2 post-RT) the following additional assessments will be performed:
- Blood collection for hematology and clinical chemistry panels
- Physical examination
- Quality of Life assessment

6.3.6 Week 3 Post-RT Visit

Patients will be seen once in the third week following completion of RT for the following:

- Interim Medical History
- Vital signs
- Adverse events
- Clinical evaluation of mucositis (WHO Score)
- Record details of gastrostomy tube use (if applicable)
- History of pain and opioid use
- Assessment of Infections

6.3.7 Week 4 Post-RT Visit

Patients will be seen once in the fourth week following completion of RT for the following:

- Interim Medical History
- Vital signs

- Adverse events
- Clinical evaluation of mucositis (WHO Score)
- Record details of gastrostomy tube use (if applicable)
- History of Pain and opioid use
- Assessment of Infections
- Blood collection for hematology and clinical chemistry panels

6.3.8 **Week 5 Post-RT Visit** (only to be done if WHO score is ≥2 at Week 4 Post-RT)

Patients will be seen once in the fifth week following completion of RT if the patient had an OM grade in Week 4 post-RT that was ≥2 for the following:

- Interim Medical History
- Vital signs
- Adverse events
- Clinical evaluation of mucositis (WHO Score)
- Record details of gastrostomy tube use (if applicable)
- History of Pain and opioid use
- Assessment of Infections

6.3.9 **Week 6 Post-RT Visit**

Patients will be seen once in the sixth week following completion of RT for the following:

- Interim Medical History
- Vital signs
- Adverse events
- Clinical evaluation of mucositis (WHO Score)
- Record details of gastrostomy tube use (if applicable)
- Blood collection for hematology and clinical chemistry panels
- History of pain and opioid use
- Assessment of Infections
- Physical examination
- Serum HCG pregnancy test (women only)

6.3.10 **Monthly (2- to 11-Month Post-RT) Follow-up Contacts**

All patients will be contacted at least once per month (±2 weeks) through 11 months (except for the 12 week/3 month follow-up visit) following completion of their last RT treatment through

either clinic visits or telephone contacts. For each contact, the following information that will be entered into the eCRF:

- Vital status
- Evidence of recurrence of the primary tumor
- Initiation of additional anti-cancer therapy

6.3.11 12 weeks (3-Month) Post-RT Follow-up Visit

Patients will have a clinic visit at 12 weeks (±3 weeks) and the following will be performed:

- Interim Medical History
- History of pain and opioid use
- Repeat of the same scans used at the initial tumor staging to be used in a RECIST 1.1 comparison
- Record of tumor status including evidence of tumor recurrence and additional anti-cancer therapies

6.3.12 12 Month Post-RT Follow-up Visit

Patients have their last study visit at 12 months (± 28 days) post-RT and the following will be performed:

- Interim Medical History
- History of pain and opioid use
- Evaluation of tumor status
- Repeat of the same scans used at the initial tumor staging to be used in a RECIST 1.1 comparison

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

Patients enrolled into this trial must meet **all** of the following criteria:

1. Willing and able to understand and sign an informed consent
2. Males or females age greater than or equal to 18 years
3. Biopsy-proven squamous cell carcinoma of the oral cavity or oropharynx without distant organ metastases that has been evaluated for human papillomavirus (HPV)
4. Scheduled to receive cisplatin chemotherapy of 80-100 mg/m^2 given every third week
5. Scheduled to receive a continuous course of conventional external beam irradiation delivered by IMRT as single daily fractions of 2.0 to 2.2 Gy, with a cumulative radiation dose between 55 and 72 Gy at each site
6. Planned radiation treatment fields must include at least 2 oral sites (retromolar trigone, buccal mucosa, floor of mouth, tongue, or soft palate), with each site receiving ≥55 Gy
7. All women of childbearing potential (WOCBP) and males with female partners who are WOCBP must agree to the use of effective contraception during the trial

    - Women are considered to be WOCBP following menarche and until becoming post-menopausal unless permanently sterile (hysterectomy, bilateral salpingectomy and bilateral oophorectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

      Effective contraception methods for WOCBP should be started prior to randomization and continued for a minimum of 35 days following completion of study drug administration.

    - Acceptable contraceptive methods for WOCBP are those that achieve a failure rate of less than 1% per year and include:
        - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
            - Oral
            - Intravaginal
            - Transdermal
        - Progestogen-only hormonal contraception associated with inhibition of ovulation:
            - Oral
            - Injectable
            - Implantable
        - Intrauterine device (IUD)

- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments

- Male subjects should use condoms during treatment and for 98 days following the last study drug administration period.

7.2. Subject Exclusion Criteria

Patients with any of the following criteria are **NOT** eligible for enrollment:

1. Current mucositis
2. Current clinically significant active infection that in the opinion of the Investigator would make them an unfit participant in the trial
3. Planned to receive Erbitux™ (Cetuximab) or similar targeted therapy between baseline and 6 weeks post-radiation therapy
4. Current use of prohibited therapies listed in Section 8.2
5. Prior radiation to the head and neck
6. Chemotherapy treatment within the previous 12 months
7. Tumors of the lips, sinuses, salivary glands, nasopharynx, hypopharynx, or larynx
8. Evidence of significant renal, hepatic, hematologic, or immunologic disease determined by any one of the following: (the below are examples of evidence of significant disease, not required tests)
    a. Estimated creatinine clearance <30 mL/min
    b. ALT or AST level greater than 10-fold the upper limit of normal or total bilirubin greater than 3-fold the upper limit of normal
    c. Manifestations of end-stage liver disease, such as ascites or hepatic encephalopathy
    d. Thrombocytopenia (less than 60,000 cells/mm^3)
    e. $CD4^+$ T cell count below 200 cells per µL (verification only required if there is a clinical diagnosis of HIV infection)
9. Evidence of immediate life-threatening disease or a life expectancy of less than 3 months
10. Women who are pregnant or breast-feeding
11. Participation in any study involving administration of an investigational agent within 30 days of randomization into this study
12. Any condition that, in the opinion of the Investigator, would compromise the safety of the subject or quality of the data

7.3. Patient Withdrawal Criteria

Patients have the right to withdraw from this trial at any time (as described in the informed consent document) without prejudice to further care. An investigator may withdraw a patient from the study at any time for any of the following reasons:

- The patient withdraws his/her consent or refuses follow-up evaluations.
- The patient is lost to follow-up and will not attend further study visits.
- The investigator determines that further participation would be detrimental to the patient's health or well-being.
- The patient fails to comply with the study requirements to cause harm to self or seriously interfere with the validity of the study results.
- The female patient becomes pregnant during the treatment period. In this case, treatment should be halted and the patient followed until the end of the pregnancy. If a child is born, the infant should be followed through at least 6 months of age.
- At the discretion of the site investigator if he/she feels that it is in the best medical interest of the patient.
- The patient misses more than 5 consecutive scheduled RT sessions.
- Patients withdrawn from the study will have as many of the trial assessments completed as the patient permits including blood tests and scans but not including OM scoring. All other therapies including radiation therapy, the type and frequency of chemotherapy, and oral treatments will remain at the discretion of the clinical team. Patients will be censored in the efficacy analyses at the time of withdrawal.
- Patients withdrawn from the trial will not be replaced but enrollment will continue until a minimum of 260 patients have been enrolled.

7.4. Termination of the Study

The study may be terminated early for any of the following reasons:

- A health authority or DMC requests termination of the study.
- It has been determined that the risk level associated with the experimental drug is significant and warrants termination of the study.
- Soligenix, for reasons other than safety, may terminate the study at any time by written notice of intended termination provided at least thirty (30) days prior to termination.
- The investigator or IRB/EC, for reasons other than safety, may terminate participation of this site in the study by written notice of intended termination provided at least thirty (30) days prior to termination.
- Any other clause described in the individual site Study Agreement (e.g., if GCPs or other regulatory procedures are not followed; if enrollment rate is not sufficient to meet study goals).

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug

Appropriate doses of study drug will be administered to subjects within 3 days of the first day of RT and then twice weekly (every third day ± 1 day) thereafter until 2 weeks after completion of RT.

Patients will be seen 3, 4, 5 and 6 weeks and then at 12 weeks and 12 months after the last dose of RT, but will not be treated with study drug at those times.

8.2. Concomitant Medications

Subjects will be treated on an outpatient basis. If patients require hospitalization for non-study related complications of therapy, all possible study procedures will be performed. RT and assessment of tumor burden in all subjects will be conducted as clinically appropriate, following study-specified protocols. All subjects will receive concomitant cisplatin chemotherapy (80-100 mg/m^2) for treatment of cancer of the oral cavity and oropharynx.

Concomitant drugs taken by the patient during the treatment phase and through the 6-week post-RT visit should be recorded in the eCRF. In general, the generic name of the drug should be used. Drug names, especially combination preparations, should not include the dose of each component drug in the name but should be noted in the dose- Name: "Docusate/Senna" Dose "50/8.6" rather than Name: "Docusate 50 mg - Senna 8.6 mg". Components of any mouthwash prescribed should be listed- instead of "Magic Mouthwash" recorded "Mouthwash-Maalox/Lidocaine".

The following medications/therapies should ***NOT*** be used in enrolled patients (from baseline through 6 weeks post-RT):

- Amifostine (Ethyol®)
- Benzydamine hydrochloride
- Cetuximab (Erbitux®)
- Cevimeline hydrochloride (Evoxac®)
- Glutamine as a prophylactic agent for mucositis
- Devices for mucositis including GelClair, MuGard, Episil and Caphosol
- GM-CSF (e.g., Leukine®)
- IL-11 (Neumega®)
- 'Magic mouthwash', 'Miracle mouthwash' or other mouthwash solutions containing any of the following:
    - Chlorhexidine
    - Hydrogen peroxide
    - Diphenhydramine

- Tetracycline
- Palifermin (Kepivance®) or other keratinocyte or fibroblast growth factor
- Pilocarpine hydrochloride (Salagen®)
- Povidone-iodine rinses
- Steroid rinses
- Sucralfate in suspension form (use of sucralfate tablets is not proscribed)
- Other biologic response modifiers – except hematopoietic growth factors for the management of anemia or myelosuppression
- Low level laser therapy
- Other investigational agents for mucositis

8.3. Treatment Compliance

Patients will be treated with an IV infusion witnessed by site personnel during their daily radiation treatment clinic appointments and, therefore, compliance with study clinic visits is expected to be high while the chemoradiation treatments are continuing.

Every effort will be made by the patient and the study staff to ensure that patients can complete the assigned tasks of the trial on schedule and as per protocol prior to being consented. Every effort should be made, when medically responsible, to avoid treatment breaks or delays.

8.4. Randomization and Blinding

Patients will be randomized 1:1 to SGX942:placebo using a randomization code generated by an independent statistician. Randomization will be performed using an Interactive Web Response System (IWRS) in a double-blind fashion. Each vial of SGX942 and the identically appearing placebo vials will be supplied and labeled with a unique blinded identifying code. The IWRS will assign vial(s) of the appropriate study material to be used for each patient and each infusion using this blinded code.

Patients will be stratified at randomization by HPV status, presence of a gastrostomy tube at randomization, and study site.

Given the extremely short half life of SGX942 (minutes), it is anticipated that knowledge of whether the patient received placebo or SGX942 will rarely be needed. If, however, the PI and/or the primary care clinical team believe that this information is necessary to optimally treat an enrolled patient, the clinical data management team (DSG) should be contacted (24 hour/7 day availability) using the contact directions available in the eCRF portal. The study drug assignment for that patient will be determined and confirmation of the study drug received will be immediately sent.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

SGX942 is [redacted] sterile solution for injection, supplied in glass vials containing 2.5 mL or 5.0 mL of a 60 mg/mL solution (150 mg or 300 mg of dusquetide). [redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

10. ASSESSMENT OF EFFICACY

10.1. Primary Efficacy Endpoint

Clinical evaluation of mucositis will be performed and graded by trained study evaluators in accordance with WHO Oral Mucositis Grading system, as detailed in Table 8 at each study drug administration visit and once a week through 6 weeks post-RT.

The duration of SOM is the primary endpoint for this clinical trial.

SOM is defined a WHO score of ≥3 (3 or 4). Resolution of SOM is defined as the first assessment with a WHO score <3 with no further reports of a WHO grade of ≥3. The duration of SOM is defined as the number of days from the first WHO score ≥3 to the first day with WHO score ≤3 with no further occurrence of WHO score ≥3. If the patient has not met the requirements for resolution of SOM by the 6-week post-RT visit, he/she will be considered censored at that visit (or point of discontinuation of the study, if the patient discontinues prior to that timepoint). To facilitate calculation of a log-rank test without censoring patients with desirable outcomes (no SOM), patients who do not experience SOM will be treated as having a duration of SOM of 0.01 days. The primary endpoint analysis will be conducted in the mITT population.

10.2. Secondary Efficacy Endpoints

10.2.1 Primary Secondary Analyses

The primary secondary endpoints are listed below in hierarchical order and will be compared in the mITT population.

10.2.1.1. Severity-weighted Duration of SOM (Area-Under the SOM-Time Curve)

The severity-weighted duration of SOM will be calculated by the AUC of the SOM versus time curve. This will be calculated by the formula for baseline (t_a) to time the last reported WHO score recorded (t_b):

$$AUC(t_b - t_a) = \sum_{i=a}^{b-1} \frac{(y_i + y_{i+1})(t_{i+1} - t_i)}{2}$$

where t_i represents the date of the i^{th} WHO assessment, and y_i represents the value of the i^{th} WHO assessment for WHO assessments for which the score is ≥3.

10.2.1.2. Severity-weighted Duration of UOM (Area-Under the SOM-Time Curve)

The severity-weighted duration of UOM will be calculated by the AUC of the UOM versus time curve. This will be calculated by the formula for baseline (t_a) to time the last reported WHO score recorded (t_b):

$$AUC(t_b - t_a) = \sum_{i=a}^{b-1} \frac{(y_i + y_{i+1})(t_{i+1} - t_i)}{2}$$

where t_i represents the date of the i^{th} WHO assessment, and y_i represents the value of the i^{th} WHO assessment for WHO assessments for which the score is ≥2.

10.2.1.3. Incidence of SOM

The incidence of SOM will be calculated as the percent of patients within each treatment group who have at least one WHO score ≥3.

10.2.1.4. Quality of Life

A Quality of Life Questionnaire (QoL) will be completed by each patient at Baseline, 4 weeks and at the end of study drug treatment (2 weeks post-RT) and reviewed and entered by the site personnel into the eCRF. The EORTC QLQ-C30 (version 3) and the EORTC QLQ-H&N43 instrument will be used for these assessments. The change from Baseline in the QoL at the end of the study will be compared between treatment groups.

10.2.1.5. Amount of Opioid Medication Used

At each study visit, study personnel will record the amount of opioid medication that the patient reports having taken over the previous 24 hours. Each type of medication and whether it was used because of OM pain or other types of pain will be noted in the eCRF. Each opioid dose will be converted to an "oral morphine dose equivalent dose" and the total amount of opioid used for each patient summed over each visit from baseline to 6 weeks post-completion of the radiation therapy. Patients with missing visits will have their opioid usage estimate for the missing data by using an average of their opioid use for the available visits using formula detailed in the SAP. The mean and median amount of total opioids used in each of the treatment groups will be compared.

10.2.2 Other Secondary Analyses

In addition to the primary secondary analyses performed in hierarchical order, several additional secondary analyses will be performed.

10.2.2.1. Cumulative Number of Treatment Breaks

For the analysis purposes for this study, treatment breaks will be defined as missing 3 or more scheduled consecutive RT treatment sessions. The cumulative duration of treatment breaks for each patient will be calculated by summing the actual number of treatment break days (≥3 days per break) through the final RT treatment and comparing these between treatment groups.

10.2.2.2. Duration of SOM in the ITT Population

Using the above definitions, the duration of SOM will be compared between treatment groups in all patients randomized (ITT population).

10.2.2.3. Duration of Ulcerative Oral Mucositis (UOM)

UOM is defined as a WHO score ≥2. Resolution of UOM is defined as the first assessment with a WHO score <2 with no further reports of a WHO grade of ≥2. The duration of UOM is defined as the number of days from the first WHO score ≥2 to the first day with WHO score <2 with no further occurrence of WHO score ≥2. If the patient has not met the requirements for resolution of

UOM by the 6-week post-RT visit, he/she will be considered censored at that visit (or point of discontinuation of the study, if the patient discontinues prior to that timepoint). For statistical reasons, patients who do not experience SOM will be treated as having a duration of UOM of 0.01. The analysis will be done in the mITT population.

10.2.2.4. **Assessment of Pain**

At each study visit, the patient's assessment of their pain over the previous 24 hours will be recorded by study personnel using a scale of 1-10. Patients with missing visits will have their pain estimated for the missing data by averaging their pain scores reported using the formula detailed in the SAP.

10.2.2.5. **Alternative Measurement of the Duration of SOM**

The duration of SOM defined as the number of days from the first oral examination with WHO grade ≥3 through the last assessment with a WHO score ≥3 (and not to the first assessment with a WHO grade <3) with no further reports of a WHO grade ≥3.

10.2.2.6. **Duration of SOM in the Per-Protocol Population**

The duration of SOM in the Per-Protocol Population defined as patients receiving a cumulative radiation dose of at least 55 Gy and having received all scheduled study drug doses.

11. ASSESSMENT OF SAFETY

11.1. Overall Assessments

Safety in this trial will be assessed by the following comparisons between treatment groups:

- Assessment of the incidence, type, and body system categorization of AEs
- Assessment of the incidence, type, and body system categorization of SAEs
- Assessment of the changes from baseline for hematology parameters, clinical chemistry parameters, and vital signs
- Assessment of tumor progression at 12 weeks and 12 months following completion of RT classified using the RECIST tumor status system
- The incidence and severity of infections graded using CTCAE criteria
- Assessment of mortality through the 12-month post-RT clinic visit

11.1.1 Assessment of AEs

Site personnel will question and record in the eCRF all reported AEs, as defined in Section 11.2.1 that are reported between randomization through the 6 week post-RT visit. The PI will assess of the severity of the AE using the CTCAE criteria (Appendix 1). The AEs will be coded as to preferred terminology, and body system using the Medical Dictionary for Regulatory Activities (MedDRA) using a computer auto-coder and all assignments reviewed by a blinded medical reviewer. The number of events and the number of patients with each event defined by the preferred term and by body system category will be presented. Additional tables will compare the reported AEs by preferred term and body system classification classified by CTCAE severity grade (1-5) and separately by PI assessment of relationship to study drug.

11.1.2 Assessment of SAEs

Site personnel will question and record in the eCRF all reported SAEs, as defined in Section 11.2.2 that are reported between randomization through the 6 week post-RT visit. The SAEs will be coded as to preferred terminology, and body system using the Medical Dictionary for Regulatory Activities (MedDRA) using a computer auto-coder and all assignments reviewed by a blinded medical reviewer. Summary tables including the number of events and the number of patients with each event defined by the preferred term and by body system category will be presented. Additionally, the reported SAEs by preferred term and body system classification classified by CTCAE severity grade (1-5) and separately by PI assessment of relationship to study drug. A narrative summary of the patient's SAE will be included in the final Clinical Study Report.

11.1.3 Assessment of Laboratory and Vital Signs

Each of the laboratory tests outlined in Section 6.2.5 and each of the vital signs outlined in Section 6.2.6.4 will be summarized for each collection period by treatment group as:

- Group mean

- Group standard deviation
- Group median
- Group range

Additionally, each evaluation will be summarized as a change from baseline for each patient by treatment group as:

- Group mean
- Group standard deviation
- Group median
- Group range

Using the Central Laboratory's normal ranges and standard table of normal vital signs, each assessment will be classified as "normal", "low", or "high" and shift tables for each parameter shown of each assessment by treatment group will be displayed.

11.1.4 Assessment of Tumor Progression at 12 weeks and 12-months Post-RT

Scans at 12 weeks and 12-months post-RT will be compared to the initial images using the RECIST 1.1 system as outlined in Table 9, Table 10, and Table 11. The percent of the patients categorized as having a "complete tumor response" at 12 weeks and 12 months post-RT will be compared between the treatment groups. Additionally, the percent of the patients categorized as having a "complete tumor response" or "partial tumor response" at 12 weeks and 12 months post-RT will be compared between the treatment groups.

11.1.5 Infections

Patients will be assessed at each clinical visit through the 6-week post-RT visit as to the presence of probable clinical infections. All clinical diagnoses of infections will be classified as presumed fungal, presumed viral, or presumed bacterial. The severity of each infection will be graded using the CTCAE (Appendix 1). The incidence of all reported infections, the number of patients with reported infections, the number of presumed fungal, the number of presumed viral and the number of presumed bacterial infections will be compared between treatment groups. The incidence of each type of infection (fungal, viral, and bacterial) by severity grade (1-5) will be displayed.

11.1.6 Assessment of Mortality Through the 12-month Post-RT Clinic Visit

All deaths through the 12-month follow-up visit will be collected. The number of deaths in each group will be compared using a standard chi-squared analysis. The number of deaths over time will be compared using a Kaplan-Meier survival curve and the survival curves compared using a log-rank test.

11.1.7 Progression-free Survival

The duration of progression free survival will be calculated from the date of randomization to the earliest date of the following:

- The patient died
- The patient had an imaging report of tumor progression (RECIST 1.1 evaluation of less than "Complete Response")
- The patient completed their 12 month follow-up assessment.

Patients lost-to-follow-up will be censored at the time of their last assessment.

11.2. Safety Parameters

11.2.1 Adverse Experience (AE)

Any noxious or unintended event that occurs in association with the use of an investigational agent in humans***, whether considered related to the investigational agent or not***. This definition encompasses symptoms or signs reported by the subject or detected by the investigator or other competent observer, as well as medically important deviations from normality in the results of ancillary investigations. If present at time of first dose of study drug, such AEs must be recorded as part of the medical history.

Treatment-Emergent Adverse Experience: An AE that is new in onset or aggravated in severity or frequency following entry into the study. In addition, any pathological finding on physical examination or diagnostic procedure that is new in occurrence or exacerbated in comparison with the subject's status at study entry is considered a treatment-emergent AE if it requires any medical or surgical intervention whatsoever (including, but not limited to, additional diagnostic procedures or alteration of prescribed therapy).

All AEs, whether judged to be related or not to the study drug, should be recorded in both the medical record and the eCRF. The start and resolution dates, the judgment of the severity of the AE, the judgment of the relationship of the AE to the study drug, the action taken for subsequent dose of study drug, and the outcome should be noted.

11.2.2 Serious Adverse Experience (SAE)

Any AE occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening AE
- Prolongation of existing hospitalization or subsequent need for hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medical or surgical intervention to prevent one of the above

11.3. Relationship to Study Drug

The relationship of an AE to the assigned study drug is assessed using the following definitions:

Not Related: The drug experience is clearly related to other factors such as the patient's/subject's clinical state, therapeutic interventions, or concomitant drugs.

Possibly Related: The drug experience follows a reasonable sequence from the time of drug administration and/or follows a known response pattern to the study drug, but could have been produced by other factors such as the patient's/subject's clinical state, therapeutic interventions, or concomitant drugs.

Related: The drug experience follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, and cannot be reasonably explained by other factors such as the patient's/subject's clinical state, therapeutic interventions, or concomitant drugs.

11.4. Severity of Adverse Event

A clinical determination of the intensity of an AE should be done for all reported AEs. The severity assessment should use the CTCAE grading system that assesses the severity of each AE from grades 1-5. The grading system can be found in Appendix 1.

11.5. Reporting Adverse Events

11.5.1 Adverse Events

All AEs that occur after any patient/subject has been enrolled, before treatment, during treatment, or within 6 weeks (± 4 days) following the cessation of RT treatment, whether or not they are related to the study, must be recorded in the eCRF. All AEs should be noted in the eCRF within 3 days of being recognized. Any adverse event that is either a SAE or potential SAE should be handled within the timeframes given in section 11.5.2, below. Each treatment-emergent AE should be reported spontaneously or in response to general, non-directed discussion with the attending nurse or physician (e.g., has there been any change in subject status since the last assessment period?). For each treatment-emergent AE, the investigator should obtain all the information required to complete the AE page of the case report form, in accordance with the guidelines that accompany it.

All treatment-emergent AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology consistent with the source document and on the AE page. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology. Investigators must record their opinion concerning the relationship of the AE to study therapy on the AE page.

All treatment-emergent AEs must be followed until resolution or until the 6-month follow up visit. All measures required for AE management and the ultimate outcome of the AE must be recorded in the source document and reported on the AE page. The resolution date for all recorded AEs should be entered within 3 days of determination that the AE has resolved.

11.5.2 Serious Adverse Events

All SAEs that occur after any patient/subject has been enrolled, before treatment, during treatment, or within six weeks (±4 days) following the last RT, whether or not they are related to the study, must be recorded on forms provided in the eCRF.

When the investigator, or trained designee, becomes aware that a serious or potentially serious AE (as defined above) has occurred, the site monitor or Medical Monitor must be notified

immediately (and no later than 24 hours after notification) by telephone, regardless of the relationship (or lack thereof) of the AE to study therapy.

All reports of serious or potentially serious AEs must be followed within 24 hours (or sooner at the request of the Soligenix Medical Monitor) by the completion of a serious AE form signed by the investigator. This should be emailed (or faxed if email impractical) to the site monitor ***and*** Medical Monitor.

In accordance with Soligenix SOPs and Health Authority regulations, investigators may be notified from time to time of the occurrence of serious, unexpected AEs. If such AEs are associated with the use of the study drug (i.e., there is a reasonable possibility that the AE may have been caused by the drug) and are thus deemed significant new adverse experiences or risks with respect to the drug, the investigator must promptly inform the relevant IRB/EC, in accordance with the ICH Guidance on GCPs (E6, April 1996).

FOR ADVERSE EXPERIENCE REPORTING OR MEDICAL QUESTIONS THE MEDICAL MONITOR SHOULD BE CONTACTED:

Richard Straube, MD,
Senior Vice President & Chief Medical Officer, Study Medical Monitor
Phone: +1 (609) 538-8200 x 30

[redacted]

Email: rstraube@soligenix.com

If above contact is not accessible, please call:

Soligenix, Inc., 29 Emmons Drive, Suite B-10, Princeton, NJ 08540
Phone: +1 (609) 538-8200

FOR ADDITIONAL ASSISTANCE:

For additional assistance, please contact your clinical research monitor(s) OR

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[redacted]

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11.6. Data Monitoring Committee

An independent DMC consisting of one Biostatistician and two clinicians that includes at least one Oncologist with expertise in head and neck cancer will be formed to monitor the safety and conduct of the study on an ongoing basis. Parameters to be evaluated will include AEs (clinical and laboratory), number of dropouts overall, those withdrawals specifically due to worsening of disease, and those withdrawals due to failure to improve in a timely fashion. Data will be presented as to the DMC as treatment groups A and B to maintain the study blind. However, the DMC, as part of its charter to evaluate and ensure the safety of subjects participating in the trial, has the authority to unblind the data as appropriate.

The DMC may request any safety data including, but not limited to, SAEs, AEs, and laboratory values. The DMC may also request any efficacy data including, but not limited to the primary and secondary outcomes to evaluate benefit to risk.

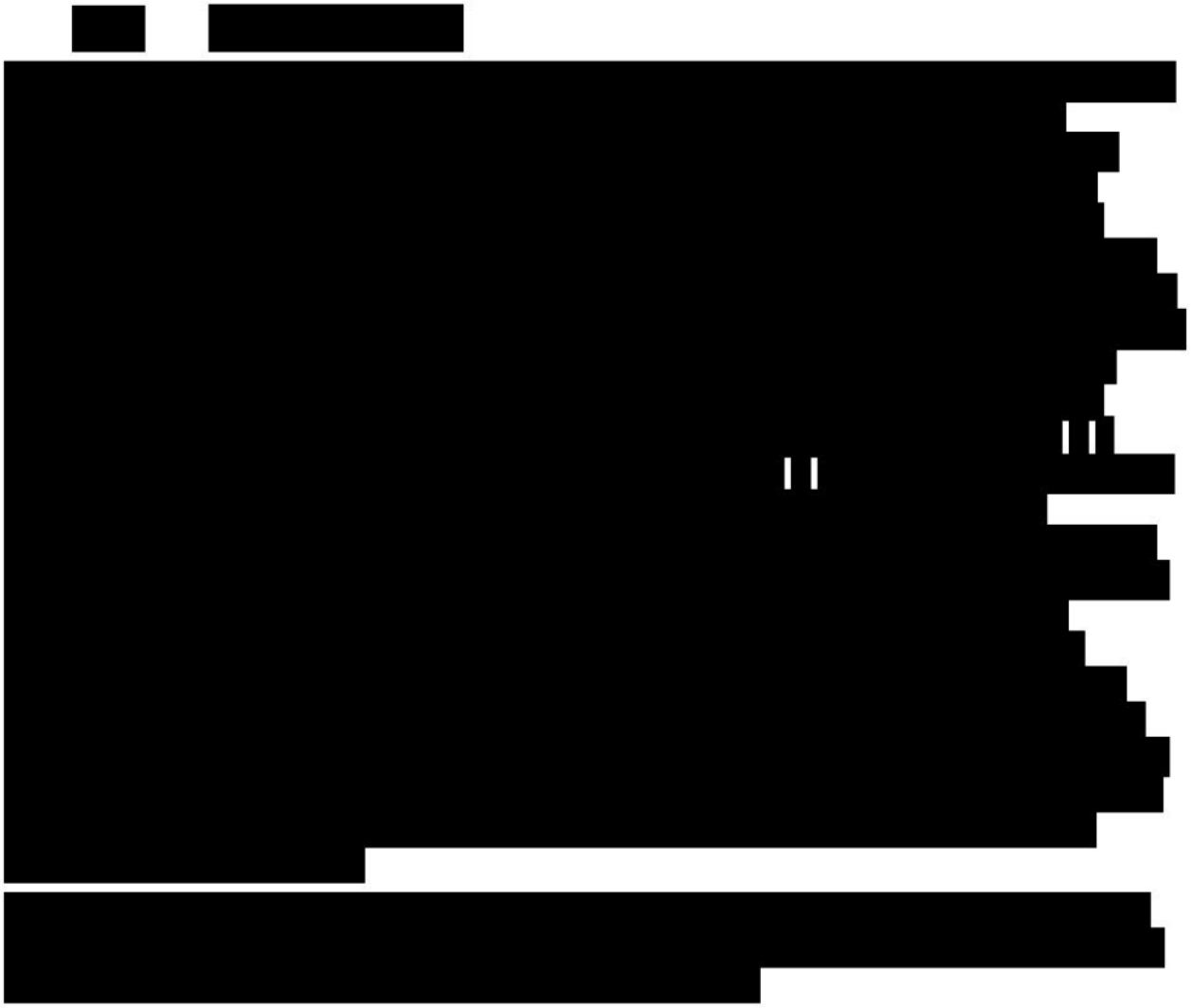
The DMC will review unblinded data at the interim analyses and make recommendations to halt the trial for overwhelming efficacy, or safety concerns, or for futility; continue the trial as written; or resize the trial based on the placebo duration of SOM.

12. STATISTICS

12.1. Overview

Complete details of analyses and relative order of importance of each analysis are more fully delineated in the Statistical Analysis Plan.

Given the anticipated non-Gaussian distribution of values for duration of OM, the severity-weighted OM calculations (AUC), and the days to onset of OM, treatment groups will be compared for these variables using a log-rank test of the differences in the duration of SOM between the SGX942 and placebo treated groups. The incidence of OM, percent of RECIST complete responders, and percent of patients with each category of infection will be compared using chi-squared tests. The primary analysis population will be patients who have received enough radiation exposure to put them at significant risk of developing SOM (defined as a cumulative radiation dose of at least 55 Gy).



12.3. Final Analysis

Upon completion of enrollment, the study database is to be locked, released, and analyzed in two parts, the first being an analysis of data through the 6-week visit from the last RT for the last patient, and the second final analysis of all data including all long-term visit data. During these two data analyses, all site personnel will remain blinded as to individual patient dose-group assignments.

12.4. Sample Size Calculation

Sample size assessments are based on testing the hypothesis of superiority with a two-sample log rank test using the median duration of SOM, an equal allocation ratio, a 90% power (1-β), and an α level of 0.05. In the Phase 2 clinical trial, the median duration of SOM was 30 days in the placebo group and 10 days in the 1.5 mg/kg SGX942 treatment group. Because of the variability of reported results for SOM in patient population, a conservation assumption was made that the median duration of SOM among patients receiving a minimum of 55 Gy of cumulative radiation will be 13 days in the placebo group and 8 days in the SGX942 group. Using this assumption, approximately 95 evaluable patients per arm (190 patients total) will need to complete the trial.

[redacted]

12.5. Selection of Primary Analysis Population

Given that OM does not occur at a significant rate in patients that have not received at least 55 Gy of cumulative radiation, the primary analysis population will be limited to those patients that have received at least 55 Gy of radiation. Only those patients that receive sufficient radiation therapy are at risk of developing the disease (i.e., SOM). Should SGX942 reduce the most severe cases of OM prior to reaching 55 Gy of radiation such that there is a reduced dropout rate from anticancer therapy, the worst cases of OM in the placebo group, but not the SGX942 group, will be eliminated from the analyses. Thus, if bias is introduced, it is likely to lead to a conclusion that SGX942 is less efficacious than it actually is.

The primary efficacy analysis will be based on this mITT population that is defined as all randomized subjects receiving a minimum of 55 Gy of cumulative radiation analyzed per treatment groups defined by their randomization treatment assignment.

12.6. Direct Access to Source Data/Documents

It is the responsibility of the Principal Investigator (PI) and the participating institution to assure that appropriate trial-related monitoring, audits, IRB/EC review, and regulatory inspection(s) can be carried out by assuring direct access to source data/documents.

12.6.1 Study Monitoring

It is the responsibility of the PI and site personnel to assure that the data recorded in the CRFs are accurate, complete, and can be verified from the medical records.

In accordance with the Guidelines for the Monitoring of Clinical Investigations presented in the International Conference on Harmonisation (ICH) Guidance on GCPs (E6), Soligenix will select, either directly or through subcontract, qualified individuals to monitor the progress of the study and adherence to protocol by the individual clinical sites.

12.6.2 Pre-study Evaluation

This initial encounter with the site will establish that the site has all of the necessary elements to successfully participate in the proposed protocol including adequate trained staff, adequate free time of the staff, adequate facilities for safe and proper trial conduct, evidence for potential enrollment of suitable patients, adequate research pharmacy support, the presence of an IRB/EC meeting the local and FDA requirements, and a commitment for training of all involved staff on the protocol.

12.6.3 Site Initiation Visit

The Medical Monitor (or trained designee) will initiate the study after on-site training of the participating staff at the institution. Topics covered will include training on:

- The investigational status of the study drug and the requirements for its accountability
- Background on the study drug
- Details of the protocol including patient selection, study drug administration, procedures to be performed, and visit schedules
- Critical nature of obtaining informed consent in accordance with the Declaration of Helsinki and ICH Guidance on GCPs (E6) before enrolling each subject in the study
- The obligation to ensure IRB review and approval for the study, including the protocol, amendments, ICF and any advertisements, is obtained prior to its initiation at his/her clinical site, to ensure continuing review of the study by the IRB, and to keep Soligenix informed of such approval and subsequent actions concerning the study

12.6.4 Monitoring Visits

Soligenix or their trained designee will perform on-site monitoring visits as frequently as it deems necessary. At these visits, the site monitor will compare the data entered into the eCRF with the source documents and check for protocol compliance including a record of informed consent, enrollment criteria, all subject assessments, all adverse experiences, and all concomitant medications. In addition, study drug and supporting records will be reviewed. Additionally, they assure that all serious, life-threatening or fatal adverse experiences are being reported immediately [and in no case later than twenty-four (24) hours after the event] to the Medical Monitor or designee at Soligenix.

Findings from these reviews will be discussed with the investigator and staff. Completed pages of the eCRF will be evaluated at each visit. The dates of the monitoring visits will be recorded in a sign-in log that will be kept at the site. The study coordinator and investigator are expected to be available for questions, the source documentation readily available, and a suitable environment provided for review of study-related documents.

12.6.5 Close-out Visit

The clinical research monitor(s) will perform an end of trial visit to ensure that:

- All drug reconciliation forms are accurate and complete.
- All unused study drug is returned to the appropriate location.
- All data issues are resolved and eCRF are completed and verified.
- The IRB has been notified that the study has been completed.
- The investigator at each site is aware that the study has been completed and no further subjects are enrolled.

12.7. Audits and Inspections

Health Authorities (e.g., FDA, the EMA, or country Health Authorities), in the person of a trained and properly authorized employee, may request access to all study records, including source documents, for inspection and copying. The investigator will immediately notify Soligenix of any upcoming inspections.

Periodic auditing inspections may also be conducted by a representative of the Quality Assurance Department of Soligenix or its trained designee(s).

13. INSTITUTIONAL REVIEW BOARD (IRB)/ETHICAL COMMITTEE (EC)

All participating centers must have in place either an IRB or the EC that meets all of the criteria outlined in Section 3 of the ICH "Guidance for Industry; E6 Good Clinical Practice: Consolidated Guidance". Copies of the IRB/EC membership list and procedures should be provided to the Soligenix.

It is the responsibility of the site's Principal Investigator (PI) to obtain IRB/EC written approval of the protocol, the Informed Consent Form, patient compensations details, and any advertisements to be used in conduct of the trial. No patient can be enrolled into the trial prior to obtaining these documents. It is also the site's PI responsibility to:

Assure that no deviations from, or changes of, the protocol should be initiated without prior written IRB/EC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s))

Promptly report to the IRB/EC:

- All deviations from, or changes to, the protocol to eliminate immediate hazards to the trial subjects
- Any changes increasing the risk to subjects and/or affecting significantly the conduct of the trial
- All AEs that are both serious and unexpected whether seen at that institution or reported from Soligenix
- Any new information that may affect adversely the safety of the subjects or the conduct of the trial.

14. QUALITY CONTROL AND QUALITY ASSURANCE

It is the responsibility of the PI or his/her designee to assure that all information in the eCRF is accurate and complete. The eCRF will perform immediate internal consistency checks to minimize potential for erroneous data (e.g., date of birth after date of randomization). Soligenix will use monitors to review entered data in the eCRF and make periodic site visits to compare eCRF data with source documents. Periodic interim audits from Soligenix's Quality Department or their designee will be conducted to assure that all ICH guidelines are being followed and identify any systemic problems with the data or procedures. Final audits will be conducted at representative sites.

15. ETHICS

15.1. Ethical Review of Trial

The final study protocol, including the final version of the Subject Information and Consent Forms, must be approved in writing by IRB/EC before enrollment of any subject into the study. The PI or their designee is responsible for informing the IRB/EC of any SAEs and amendment(s) to the protocol as per regulatory requirements.

15.2. Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles in the Declaration of Helsinki, GCPs and applicable regulatory requirements.

15.3. Written Informed Consent

The Investigator will ensure that the subject or a legally authorized representative of the subject are given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. ***The subject's signed and dated informed consent must be obtained before conducting any study specific procedure***. The consent form that is used must meet the requirements as outlined in the ICH Guidance on GCPs (E6) and must be approved by both the reviewing IRB/EC and by Soligenix.

15.4. Subject Data Protection

The Subject Information and Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality. Subjects in this database will be identified by initials or enrollment code/subject number only. An authorized representative of a regulatory authority may require direct access to parts of the trial site records relevant to the study, including subjects' medical history for data verification purposes.

15.5. Financial Disclosure

The FDA has issued regulations (21 CFR Part 54) that require Sponsors (in this case Soligenix) to submit complete and accurate certification or disclosure statements to certify the absence of certain financial interests of clinical investigators and/or disclose those financial interests, as required, when clinical studies are submitted to the FDA in support of marketing approval of a new drug application (NDA). These regulations are intended to ensure that financial interests and arrangements of clinical investigators, that could affect reliability of data submitted to the FDA in support of marketing approval, are identified and disclosed by the Sponsor.

Regardless of the location of the clinical site, all clinical investigators participating in this clinical trial shall be asked to disclose proprietary (e.g., patent, licensing agreement) and financial (e.g., stock options, royalty) interests as they pertain to Soligenix, prior to participating in the study. In addition, clinical investigators will be required to consult with Soligenix before acquiring any financial interest in the company and must disclose any change in their proprietary

or financial interests if it occurs during the course of the study and for one year following study completion. Clinical investigator is defined under Title 21 CFR Part 54 as an investigator or sub-investigator listed on the FDA Form 1572 that is directly involved in the treatment or evaluation of research subjects. The requirement for proprietary and financial disclosure also includes any ownership by the spouse or any dependent child of the investigator.

If the FDA determines that the financial interests of any clinical investigator raise serious questions about the integrity of the data, the FDA will take any action it deems necessary to ensure the reliability of the data, including:

Initiating agency audits of the data derived from the clinical investigator in question;

Requesting that the Sponsor submit further analyses of data, e.g., to evaluate the effect of the clinical investigator's data on overall study outcome;

Requesting that the applicant conduct additional independent studies to confirm the results of the questioned study; and/or

Refusing to treat the covered clinical study as providing data that can be the basis for an agency action.

If the Sponsor does not include certification or disclosure, or both, if required, or does not certify that it was not possible to obtain the information, the FDA may refuse to file the NDA.

16. DATA HANDLING AND RECORDKEEPING

16.1. Inspection of Records

As noted in Section 13.6, it is the responsibility of the PI and the participating institution to assure that appropriate trial-related monitoring, audits, IRB/EC review, and regulatory inspection(s) can be carried out by assuring direct access to source data/documents. These inspections may be conducted by Soligenix or its designee or representatives of the FDA, EMA, or local Health Agencies.

16.2. Retention of Records

It is the joint responsibility of both the site PI and the institution to take measures to prevent accidental or premature destruction of all study documents including the source documents. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product; or 7 years since the close-out of the clinical trial. Soligenix will inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reason withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Soligenix must be notified in writing and approve of the name and address of the new custodian.

16.3. Publication Committee

The Sponsor, Soligenix, is committed to the prompt publication of the results of this trial regardless of the outcome. A Publication Committee will be appointed to review and prepare a manuscript for submission to an appropriate peer-reviewed scientific journal. Membership to the committee will be offered, at a minimum, to the study's PI, the 6 sites enrolling the highest number of evaluable patients into the trial, the study statistician, and representatives of Soligenix. Other members may be appointed at the initial Publication Committee meeting.

17. INVESTIGATOR AGREEMENT

I have read the foregoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein, in accordance with local and federal regulations, Good Clinical Practices and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the study drugs and the conduct of the study.

I will use only the informed consent form approved by the Institutional Review Board/Ethics Committee and Soligenix and will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board/Ethics Committee responsible for this study.

I further agree that the Health Authorities, Soligenix, or their designee(s) shall have access to any source document from which case report form information may have been generated.

I agree that I and all investigators listed on the FDA Form 1572 shall inform Soligenix of any equity interest in the company prior to and during participation in this trial. I further agree that I and all listed investigators will consult with Soligenix before acquiring any financial interest in the company during the study and for one year after the study's completion.

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Investigator's Signature Date

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Name of Investigator (Typed or Printed)

18. REFERENCES

1. Yu, H.B., et al., *Sequestosome-1/p62 is the key intracellular target of innate defense regulator peptide.* J Biol Chem, 2009. **284**(52): p. 36007-11.
2. North, J.R., et al., *A novel approach for emerging and antibiotic resistant infections: Innate Defense Regulators as an agnostic therapy.* J Biotechnology, 2016. **226**: p. 24-34.
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7. Sonis, S.T., *New thoughts on the initiation of mucositis.* Oral Dis, 2010. **16**(7): p. 597-600.
8. Mehta, C.R. and S.J. Pocock, *Adaptive increase in sample size when interim results are promising: a practical guide with examples.* Stat Med, 2011. **30**(28): p. 3267-84.