Phase II, Open-Label Study to Evaluate Lazanda in Cancer Patients Receiving Palliative Radiation

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Study Agent: Fentanyl nasal spray, Lazanda®

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

UCSD Principal Investigator

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Printed Name

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Signature Date

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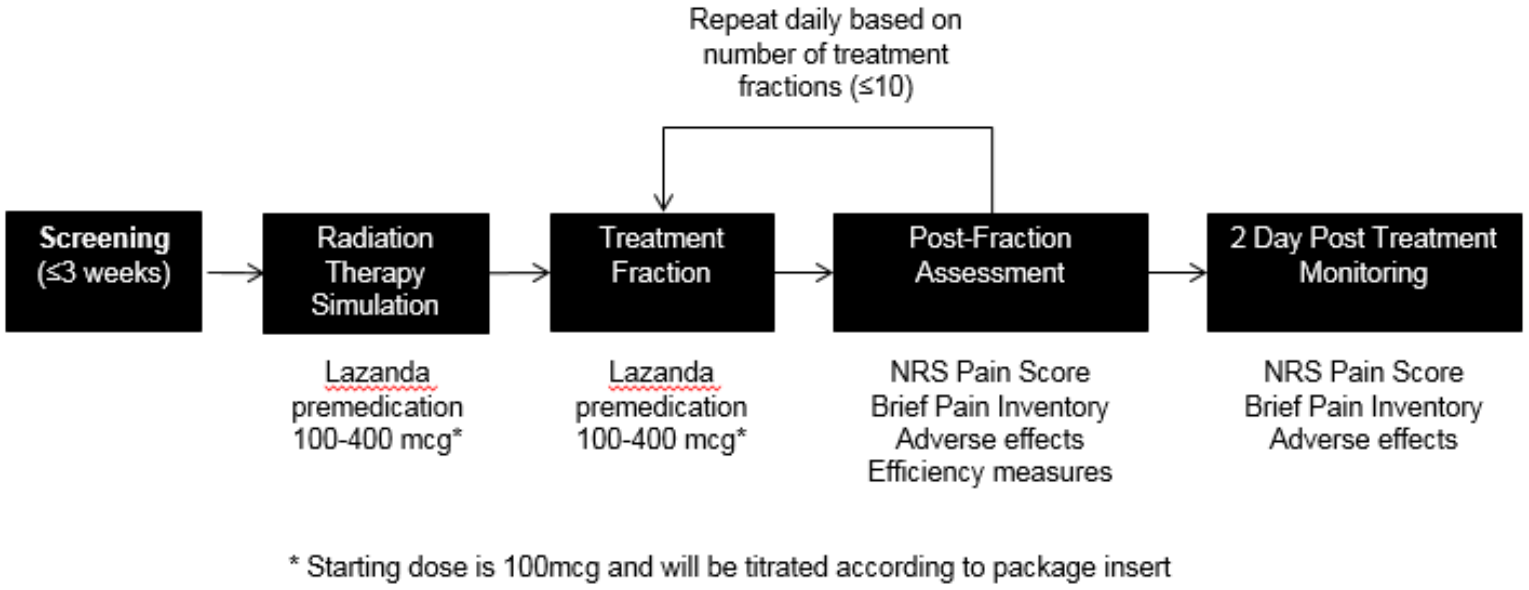
LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine transaminase
AST	Aspartate Transaminase
BPI-sf	Brief Pain Inventory-short form
BTCP	Breakthrough Cancer Pain
BUN	Blood Urea Nitrogen
cGy	Centigray
Cmax	Maximum Concentration
CNS	Central Nervous System
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTRI	Clinical and Translational Research Institute
CURES	Controlled Substance Utilization Review and Evaluation System
CYP	Cytochrome P450
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
HEENT	Head, Eyes, Ears, Nose, and Throat
HIPAA	Health Insurance Portability and Accountability Act
HRPP	Human Research Protections Program
ICH	International Conference on Harmonization
IDS	Investigational Drug Services
IQR	Interquartile Range
IR	Immediate Release
IRB	Institutional Review Board
IMRT	Intensity Modulated Radiation Therapy
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NRS	Numerical rating system
NSAID	Non-steroidal Anti-inflammatory Drug
ORT	Opioid Risk Tool
PDMP	Prescription Drug Monitoring Program
PI	Pain Intensity
PID	Pain Intensity Difference
prn	As needed
REMS	Risk Evaluation and Management Strategy
RT	Radiation Therapy

SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiation Therapy
SD	Standard Deviation
SPID	Sum of Pain Intensity Differences
SRS	Stereotactic Radiosurgery
TIRF	Transmucosal Immediate-Release Fentanyl
Tmax	Time to Maximum Concentration
UPR	Unanticipated Problems involving Risk to subjects or others

STUDY SCHEMA



* Starting dose is 100mcg and will be titrated according to package insert

STUDY SUMMARY

Title	Phase II, Open-Label Study to Evaluate Lazanda in Cancer Patients Receiving Palliative Radiation
Short Title	Lazanda for Cancer Pain with Palliative Radiation
Phase	Phase II
Methodology	Single-center, open-label case series study
Study Duration	The anticipated total duration of this study is 1 year. Individual subject participation is limited to approximately 4-5 weeks.
Study Center(s)	University of California, San Diego (UCSD) Moores Cancer Center UCSD Medical Center - La Jolla
Objectives	**Primary Objective** Our primary objective is to assess the change in patient reported positional pain intensity (PI) as measured by an 11-point numerical rating scale (NRS-11) in cancer patients with bone metastases assessed at each daily palliative radiation fraction. Our primary objective will be measured using the pain intensity difference (PID) of the NRS-11 from baseline to 15-minutes post administration (PID_{15}= PI_{0-} PI_{15}). **Secondary Objectives** Our secondary objectives are to: 1) Assess change, baseline to 15 minutes, in patient reported pain severity using the Brief Pain Inventory Short Form (BPI-sf).[1] 2) Evaluate adverse effects associated with Lazanda use utilizing the NCI CTCAE version 4.03 before and after palliative radiation. 3) Contribute to the body of knowledge to improve patient care measures that address discomfort associated with radiotherapy for patients with bone metastases. **Exploratory Objective** To assess the impact on radiation treatment delivery efficiency. This will be quantified by determining the total time of radiation treatment.
Number of Subjects	6
Diagnosis and Main Inclusion Criteria	Patients with a pathologically-confirmed solid tumor or hematologic malignancy with symptomatic bone metastases. **Key Inclusion Criteria:** 1. Patient is planned to receive hypofractionated palliative radiation ≤ 10 fractions. 2. Patient must be opioid-tolerant (≥60mg morphine or equivalent) and on a stable dose of oral opioids for ≥ 1 week. Stable baseline opioid dosage defined as a dosage that does not fluctuate by > 50% from the average dosage over one week prior to screening. 3. Patient must be on a stable dose of adjuvant pain therapies for one week prior to screening or after 4-5 half-lives of adjuvant

	pain therapies (i.e., glucocorticoids, NSAIDs, anticonvulsants, pharmaceutical cannabinoids, tricyclic antidepressants). 4. Patient is ≥ 18 years of age. 5. ECOG Performance Status ≤ 3 6. Negative pregnancy test prior to initiating study treatment for females of childbearing potential. **Key Exclusion Criteria** 1. Patient is currently receiving or has received another investigational agent within 30 days or monoamine oxidase inhibitor within 14 days prior to study drug administration. 2. Patients who require immobilization with a thermoplastic mask for radiation treatment. 3. Patient is planned to receive interventional procedures (i.e., surgery) that may affect study outcomes. 4. Patient has a history of hypersensitivity to fentanyl or opioids. 5. Patient is pregnant or nursing. 6. Patient is being treated with oxymetazoline for allergic rhinitis or has a disorder or current medication use likely to adversely affect normal functioning of the nasel mucosa. 7. Patient has uncontrolled or rapidly escalating background pain. 8. Patient has bradyarrhythmia. 9. Patient is medically unstable. 10. Patient is thought to be at risk for misuse, abuse, addiction or overdose for Schedule II controlled substance, as evidenced by an Opioid Risk Tool (ORT)[2] score ≥ 8 and review of the California Prescription Control Monitoring Program (PDMP) Controlled Substance Utilization Review and Evaluation System (CURES) report demonstrates multiple prescribing providers and/or multiple pharmacies in the last 30 days.
Study Product(s), Dose, Route, Regimen	Lazanda (fentanyl) nasal spray is supplied as a 5-mL bottle containing 8 sprays of 100 mcL of solution containing either 100 mcg or 400 mcg fentanyl base. Lazanda will be self-administered intranasally by subjects participating in this study. Subjects will undergo dose titration with Lazanda to determine the minimum effective and tolerable dose during their radiation simulation visit. This dose will be used as pre-medication prior to any further radiation therapy.
Duration of administration	Subjects will receive Lazanda at their radiation simulation visit and again as pre-medication prior to each radiation treatment (fraction), for an estimated treatment period of 10 days based on the patient's radiation treatment plan.
Statistical Methodology	Descriptive statistics will be used to characterize overall pain change (base to 15) and pain change (base to 15) per treatment day (1,…,n). To analyze our secondary aim, change in our secondary aim, change in patient reported pain severity; we will use the BPI-sf. The BPI-sf will be used to calculate "worst pain" (calculated as the arithmetic mean of the four severity items measuring pain severity

	in the BPI-sf). We will assess changes in BPI-sf using the same approach as our primary aim. Namely, change in BPI-sf "worst pain" score will be analyzed using a linear mixed-effects model to account for the repeated daily dosing. Modeling the difference in BPI-sf from baseline and 15 minutes at each fractionation visit; with a fixed effect for time and a subject level random intercept to account for within-patient variability. Descriptive statistics will be provided for overall pain severity change and pain severity change at each treatment day (1,…,n). As part of our secondary aim we will also provide descriptive statistics for adverse effects associated with Lazanda use utilizing the NCI CTCAE version 4.03 stratified as before and after palliative radiation. Our exploratory aim will assess the impact of Lazanda on treatment delivery efficiency. This will be assessed by comparing treatment delivery efficiency in the Lazanda treated patients to the historic average. To assess this we will quantify each subjects average total time on the treatment table (averaged across each subjects fractionation visits, in minutes). This average will be compared to the clinic's historic average of 6 minutes using a one-sample t-test of the null hypothesis that the average time on the treatment table for Lazanda study patients equals 6 minutes. As a further exploratory aim we will also consider the effects of baseline pain intensity score, 24-hour opioid use (oral morphine equivalents) and total treatment time at each fraction (minutes) on change in pain intensity (PID_{15}) by including each of them as fixed effects in the linear mixed-effects models. This trial will enroll approximately **6 subjects** meeting the eligibility criteria described above. Conservatively assuming a 10% drop out rate, this will leave an analytic sample size of 5.

SCHEDULE OF EVENTS

	Screening (≤21 days from baseline)	Radiation Therapy Simulation[7] (≤14 days RT)	Radiation Fraction (Daily, up to 10 fractions)	Post Treatment Follow-Up (Daily, for 2 days)
Informed consent	X			
Medical and surgical history	X			
Demographics	X			
Eligibility criteria	X			
ECOG Performance status	X	X	X	
Document location of bone lesion	X			
Pregnancy test (if applicable)[1]	X			
Physical exam	X	Per routine care frequency		
Vital signs	X	Per routine care frequency	Per routine care frequency	
Weight	X	X	X	
Concomitant medications		X	X	X
Adverse events		X	X	X[4]
Comprehensive metabolic panel	X[5]	Per routine care frequency		
Record baseline 24-hour opioid dose	X			
Record total time in radiation therapy unit		X	X	
Record recumbent time		X	X	
Lazanda dispensing & administration		X[6]	X[6]	
Radiation Therapy (hypofractionation)			X	
Study drug diary		X	X	
Brief Pain Inventory Short Form	X	X	X	X
Numerical Rating System Pain Score[2]		X	X	X
Patient medication use diary[3]	X	X	X	X
Patient nausea/vomiting diary		X	X	X
Patient laxation diary		X	X	X

1) Females of childbearing potential only; must be performed within 72 hours of baseline.
2) NRS Pain Score will be collected at a total 2 events: (1) radiation therapy simulation, and (2) at each radiation fraction (up to 10 fractions total). At each event, NRS pain scores will be recorded at T-15 (15 minutes prior to laying down on treatment surface), T0 minutes (laying down on treatment surface), and T+15 after laying down on the treatment surface.(Appendix I- NRS Scale log)
3) To include a record of any anticancer therapy, vitamins, homeopathic/herbal remedies, nutritional supplements, opioid medication use, over-the-counter analgesics, and all other over-the-counter and PO medication use.
4) Patients will be monitored for adverse events until 30 days following the last study drug administration.
5) Serum chemistries performed within six weeks of baseline may be used to fulfill screening requirements.
6) Lazanda will be self-administered by the subject 15 minutes (± 5 minutes) prior to laying on the hard surface.
7) If the 100-mcg dose does not achieve adequate pain control at the first assessment of the simulation visit, the subject will receive a second dose 2 hours later as per label until the optimal dose is obtained. If not practical the subject will delay or reschedule the next assessment of the simulation (within a 14 days period) or XRT delivery.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

1.1.1. Breakthrough Cancer Pain and Use of Opioids

Pain is one of the most common symptoms for cancer patients. A subtype of pain is breakthrough cancer pain (BTCP), which is generally considered as any transitory pain experienced while a cancer patient has a controlled baseline pain management regimen in place.[3] The time course of BTCP is characterized by a rapid onset of intense pain with a maximum intensity occurring around 15 minutes, followed by a short duration (median ~60 minutes) or plateau period.[4,5] The prevalence of cancer patients presenting with pain ranges from 30-40% at the time of diagnosis and increases up to 70-90% in advanced stages.[6] The etiology of cancer pain can be attributed to the tumor itself as well as to treatments such as surgery, chemotherapy, or radiation.

Opioids are used to treat moderate to severe BTCP and are considered the highest, “Step 3,” level of pain management by the World Health Organization.[7] Oral short-acting opioids (e.g. morphine immediate-release [IR], oxycodone IR, and hydromorphone) have an estimated onset of action of 30-45 minutes and duration of effect of 3-6 hours. Even though the onset of action is quicker with short-acting opioids compared to long-acting opioids, 30-45 minutes may be too prolonged when experiencing BTCP. During a BTCP episode, parental opioids may be needed. An alternative to parental opioids and/or short-acting opioids for BTCP treatment is transmucosal immediate-release fentanyl (TIRF), such as a pectin-based nasal spray. In contrast to oral short-acting opioids, TIRFs have an immediate onset of action within minutes and duration of action of 1-2 hours. The onset of action and duration of action for a pectin-based nasal spray associates well with the time course of BTCP [5,8].

1.1.2. Radiation Therapy

Radiation therapy, also called radiotherapy, X-ray therapy or irradiation, uses high doses of radiation energy to destroy or damage cancer cells. Radiation breaks down DNA inside cancer cells, reducing cell growth by restricting cell division. Although surrounding normal cells may be affected by radiation, most healthy cells recover and resume their regular functions. Unlike chemotherapy, which exposes the entire body to cancer-directed therapy, radiation therapy is a localized treatment. Radiation therapy is a common treatment for many types of cancer.

There are two main types of radiation therapy: external beam radiation therapy and internal beam therapy (brachytherapy). External beam radiation therapy is the most widely used type of radiation therapy, and can be used to treat large areas of the body. Palliative radiation therapy is typically delivered using 3-dimensional conformal radiotherapy (3DCRT) to direct radiation therapy towards at tumors while minimizing exposure to sensitive normal structures near the tumor in order to avoid treatment-related side effects. **Palliative radiation treatments average 6 minutes, usually last 15 minutes or less, and are completed once a day, five days a week, up to 10 days in duration**.

Advanced cancer patients often require palliative radiotherapy to treat cancer-related symptoms. A total dose of safe and effective radiotherapy is determined quantified in centigray (cGy) and this total dose is delivered over several treatments called *fractions*. Palliative radiation therapy regimens are typically delivered in daily doses of 300-800 cGy per day. This approach

is also known as hypofractionation. Precise delivery of radiation requires patients to lie still on a hard, flat surface that can result in significant acute pain, especially in the setting of painful bone metastases.

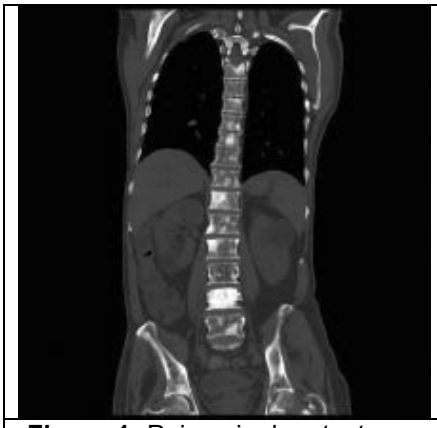


Figure 1: Pain spinal metastases on CT scan.

Figure 2: Patient in recumbent position during radiation therapy

Radiation Oncology at UCSD

UCSD Moores Cancer Center offers a comprehensive radiation oncology center with advanced radiation therapy services available, including:

- External beam radiation, which 3DCRT, intensity-modulated radiation therapy, image-guide radiation therapy, and volumetric-modulated arc therapy
- Stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT)
- Brachytherapy (internal radiation therapy)
- Proton therapy

Radiation therapy is a **five-step** process:

1) During **consultation**, the patient meets with a physician and other members of the radiation oncology team to discuss best treatment options.
2) A CT **simulation** is the most accurate way to precisely define the radiation treatment area. Simulation will determine a patient's proper positioning on the treatment table that will be used throughout the course of treatment. Customized immobilization devices (to help patients remain still during treatments) are often created during simulation sessions. Small tattoos may be used to ensure proper alignment and treatment delivery.
3) Using information from the CT simulation, dosimetrists work with the radiation oncologist and medical physicist to develop a **treatment plan,** which includes a total radiation dose (cGy), consideration of minimizing exposure to healthy tissue, and the number of fractions.
4) **Radiation Treatment** usually begins less than one week after the simulation appointment. Radiotherapy treatments are usually five days per week with the total number of fractions determined by the treating physician. At each appointment, a therapist will position the patient on the table exactly as they were at the time of simulation.
5) **Follow-up Care** visits are intended to monitor patient progress and address any side effects. These appointments are generally scheduled at three or six-month intervals.

The Radiation Oncology department, located at the UCSD La Jolla campus adjacent to the Moores Cancer Center, is comprised of a team of physicians and medical physicists with expertise in leading-edge treatments and technologies, including 11 radiation oncologists, 11

radiation nurses, 22 radiation therapists as well as social workers who specialize in radiation oncology.

1.1.3. Treatment of Pain During Palliative Radiation

Advanced cancer patients often require palliative radiotherapy to treat cancer-related symptoms. Precise delivery of radiation requires patients to lie still on a hard, flat surface, which can result in significant acute pain and/or BTCP, especially in the setting of painful bone metastases. Ideally, this acute treatment-related pain associated with lying on the radiation treatment table could be pretreated with a short-acting opioid with a rapid onset of action. The outpatient radiation oncology setting limits the use of parenteral opioids. Current care for most cancer patients receiving hypofractionated radiation is an oral opioid pre-medication, which again is characterized by a one-hour onset of action and duration of effect of 3-6 hours, which does not associate with the time course of BTCP. A fentanyl pectin-based nasal spray would be ideal in this cancer patient population to treat acute, episodic, BTCP pain and maximize radiation treatment delivery efficiency given its quick onset of action and convenient mode of delivery.

1.2 Study Agent(s)

Fentanyl pectin nasal spray (Lazanda is commercially available and indicated for the management of BTCP in adults 18 years of age and older who are already receiving and who are tolerant to opioid therapy for treatment of cancer pain. Lazanda's mechanism of action is a pure opioid agonist. Lazanda pharmacokinetics in healthy subjects and in patients with a history of allergic rhinitis have been published [9-11]. In summary, median (range) time to maximum concentration (T_{max}) is 15-30 (10.2-60) minutes. After single dose administration, maximum concentrations (C_{max}) ranged from 0.3 to 1.74 ng/mL; elimination half-life is approximately 5.5 to 9.7 hours. Fentanyl is metabolized in the liver and intestinal mucosa to norfentanyl by cytochrome P450 (CYP) 3A4. Concomitant use of Lazanda with a CYP3A4 inhibitor (***Appendix B***) may result in a potentially dangerous increase in fentanyl plasma concentrations, which could prolong adverse drug effects. Patients receiving Lazanda who begin or increase the dose of a CYP3A4 inhibitor drug should be carefully monitored for signs of opioid toxicity. More than 90% of fentanyl is eliminated via biotransformation to N-dealkylated and hydroxylated inactive metabolites. The metabolites are mainly excreted in urine.

In a randomized, double-blind, placebo controlled study, cancer patients (n=73) were titrated to an effective pain relief dose (100, 200, 400, or 800 mcg) of Lazanda. The sum of pain intensity difference at 30 minutes ($SPID_{30}$) was 6.57 ± 4.99 (mean ± SD) and 4.45 ± 5.51 for Lazanda versus placebo, respectively ($p<0.05$). Other secondary pain measures including pain intensity (PI) scores, pain intensity difference (PID), and pain relief were all statistically significant compared to placebo at 10, 15, 30, 45, and 60 minutes after administration. Decreases in pain intensity by 2 or more were seen in 49% and 63% of patients 15 and 30 minutes after fentanyl pectin nasal spray administration.[12] These results, specifically a statistically significant higher SPID and decreased pain intensity, are consistent in another randomized, placebo controlled, study in cancer patients (n=83).[13]

In comparison to morphine sulfate IR, higher PID scores and a greater proportion of patients achieving >33% or >2 point pain intensity score reduction have been reported with Lazanda®.[14,15] In one study, pain intensity difference at 15 minutes (mean ± SD) was 3.0 ± 0.2 and 2.7 ± 0.2 ($p<0.05$) for Lazanda and morphine sulfate IR, respectively.[15] Decreases in pain intensity by 2 or more was seen in 52.4% and 45.4% of patients ($p<0.05$) 10 minutes after Lazanda and morphine sulfate IR administration.[14] In another study, PI scores after 5 minutes

(5.6 vs. 5.8) and after 20 minutes (3 vs 3.4) were significantly lower for Lazanda versus intranasal fentanyl. Five minutes after administration, more patients experienced a >33% pain intensity reduction (~13% vs. <5%; p<0.05), while at 20 minutes after administration, more patients experiences a >50% pain intensity reduction (~71% vs. ~55%; p<0.05) with Lazanda.[16]

Common adverse events are drowsiness, nausea, vomiting, and constipation, with most these symptoms mild to moderate in severity. Nasal symptoms, including obstruction, discomfort, itching, sneezing, dryness, and crusting have also been mostly reported as mild and moderate in severity.[12-17] Ninety-nine serious adverse events have been reported in 3 studies, with 25 of these deemed related to fentanyl pectin nasal spray.[12,15,17] Two deaths possibly related to fentanyl pectin nasal spray have been reported.[15,17]. In one death, the patient developed cyanosis, loss of consciousness, and upper airway obstruction after an apparent unintentional overdose during a breakthrough pain episode.[17]

The initial starting dose for this study will be Lazanda 100 mcg prior to radiation therapy simulation. A 100 mcg dose is the initial dose of Lazanda for all patients as detailed in the product package insert. Lazanda dose titration will follow the guidelines as indicated in the product package insert from the baseline visit through the end of radiation therapy. If the subject does not experience relief after 30 minutes, he or she may take another 100 mcg but must wait at least 2 hours from the first spray before administering this second 100 mcg dose.

1.3 Rationale

Precise delivery of radiation requires patients to lie still on a hard, flat surface which can result in significant acute pain and/or BTCP, especially in the setting of painful bone metastases. Ideally, this acute treatment-related pain associated with lying on the radiation treatment table could be pretreated with a short-acting opioid with a rapid onset of action. Currently most cancer patients receiving hypofractionated radiation are limited to oral opioid pre-medication characterized by a one-hour onset of action and a half-life of four hours which does not associate with the time course of BTCP. Pain medication delivered via an intranasal route would be ideal in this cancer patient population to treat acute, episodic BTCP pain and maximize radiation treatment delivery efficiency given its quick onset of action and convenient mode of delivery.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

Our primary objective is to assess the change in patient reported positional pain intensity (PI) as measured by an 11-point numerical rating scale (NRS-11) in cancer patients with bone metastases assessed at each daily palliative radiation fraction. Our primary objective will be measured using the pain intensity difference (PID) of the NRS-11 between 0 minutes and 15 minutes after laying down on the hard surface ($PID_{15}= PI_{0-} PI_{15}$).

2.2 Secondary Objectives

1. To assess change in patient reported pain severity using the Brief Pain Inventory Short Form (BPI-sf).[1]
2. To evaluate adverse effects associated with Lazanda use utilizing the NCI CTCAE version 4.03 before and after palliative radiation

2.3 Exploratory Objectives

1. To assess the impact on radiation treatment delivery efficiency. This will be quantified by determining the total radiation treatment time.

2. To examine the effect of baseline pain intensity score, 24-hour opioid use (oral morphine equivalents) and total treatment time at each fraction (minutes) on change in pain intensity (PID_{15})

2.4 Endpoints

The primary endpoint on this study is change in positional pain intensity as measured by NRS-11 pain scores (***Appendix C***) (PID_{15}= PI_{0-} PI_{15}). Change in NRS-11 pain scores will be calculated from the time of laying down on the hard surface (0 minutes) to the 15-minute time point. NRS-11 (at time 0 and time 15) will be collected at the radiation simulation and at each subsequent radiation therapy visit. The rationale for obtaining a PID at 15 minutes, is based on the reported intranasal fentanyl C_{max} of 15-30 min.

Secondary endpoints include pain severity difference as measured by the Brief Pain Inventory Short Form (BPIsf)[18] (***Appendix D***).We will compare the BPIsf pain scores from the time of laying down on the hard surface (0 minutes) to 15 minutes after laying down at each fractionation visit . As a secondary endpoint we will also examine Lazanda safety, defined as the rate of drug-related adverse events experienced assessed according to the NCI's CTCAE v4.03 toxicity criteria.

Exploratory endpoints will include total recumbent time at each fractionation visit, measured in minutes.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study.

1. Patient able to understand and the willingness to sign a written informed consent.
2. Pathologically-confirmed solid tumor or hematologic malignancy with symptomatic bone metastases.
3. Patient is planned to receive hypofractionated palliative radiation ≤ 10 fractions.
4. Patient must be opioid-tolerant (greater than or equal to 60mg morphine or equivalent) and on a stable dose of oral opioids for greater than or equal to 1 week. Stable baseline opioid dosage defined as a dosage that does not fluctuate by more than 50% from the average dosage over one week prior to screening.
5. Patient must be on a stable dose of adjuvant pain therapies for one week prior to screening or after 4-5 half-lives of adjuvant pain therapies (i.e., glucocorticoids, NSAIDs, anticonvulsants, pharmaceutical cannabinoids, tricyclic antidepressants).
6. Patient is ≥ 18 years of age.
7. Both men and women of all races and ethnic groups are eligible for this trial.
8. ECOG Performance Status ≤ 3 (see ***Appendix A****)*
9. Women of child-bearing potential and men with partners of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 28 days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
   - A woman of child-bearing potential is any female (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or

10. Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months). Women of child-bearing potential has negative pregnancy test prior to initiating study drug dosing.

3.2 Exclusion Criteria

Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.

1. Patient is currently receiving or has received another investigational agent within 30 days or monoamine oxidase inhibitor within 14 days prior to Lazanda administration.

2. Patients who require immobilization with a thermoplastic mask for radiation treatment.

3. Patient is planned to receive interventional procedures (i.e. surgery) that may affect study outcomes.

4. Patient has a history of hypersensitivity to fentanyl or opioids.

5. Patient is pregnant or nursing. There is a potential for congenital abnormalities and for this regimen to harm nursing infants.

6. Patient is being treated with oxymetazoline for allergic rhinitis or has a disorder or current medication use likely to adversely affect normal functioning of the nasal mucosa.

7. Patient has uncontrolled or rapidly escalating background pain.

8. Patient has bradyarrhythmia.

9. Patient is considered medically unstable.

10. Patient is thought to be at risk for misuse, abuse, addiction or overdose for Schedule II controlled substance, as evidenced by the following:
    a. An Opioid Risk Tool (ORT) score of greater/less than or equal to 8.[2]
    b. A review of the California Prescription Control Monitoring Program (PDMP) Controlled Substance Utilization Review and Evaluation System (CURES) report demonstrates multiple prescribing providers and/or multiple pharmacies in the last 30 days. The CURES report will also be used to verify opioid use, opioid dose, and current prescribing providers.

4.0 TREATMENT PLAN

4.1 Study Design

This is a phase II, single-center, open-label study. We anticipate recruitment of approximately 15 total study participants at the UCSD Moores Cancer Center. Study participants will be recruited across all oncology disease teams. Potential participants will be identified in weekly palliative care or disease team patient triage meetings.

To meet eligibility for participation, a patient must be greater than or equal to 18 years old, have histologically-confirmed cancer with symptomatic bone metastases, an ECOG performance

status less than or equal to 3, and are planned to receive hypofractionated palliative radiation less than or equal to 10 fractions. Qualifying subjects must be opioid-tolerant, defined as greater than or equal to 60mg morphine or equivalent, and be on a stable dose of oral opioids for greater than or equal to 1 week. Stable baseline opioid dosage is defined as a dosage that does not fluctuate by more than 50% from the average dosage over one week prior to screening. Patients must also be on a stable dose of adjuvant pain therapies for one week prior to screening or after 4-5 half-lives of adjuvant pain therapies. Patients will be excluded if they are receiving or have received another investigational agent within 30 days or monoamine oxidase inhibitor within 14 days prior to Lazanda administration, have known hypersensitivity to fentanyl or opioids, have known, planned interventional procedures such as surgery that may affect study outcomes, are pregnant or nursing, have a disorder or current medication use likely to adversely affect normal functioning of the nasal mucosa, have uncontrolled or rapidly escalating background pain, or are medically unstable.

The primary objective of this study is to assess the change in patient reported positional pain intensity (PI) as measured by an 11-point numerical rating scale (NRS-11) (***Appendix C***) in cancer patients with bone metastases assessed at a simulation visit and each subsequent daily palliative radiation fraction. Our primary objective will be measured using the pain intensity difference (PID) of the NRS-11 from the time of laying down on the hard surface (0 minutes) to the 15 minutes after laying down on the hard surface timepoint at baseline (the simulation visit) and at each subsequent study visit (PID_{15}= PI_{0-} PI_{15}).

Secondary objectives will seek to assess patient reported pain severity using the BPI-sf (***Appendix D***), and evaluate adverse effects associated with Lazanda use utilizing the NCI CTCAE version 4.03 before and after palliative radiation.

Exploratory objectives will assess the impact on radiation treatment delivery efficiency, which will be quantified by determining the total time of radiation treatment, defined as the average time on the treatment table for each fractionation visit. A second exploratory objective will be to examine the effect of: baseline pain intensity score, 24-hour opioid use (oral morphine equivalents) and total treatment time at each fraction (minutes) on change in pain intensity (PID15)

After obtaining written informed consent, patients will have the following procedures completed to confirm eligibility: physical exam with vital signs and weight, ECOG performance status, comprehensive metabolic panel, and a serum pregnancy test (women of child-bearing potential only). During this screening period, patients will also complete a baseline NRS pain score and BPI-sf questionnaire (***Appendix D***), and report baseline 24-hour opioid dose.

Event	NRS-11	BPI-sf	Diaries		
			Medication Use	Nausea Vomiting	Laxation
Simulation	T-15, T0, T+15	T15+	X	X	X
Daily radiation fraction	T-15, T0, T+15	T15+	X	X	X

Table 1: Summary of Assessments; NRS-11 = numerical rating scale; BPI-sf = Brief Pain Inventory short form; T-15= 15 minutes prior; T0=at point of laying down; T+15 = 15 minutes after layind down; T15+ = any point after 15 minutes from laying down; X = once daily

Simulation Evaluation
The subject will then undergo radiation therapy simulation procedures (within approximately 2 weeks of radiation therapy) followed by hypofractionated radiation therapy, according to UCSD Radiation Oncology standard procedure and treatment plan determined by the subject's radiation oncologist. During radiation simulation and daily during each visit to the radiation center for hypofractionation delivery, subjects will have vital signs and weight collected per routine care. An ECOG performance status will also be assessed daily during radiation therapy. At the time of radiation simulation and daily during radiation therapy, subjects will complete the BPI-sf (***Appendix D***), Medication Use Diary (***Appendix E***), Laxation Diary (***Appendix F***), and Nausea/Vomiting Diary (***Appendix G***). NRS pain scores will also be collected at three time points during each visit to the radiation center: 15 minutes prior to laying on the hard surface (T-15), at the time of laying on the hard surface (T0), and at 15 minutes after laying on the hard surface(T+15). Exact time of each pain score rating will also be collected. The study coordinator will record total time in radiation therapy unit and total recumbent time (time laying down) during the simulation and each radiation treatment visit. Additionally, radiation treatment parameters, the presence of any adverse effects (NCI CTCAE v 4.03), and concomitant medications will be recorded.

Lazanda Dosing During Simulation
Subjects will receive study drug, Lazanda at 100mcg dose, 15 minutes prior to simulation (T-15) at the radiation therapy simulation visit. Lazanda dose titration will follow the guidelines as indicated in the product package insert from the radiation simulation visit through the end of radiation therapy. Lazanda dose titration procedures are further detailed in **Section 4.2**.

Subjects will undergo a post treatment follow-up period after completion of their radiation therapy. During this follow-up period, subjects will complete the BPI-sf (***Appendix D***), Medication Use Diary (***Appendix E***), Laxation Diary (***Appendix F***), and Nausea/Vomiting Diary (***Appendix G***) daily for 2 days. Concomitant medication use will also be recorded. Subjects will be monitored for the presence of any adverse effects (NCI CTCAE v 4.03) until 28 days following their last dose of Lazanda.

4.2 Treatment Dosage and Administration
Study drug, Lazanda, will be self-administered intranasally during this study. The dose of Lazanda is not predicted from the daily maintenance dose of opioid used to manage persistent cancer pain and must be determined by dose titration. Due to differences in pharmacokinetic

properties and individual variability, do not switch patients on a mcg per mcg basis from any other fentanyl product as Lazanda is not equivalent with any other fentanyl product.

4.2.1 Radiation Simulation Visit(s)

To determine an individual patient's effective and tolerable Lazanda dose, each subject will undergo dose titration during the radiation simulation visit. Lazanda dose for all subjects on study, including those switching from another fentanyl product, will be determined according to the following procedures:

- 15 minutes prior (T-15) to beginning the radiation therapy simulation, subjects will receive an initial dose of 100 mcg (1 spray) of Lazanda in one nostril prior to lying on the CT simulation hard surface.
- If adequate analgesia is obtained within 30 minutes of administration of the 100-mcg single spray, subsequent pain episodes will be treated with this dose.
- If the subject does not experience relief after 30 minutes, he or she may take another 100 mcg in the opposite nostril **but must wait at least 2 hours** (i.e., T-15 + 2 hours) from the first spray before administering this second 100 mcg dose. The subject may delay or reschedule the simulation (within a 14 days period) or radiation delivery to achieve the adequate pain control dose.
- If adequate analgesia is still not achieved, the subject will continue to dose escalate in a step-wise manner at a minimum of 2 hours between each subsequent escalation until adequate analgesia with tolerable side effects is achieved. A maximum of 4 doses or 400 mcg allowed per day.
- Dose titration steps are further detailed in **Table 1.**

Table 1: Lazanda Dose Titration Steps

Lazanda Dose	Using
100 mcg	1 x 100 mcg spray
200 mcg	2 x 100 mcg spray (1 in each nostril)
400 mcg	4 x 100 mcg spray (2 in each nostril, alternate nostrils) or 1 x 400 mcg spray

Each bottle contains a total of 8 sprays. Lazanda bottles come in 100 mcg or 400 mcg dose. If using dose of 100 mcg with the 100-mcg spray, the patient would have total of 8 doses in a single bottle. If using dose of 200 mcg with the 100-mcg spray, the patient would have total of 4 doses in a single bottle. If using dose of 400 mcg with the 100-mcg spray, the patient would have total of 2 doses in a single bottle. Alternately, if using a bottle of the 400-mcg spray at a dose of 400 mcg, the patient would have total of 8 doses in a single bottle.

Lazanda titration should be done with caution in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression and in patients susceptible to intracranial effects of CO_2 retention. Caution should also be used in patients on central nervous system (CNS) depressants and potent CYP3A4 inhibitors.

The minimal effective intranasal dose from the radiation therapy simulation will be the dose used as pre-medication prior to any further radiation therapy fractions (up to 10 fractions). Lazanda should be administered 15 (T-15) minutes prior to laying on the hard surface for each simulation visit. If the response to the titrated Lazanda dose markedly changes, an adjustment of dose may be necessary to ensure that an appropriate dose is maintained as deemed by the investigator.

Subjects will be instructed on the proper use of Lazanda as follows:

1) Prime the device before use by spraying into the pouch (4 sprays in total). If study drug has not been used for 5 days, re-prime by spraying once.
2) Insert the nozzle of the Lazanda bottle a short distance (about ½ inch) into the nose and point towards the bridge of the nose, tilting the bottle slightly.
3) Press down firmly on the finger grips until hearing a “click” and the number in the counting window advances by one.

Subjects will also be advised that the fine mist spray is not always felt on the nasal mucous membrane and to rely on the audible click and advancement of the dose counter to confirm a spray have been administered.

4.2.2 Radiation Treatment Visits

Lazanda will be self-administered by the subject while attending their visit to the radiation treatment center, and will be monitored closely by the clinic staff and study coordinator. Therefore, the chance for a missed dose is rare. However, should a subject miss a Lazanda dose prior to treatment fraction, he or she will be instructed to take the dose as soon as it is remembered on the same day prior to radiation.

The dose used as pre-medication prior to any radiation therapy fractions is as described in the titration schema listed above in section 4.2.1 and described in Table 1.

If a patient takes less than the minimal effective dose of Lazanda, they should be monitored closely for evidence of opioid withdrawal symptoms and reversal of central analgesic effects. In cases of known or suspected overdose, symptomatic treatment as well as monitoring of vital functions will be performed. In cases of severe intoxication, intensive care procedures will be completed. Close medical supervision and monitoring will be continued until the patient recovers.

Subjects will be required to record each self-administered dose of Lazanda on a Study Drug Diary (***Appendix H***) from the time of the radiation simulation visit through the end of radiation therapy. Details of Lazanda administration, including date and time of administration as well as number of sprays administered and total daily dose will be recorded by the subject on the Study Drug Diary.

Lazanda will be dispensed to the patient in nasal spray bottle format, within a child-resistant outer container. The child-resistant container should be opened just prior to initial product use. Subjects will be instructed to replace the bottle in the child-resistant container and out of reach of children between doses. Subjects will also be instructed to avoid consumption of grapefruit or grapefruit juice as this is a potent inhibitor of the CYP3A4 enzyme.

There are additional no requirements for monitoring of vital signs or other parameters following Lazanda administration. Treatment with Lazanda does not require that any pre-treatment parameters be met prior to dispensing and/or administration. However, subjects will be advised not to drive during study participation and must be accompanied to all treatments.

Any adverse events or serious adverse events resulting from known or suspected overdose will be reported according to instructions in **Section 7.6** of the protocol.

4.3 Pre-Medications

There are no required pre-medications on this study.

4.4 Permitted concomitant therapy

Patients must remain on around-the-clock opioids when taking Lazanda. Throughout the study, many participants will be receiving a long-acting opioid for control of background pain and an immediate-release opioid as needed ("prn") for breakthrough pain, although some may be receiving only a short-acting opioid on a scheduled basis. If the participant experiences more than 4 episodes of breakthrough pain per day while on study, the investigator will re-evaluate and appropriate titrate short and long-acting opioids per standard of care. Changes in the opioid regimen may be made to ensure appropriate pain control. Any changes to the maintenance opioid dosing regimen will be recorded. Concomitant non-opioid analgesics will be permitted, but investigators will be encouraged to maintain such drugs at stable doses on-study.

Fentanyl is metabolized in the liver and intestinal mucosa to norfentanyl by CYP3A4. Concomitant use of Lazanda with a CYP3A4 inhibitor (***Appendix B***) may result in a potentially dangerous increase in fentanyl plasma concentrations, which could prolong adverse drug effects. Patients receiving Lazanda who begin or increase the dose of a CYP3A4 inhibitor drug is permitted, but should be carefully monitored for signs of opioid toxicity.

Medications required to treat adverse events and manage cancer symptoms, concurrent stable disease (e.g., controlled hypertension) and supportive care agents such as erythropoietin, granulocyte growth factors, or blood transfusion, and pain medications are allowed. The patient needs to notify the investigational site about any new medications he/she takes after the start of the study medication. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be recorded in the patient's medical record.

Palliative and supportive care for disease-related symptoms, including pain medications, is permitted. Hematopoietic growth factors such as erythropoietin or G-CSF are allowed if clinically indicated only after the first 28 days of study treatment. Use of growth factors will follow NCCN guidelines.

4.5 Prohibited concomitant therapy

Unless there is a need for urgent intervention, additional medication for pain control will not be allowed without prior approval from the principal investigator. This includes over-the-counter treatments for pain. Concomitant use of a monoamine oxidase inhibitor is prohibited. Other investigational therapies must not be used while the patient is on the study. If such agents are required for a patient then the patient must be discontinued from the treatment portion of the study.

4.6 Radiation Therapy

Subjects will undergo radiation therapy simulation procedures and receive palliative radiation during this trial according to UCSD Radiation Oncology standard procedure, and according to the radiation treatment plan as determined by their radiation oncologist.

4.7 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the NCI CTCAE, version 4.03.

Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Table 2: Dose Modifications for Lazanda-Related Nausea and/or Vomiting

Nausea/Vomiting	Management for Lazanda
≤ Grade 1	No action required.
Grade 2	Hold until ≤ Grade 1. Resume at same dose.
Grade 3	Hold until < Grade 2. Resume at same dose.
Grade 4	Off protocol therapy
Recommended symptom management: Treatment with a dopamine antagonist antiemetic (e.g. metoclopramide, prochlorperazine, haloperidol) and strong consideration of premedication prior to next Lazanda dose.	

Table 3: Dose Modifications for Lazanda-Related Constipation

Constipation	Management for Lazanda
≤ Grade 1	No action required.
Grade 2	Hold until ≤ Grade 1. Resume at same dose.
Grade 3	Hold until < Grade 2. Resume at same dose.
Grade 4	Off protocol therapy
Recommended symptom management: Opioid-induced constipation is managed with stimulant laxatives (senna, bisacodyl) with or without an osmotic laxative (e.g. polyethylene glycol).	

Table 4: Dose Modifications for Lazanda-Related Urinary Retention

Urinary Retention	Management for Lazanda
≤ Grade 1	No action required.
Grade 2	Hold until ≤ Grade 1. Resume at same dose.
Grade 3	Hold until < Grade 2. Resume at same dose
Grade 4	Off protocol therapy
Recommended symptom management: Evaluation including physical exam, ultrasound bladder scan, and consideration of a time-limited trial of catheter placement.	

Table 5: Dose Modifications for Lazanda-Related Somnolence

Somnolence	Management for Lazanda
≤ Grade 1	No action required.
Grade 2	Hold until ≤ Grade 1. Resume at same dose.
Grade 3	Hold until < Grade 2. Resume at half dose.
Grade 4	Off protocol therapy
Recommended symptom management: Urgent evaluation by investigator and medical management per standard of care.	

Patients requiring a delay of greater than 2 weeks or greater than 2 dose reductions in Lazanda dose for any toxicity should discontinue protocol therapy.

4.8 Duration of Study Treatment

In the absence of treatment delays due to adverse events, treatment may continue up to a total approximately 4 weeks or until:

- Inter-current illness or worsening of a medical condition that prevents further administration of treatment
- Unacceptable adverse event(s)

- Rescue pain therapy for fails to palliative pain and/or the investigator believes that other treatment options may be more beneficial
- The investigator believes that study treatment is jeopardizing patient safety
- Patient decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.9 Duration of Follow Up

Patients will be followed daily for a 2-day period following the last study drug administration. During this period, data regarding ECOG performance status, 24-hour opioid use, number of daily bowel movements and nausea/vomiting episodes, concomitant medication use, and patient-reported outcomes will be collected. Patients will be followed for occurrence of adverse events for 28 days after completion of study treatment or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

4.10 Discontinuation from Study Participation

Patients may be removed from study participation at any time or at the discretion of the investigator for any of the following reasons:

- The patient or legal representative withdraws consent for follow-up;
- The patient is lost to follow-up;
- The patient is unable to retain oral medication;
- The patient dies;
- The patient is non-compliant with study procedures;
- The study is terminated

Patients who are removed early from study participation will be asked to return all previously-completed diaries and questionnaires and remaining study drug supply to a member of the study team.

5.0 STUDY PROCEDURES

Refer to the study Schedule of Events for a list of study procedures and required time points.

All patients will be closely monitored for safety and tolerability for the duration of study participation.

5.1 Definitions of Study Assessments

5.1.1 Medical history

A complete medical, surgical and oncology history as well as history of infections are obtained at screening. Any changes from Screening (e.g., worsening severity or abnormal findings) are considered to be adverse events (AEs).

5.1.2 Demographics

Demographic profile will include date of birth, sex, patient-reported race, and ethnicity.

5.1.3 Review subject eligibility criteria

Review of eligibility criteria as described in Section 3 will be completed to ensure subject qualification for study entry.

5.1.4 Concomitant medications

All concomitant therapy, including anticancer therapy, vitamins, homeopathic/herbal remedies, nutritional supplements, opioid medication use, over-the-counter analgesic medication use, and all other over-the-counter "prn" and oral medications, received by patients from 5 days prior to baseline until 2 days after the last study dose will be recorded in the patient's medical record. If a reportable adverse event deemed related to study intervention (see Section 7) occurs within 28 days after last study dose and the patient has not started a new treatment, recording of concomitant medications related to the treatment of that adverse event should continue until resolution of the adverse event.

5.1.5 Physical exam

A complete physical examination should include the evaluation of general appearance; evaluation of head, eyes, ears, nose, and throat (HEENT); and cardiovascular, pulmonary, abdominal, musculoskeletal, skin, lymph nodes, neurological, and genitourinary systems. Subsequent exams may be targeted as appropriate.

Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if clinically significant.

5.1.6 Vital signs and weight

Vital signs should include temperature, pulse, and blood pressure and weight.

5.1.7 Performance status

Performance status is evaluated by the by the ECOG scale (see ***Appendix A***).

5.1.8 Adverse event assessment

Baseline assessment of subject status for determining adverse events. See Section 7 for Adverse Event monitoring and reporting.

5.1.9 Serum chemistries

Comprehensive metabolic panel to include: albumin, alkaline phosphatase, total protein, ALT, AST, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

5.1.10 Pregnancy test (for females of child bearing potential)

See section 3.1 for definition.

5.1.11 Patient-Reported Measures

All patient-reported measures will be completed via paper format, with materials provided to the patient by a study team member. A study member will provide initial training to the patient on how to complete study-required questionnaires and diaries. Patients are to complete the questionnaires and diaries in a quiet area, without assistance from family, friends or study team members. Patients must be able to read and comprehend the questionnaire in the language presented, and will be translated into foreign languages as needed for patient recruitment.

5.1.11.1 Numerical Rating Score (NRS) Pain Score

The NRS for pain is a unidimensional measure of pain intensity in adults (***Appendix C***). It is a segmented numeric version of the visual analog scale in which a respondent selects a whole number (0–10 integers) that best reflects the intensity of their pain. The common format is a horizontal bar or line. Similar to the pain visual analog scale, the NRS is anchored by terms describing pain severity extremes. Although various iterations exist, the most commonly used is the 11-item NRS.[19] NRS Pain Score will be collected at a total of 2 events: CT simulation and on each day of radiation. At all time points where NRS pain scores are required, pain scores will be recorded: 15 min prior to laying on the hard surface (T-15), after laying on the hard surface (T0), and 15 min after laying down on the hard surface (T+15). This pain rating takes approximately 15 seconds to complete**.**

5.1.11.2 Brief Pain Inventory-Short Form (BPI-sf)

The Brief Pain Inventory (BPI) is one of the most widely used measurement tools for assessing clinical pain. The BPI allows patients to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function. The BPI is available in two formats: the BPI-Short Form (BPI-sf), which is used for clinical trials, and the BPI-Long Form, which contains additional descriptive items that may be clinically useful. For the purposes of this study, we will use the BPI-sf, a 9-item self-administered questionnaire used to evaluate the severity of a patient's pain and the impact of this pain on the patient's daily functioning (***Appendix D***). The patient is asked to rate their worst, least, average, and current pain intensity, list current treatments and their perceived effectiveness, and rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on a 10-point scale. The BPI-sf is validated for 24-hour recall. Participants will be asked to complete this questionnaire from baseline through the end of the post-treatment follow-up period. This questionnaire takes approximately 5 minutes to complete.

5.1.11.3 Medication Use Diary

Patients will complete a daily medication use diary as a record of all oral and self-administered medications received from baseline through the end of the post-treatment follow-up period (***Appendix E***). This includes any anticancer therapy, vitamins, homeopathic/herbal remedies, nutritional supplements, opioid medication use, over-the-counter analgesic medication use, and all other over-the-counter “as needed” (prn) and oral medications. A copy of the medication use diary will be collected from the patient by a member of the study team during each visit to clinic or the radiation treatment center, and entries will be recorded on the concomitant medications case report form.

5.1.11.4 Laxation Diary

Patients will complete a daily laxation diary as a record of the number of daily bowel movements from baseline through the end of the post-treatment follow-up period (***Appendix F***). Participants will be asked to complete this diary even on days where no daily bowel movement has occurred. A member of the study team will collect a copy of the diary from the patient during each visit to clinic or the radiation treatment center.

5.1.11.5 Patient Nausea/Vomiting Diary

Patients will complete a daily nausea/vomiting diary as a record of the number of daily nausea and vomiting episodes from baseline through the end of the post-treatment follow-up period (***Appendix G***). Participants will be asked to complete this diary even on days where no nausea or vomiting has occurred. A copy of the diary will be collected from the patient by a member of the study team during each visit to clinic or the radiation treatment center.

5.1.11.6 Study Drug Diary

Patients will complete a daily study drug diary (***Appendix H***) during the time that they are receiving Lazanda. Participants will be asked to complete this diary even on days when a Lazanda dose was missed or not taken. Details of Lazanda administration, including date and time of administration as well as number of sprays administered and total daily dose will be recorded. The study drug diary will be reviewed with the patient during each visit to clinic or the radiation treatment center, and a copy will be collected by a member of the study team. This diary will be used in combination with returned nasal spray bottles to support drug accountability.

5.2 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 21 days prior to registration unless otherwise stated. The screening and baseline procedures include:

- Written informed consent
- Review of inclusion and exclusion criteria
- Complete medical/oncology history
- Demographics
- Documentation of concomitant medications
- Documentation of location(s) of bone lesion(s)
- Complete physical examination, including vital signs and weight
- ECOG performance status assessment
- Comprehensive metabolic panel (*serum chemistries performed within 6 weeks of baseline may be used to fulfill screening requirements*)
- Serum or urine pregnancy test *(within 72 hours of Study Day 1)* for females of child-bearing potential (see inclusion/exclusion criteria)
- Documentation of patient's baseline 24-hour opioid dose
- Collect single NRS pain score and time of NRS rating
- BPI-sf

Following confirmation of all eligibility criteria, subjects will be enrolled to the study through the Moores Cancer Center Clinical Trials Office.

5.3 Procedures During Treatment

During the radiation therapy simulation visit and throughout radiation therapy, physical exam and comprehensive metabolic panel will be performed per routine frequency for the participant's oncology care. If these procedures are performed as part of routine oncology care, results will be collected for the study.

5.3.1 Radiation Therapy Simulation

The radiation therapy simulation visit will occur within approximately 14 days of the start of radiation therapy, as per standard radiation oncology protocol. Patients will have the following study procedures performed at the radiation simulation visit:

- Documentation of concomitant medications and adverse events
- Vital signs and weight per routine care
- ECOG performance status assessment
- Record total time in radiation therapy unit
- Record recumbent time during radiation therapy
- Lazanda dispensing and administration (*see **Section 4.2** for dose titration steps*)
- Collect NRS pain scores and time of NRS rating at: *15 minutes prior to laying on the hard surface, at the time of laying on the hard surface (0 minutes), and at 5, 10, 15 minutes after laying on the hard surface*
- BPI-sf
- Medication Use Diary (*to be completed daily through the end of radiation therapy*)
- Nausea-Vomiting Diary (*to be completed daily through the end of radiation therapy*)
- Laxation Diary (*to be completed daily through the end of radiation therapy*)

5.3.2 Radiation Therapy (Hypofractionation)

Patients will receive radiation therapy (hypofractionation) for a period of approximately 10 days (up to 10 fractions). Patients will have the following study procedures performed **daily** during radiation therapy:

- Documentation of concomitant medications and adverse events
- ECOG performance status assessment
- Vital signs and weight per routine care
- Record total time in radiation therapy unit
- Record recumbent time during radiation therapy
- Lazanda administration (*see **Section 4.2** for details of dosing*)
- Collect NRS pain scores and time of NRS rating at: *15 minutes prior to laying on the hard surface, at the time of laying on the hard surface (0 minutes), and at 5, 10, 15 minutes after laying on the hard surface*
- BPI-sf
- Medication Use Diary (*to be completed daily through the end of radiation therapy*)
- Nausea-Vomiting Diary (*to be completed daily through the end of radiation therapy*)
- Laxation Diary (*to be completed daily through the end of radiation therapy*)

5.4 Follow-up Procedures

Patients will be followed for occurrence of adverse events for 30 days after the last dose of study drug or until death, whichever occurs first. Patients removed from treatment for

unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Patients will undergo a post-treatment follow-up period for 2 days following completion of radiation therapy. Patients will have the following study procedures performed **daily** for 2 days during the follow-up period:

- Documentation of concomitant medications
- Collect single NRS pain score and time of NRS rating
- BPI-sf
- Medication Use Diary
- Nausea-Vomiting Diary
- Laxation Diary

Follow-up may consist of the study coordinator contacting the patient by telephone contact if no in-person standard oncology or radiation oncology visit is scheduled to occur during this time.

Patients discontinuing study treatment prior to the end of the radiation therapy will undergo follow-up procedures for 2 days as described under **Section 5.5**.

6.0 Measurement of Effect

6.1 Safety/tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.03 (http://ctep.cancer.gov/reporting/ctc.html) for reporting of adverse events. Safety will be assessed from the time of informed consent through 30 days following the last dose of study drug.

6.2 Efficacy assessment

The efficacy of treatment with Lazanda will be evaluated by NRS-11 pain scores and BPI-sf assessed from the baseline assessment through the end of the post-treatment follow-up period. For our primary aim, we will assess the pain intensity difference (PID) of the NRS-11 from the time of laying down on the hard surface (0 minutes) to the 15 minutes (T+15) after laying down on the hard surface timepoint at baseline and at each subsequent study visit (PID_{15}= PI_{0-} PI_{15}).

7.0 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Progression of the cancer under study or events that are unequivocally due to disease progression should not be reported as an AE during the study (unless it is considered to be drug related by the investigator).

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in

future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

As far as possible, each adverse event should be evaluated to determine:

- duration (start and end dates)
- severity (grade)
- seriousness
- relationship to study agent
- action taken (i.e., none, study agent modification, medical intervention)
- outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

Adverse events monitoring begins at the time of informed consent signature and ends within 30 days of the last administration of the study drug.

All patients experiencing an adverse event, at least possibly related to the drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any clinically significant abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2 Severity

All adverse events will be graded according to the NCI CTCAE version 4.03. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

7.3 Seriousness

A “serious” adverse event (SAE) is defined in regulatory terminology as any untoward medical occurrence that:

1. Results in death. If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
2. Is life-threatening. The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires in-patient hospitalization or prolongation of existing hospitalization.
   Note: Hospitalization (including hospitalization for an elective procedure) for a pre-existing condition that has not worsened does not constitute a serious adverse event.
4. Results in persistent or significant disability or incapacity.
5. Is a congenital anomaly/birth defect
6. Is an important medical event.

- Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as SAE. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
- *For example:* allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.4 Relationship

Attribution categories for adverse events in relationship to protocol therapy are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

7.5 Prior experience

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the current known adverse events listed in the agent clinical experience section of this protocol and Lazanda prescribing information.

7.6 Reporting Requirements for Adverse Events

7.6.1 Expedited Reporting

A. The **Principal Investigator** must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.

B. The **UCSD Human Research Protections Program (HRPP)** and **Moores Cancer Center Data and Safety Monitoring Board (DSMB)** must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR).

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

C. The **FDA** must be notified according to the following timelines:

- within 7 calendar days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and
- within 15 calendar days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

D. A copy of all SAEs will be submitted to **Depomed's safety designee** using the approved local regulatory form within 24 hours of the Principal Investigator's awareness by email (drugsafety@depomed.com) or fax (800-941-3742).

7.6.2 Routine Reporting Requirements

A. The **UCSD HRPP** must be notified of any adverse events that are not unanticipated problems involving risk to subjects or others (non-UPRs) at the time of the annual Continuing Review.

B. The **FDA** must be notified of all non-serious adverse events annually at the time of the annual report.

C. **Depomed** will be notified of all non-serious adverse events in summary or line-item form upon Depomed's request and at the conclusion of the study.

7.6.3 Pregnancy Reporting Requirements

The **Principal Investigator** must be notified within 24 hours of any pregnancies occurring in a female patient or a female partner of a male patient along with pregnancy outcomes. Elective abortions without complications should not be considered adverse events unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered a significant adverse event. Spontaneous abortions should always be reported as significant adverse events.

The Investigator should follow-up with the study patient or the female partner of the study patient until delivery or termination of pregnancy, even if the patient was withdrawn from the clinical study or the clinical study was completed. Depomed will be informed of all pregnancy outcomes using the contact information provided above.

8.0 AGENT INFORMATION

8.1 Lazanda®

Please refer to Investigator's Brochure for more comprehensive information.

Other names for the drug: Fentanyl Nasal Spray CII

Mechanism of action (or Product description): Fentanyl is a pure opioid agonist whose principal therapeutic action is analgesia. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia. Its active ingredient, fentanyl citrate, USP is N-(1-phenethyl-4-

piperidyl) propionanilide citrate (1:1). Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816.1). Fentanyl citrate is sparingly soluable in water (1:40). The molecular weight of the free base and citrate salt are 336.5 and 528.6, respectively. The pKa is 8.4.

Lazanda nasal spray is a liquid formulation of fentanyl citrate intended for intranasal transmucosal administration. The product consists of a practically clear to clear, colorless, aqeous solution of fentanyl citrate in a glass multidose container to which is attached a metered-dose nasal spray pump with a visual and audible spray counter.

Availability: provided by Depomed, free of charge

How supplied: Lazanda is supplied in glass bottles, containing 8 sprays of 100 mcL containing 100 mcg/100 mcL or 400 mcg/100 mcL concentration solution. Each bottle is supplied in a child-resistant container. Bottles in their child-resistant containers are supplied in cartons containing 1 to 4 bottles. Each carton contains one carbon-lined pouch per bottle for disposal of priming sprays.

Lazanda contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. Lazanda® can be abused in a manner similar to other opioid agonists, legal or illicit. Because of the risk for misuse, abuse, addiction, and overdose, Lazanda® is available only through a restricted program required by the Food and Drug Administration, called a Risk Evaluation and Management Strategy (REMS). Under the Transmucosal Immediate Release Fentanyl (TIRF) REMS Access program, outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors must enroll in this program (see www.TIRFREMSaccess.com). Dr. Roeland, Dr. Ma, and Arlene Cramer, NP, have all completed their TIRF REMS education and the Moores Cancer Center provides REMS medications.

Prior to initial dosing of Lazanda, subjects will be instructed on the proper use of the study drug product, according to the instructions in **Section 4.2**. Study subjects will receive an initial supply of Lazanda, 1 bottle of 100 mcg spray, at the time of radiation therapy simulation for use during initial dose titration. A single bottle of Lazanda with increments of 100 mcg sprays will provide 8 doses. Subjects will receive additional supply of Lazanda bottles, 5 mL bottles of 100 mcg or 400 mcg or combination of both, at the first radiation treatment visit as determined by the investigator based on opioid needs and the dose established during titration procedures. If the response to the titrated Lazanda dose markedly changes, an adjustment of dose may be necessary to ensure that an appropriate dose is maintained, and may require a refill supply during the course of radiation treatment as determined by dose adjustment and in discussion with the Principal Investigator. All doses will be carefully monitored and recorded and participants will not receive surplus bottles.

Storage and stability: Lazanda will be stored at up to 25C in the Moores Cancer Center Investigational Drug Services (IDS). Do not freeze. Bottles for individual patient use will be returned to the child-resistant container and in the carbon-lined pouch in the cardboard carton for secure storage at home after each use. Lazanda must be stored out of reach of children and protected from light.

Preparation: Bottles containing Lazanda will be supplied in ready-to-use form. No further drug preparation (e.g., reconstitution, dilution) is required by IDS prior to labeling and dispensing.

Route of administration for this study: Lazanda will be administered as an intranasal spray. Each actuation on the metered-dose nasal spray counter is designed to deliver a spray of 100 mcL of solution containing 100 mcg or 400 mcg fentanyl base. This enables doses of 100 mcg or 400 mcg to be administered using a single spray into one nostril (100 mcg), a single spray into each nostril (200 mcg), or two sprays into each nostril (400 mcg), based on the effective and tolerable dose determined through titration steps described in **Section 4.2**.

Side effects: The most commonly observed adverse events (frequency ≥5%) seen with Lazanda are typical of opioid side effects, such as nausea, vomiting, constipation, dizziness, pyrexia, somnolence and headache. Please refer to the Lazanda Package Insert for additional detail on adverse events experienced less commonly (frequency ≥1%).

8.1.1 Return and Retention of Study Drug

Patients will return remaining study drug supply to a member of the study team who will log the return with IDS. Remaining drug is to be destroyed on-site, according to UCSD Moores Cancer Center IDS drug destruction policy.

8.1.2 Drug Accountability/Subject Compliance

Records of study medications used, dosages administered, and intervals between visits will be kept during the study. Subjects will be asked to fill out a daily study drug diary while taking Lazanda and bring with them, along with any unused study drug, on each visit to clinic for review with a member of the study team.

Final drug accountability will be noted at the completion of the trial. Patients will be asked to return all unused medication at the end of the study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Study Endpoints

This is an open label, single center, phase II case study. The primary endpoint is PID_{15}, the difference in pain intensity as measured by the NRS-11 between the time of laying down on the hard surface (0 minutes) and the pain intensity at 15 minutes after laying down on the hard surface. Secondary endpoints include change in bone pain severity scores as measured on the BPI-sf, and the rate of drug-related adverse events experienced assessed according to the NCI's CTCAE v4.03 toxicity criteria. Exploratory endpoints will include total recumbent time at each fractionation visit measured in minutes, as well as baseline pain intensity score and 24-hour opioid use (oral morphine equivalents).

9.2 Sample Size and Accrual

This trial will enroll approximately 6 subjects meeting the eligibility criteria described above. Conservatively assuming a 10% drop out rate, we will accrue **5 patients**. Many of the study variables are observational and descriptive. These are best analyzed as they relate to the individual participant experience.

Sample size was calculated PASS (NCSS, LLC. Kaysville, Utah).

There is limited literature relating to the change in pain intensity-NRS pain scores in cancer patients. Previous literature has reported the interquartile range (IQR) for the change in pain intensity-NRS pain score across various patient categories. These IQRs ranged between 1 and

3, thus we used and an estimated IQR of 2 to get a standard deviation of 1.48 (by assuming a normal distribution for differences in pain scores)[2].

Accrual Targets

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	6	7	13
Ethnic Category: Total of all subjects	7	8	15
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	1	1	2
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
White	5	6	11
Racial Category: Total of all subjects	7	8	15

9.3 Data Analyses Plans

All analyses will be conducted using SAS version 9.4 (Cary, NC, USA).

9.3.1 Primary Analysis

Our primary aim of assessing the change in NRS-11 scores of patients before and after receiving Lazanda will be analyzed using a linear mixed-effects model to account for the repeated daily dosing. We will model the difference in PID from baseline to 15 minutes (PID_{15}) at each radiation simulation and fractionation visit; with a fixed intercept term for time and a subject level random intercept to account for within-patient variability. We will provide descriptive statistics overall and for each treatment day (day 1, …, n). Descriptive statistics will include mean/standard deviation, min, max and IQR.

9.3.2 Safety Endpoint

Safety endpoints will be evaluated by monitoring AEs from clinical and laboratory reporting. Adverse events will be classified according to the NCI-CTCAE version 4.03. Trends in the distribution and severity of the AEs across the study groups will be assessed by examining the count of total AEs and count of AEs at each severity level over the course of the subject's participation in the study.

9.3.3 Secondary Analyses

To analyze patient reported pain severity using the BPI-sf, we will calculate the "worst pain" i.e., the arithmetic mean of the four severity items to measure pain severity. We will model the difference in "worst pain" from baseline to 15 minutes at each radiation simulation and fractionation visit; with a fixed intercept term for time and a subject level random intercept to account for within-patient variability. We will provide descriptive statistics overall and for each treatment day (mean/standard deviation and frequency distributions of "worst pain").

9.3.4 Exploratory Analyses

Our exploratory aim will assess the impact of Lazanda on treatment delivery efficiency. This will be assessed by comparing treatment delivery efficiency in the Lazanda treated patients to the historic average. To assess this we will quantify each subjects average total time on the treatment table (averaged across each subjects fractionation visits, in minutes). This average will be compared to the clinic's historic average of 6 minutes using a one-sample t-test of the null hypothesis that the average time on the treatment table for Lazanda study patients equals 6 minutes.

We will also consider the effects of baseline pain intensity score, 24-hour opioid use (oral morphine equivalents) and total treatment time at each fraction (minutes) on the change in pain intensity by including each of them as fixed effects in the linear mixed-effects models for PID_{15}. The use of continuous assessment for each individual participant strengthens the validity of the research.[20] Our final case series report will assess the overall effect of the study drug on the participant radiotherapy related pain as determined by NRS-11 scores, BPI-sf results, and AEs.

10.0 STUDY MANAGEMENT

10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed according to UCSD conflict of interest policy.

10.2 Institutional Review Board (IRB) Approval and Consent

The IRB should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.3 Registration Procedures

All patients must be registered with the UCSD Moores Cancer Center Clinical Trials Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed and an eligibility checklist completed. Once eligibility is confirmed, patient will be given a unique sequential study number.

10.4 Data Collection and Management

Records and data to be obtained from the study subjects are detailed above in the Schedule of Events. Subject outcome information will be documented in the electronic medical record and subject's research record. Data for this study will be entered into a password-protected set of electronic case report forms via the Velos eResearch web-based system. Velos eResearch is an integrated software system for managing clinical trials. This system supports several clinical trial functions, including electronic case report forms, tracking and scheduling of subject visits and events, and study reporting. The software links to the UCSD Health System's Epic Electronic Medical Record System to provide improved information and integration for clinical research projects. A robust support team assists investigators in implementing protocols and calendars and building electronic case report forms. Velos provides automated data export procedures for designated users into Excel, and then transferred into SAS and R. Access to the Velos database for this study will be limited to those users required to perform study-specific functions such as data entry and monitoring. A designated study coordinator from the UCSD Moores Cancer Center Clinical Trials Office will be responsible for entering all study data.

10.5 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

10.6 Data and Safety Monitoring/Auditing

In addition to adverse event monitoring and clinical oversight by the principal investigator and co-investigators, quality assurance of the study will be performed by a UCSD Moores Cancer Center Clinical Trials Office internal monitor. Monitoring intervals will be dependent upon the rate of enrollment, and are anticipated to occur approximately every 3-4 months.

This study will also use the UCSD Moores Cancer Center DSMB to provide oversight in the event that this treatment approach leads to unforeseen toxicities. Data from this study will be reported every 6 months and will include

1) the protocol title, IRB protocol number, and the activation date of the study.
2) the number of patients enrolled to date
3) the dates of patient enrollment
4) a summary of all adverse events regardless of grade and attribution
5) outcome data for evaluable patients when available
6) a summary of any recent literature that may affect the ethics of the study.

It will be left to the Investigator's clinical judgment whether or not an adverse event is related and of sufficient severity to require the subject's removal from treatment. Subsequent review of serious, unexpected and related adverse events by the principal investigator, DSMB, UCSD and/or HRPP, may also result in suspension of further trial interventions/ administration of study drug at a site. The principal investigator retains the authority to suspend additional enrollment for the entire study as applicable.

10.7 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, investigators are required to conduct their research according to the plans reviewed and approved by the IRB.

10.8 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate apparent immediate hazards/risks to trial subjects without prior IRB approval. Any such emergency modification implemented must be noted and reported to the IRB along the lines of a protocol deviation or violation, depending on the nature of the modification.

10.9 Protocol Violations

Any unplanned variance from an IRB approved protocol is considered a violation and must be reported to the IRB in a timely fashion.

A) Major violations must be reported to the IRB within 10 working days of awareness of the violation. Major violations include:
- Instances that have harmed or increased the risk of harm to one or more research participants.
- Instances that have damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

B) Minor violations may be reported to the IRB at the time of the continuing review. Minor violations have no substantive effect on the risks to participants or on the scientific integrity of the research plan or the value of the data collected.

10.10 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the UCSD IRB for approval prior to implementation.

10.11 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.12 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

10.13 Data Reporting

The study findings will be disseminated as a prospective case series wherein related participant medical history will be reported. The degree and length of the medical history reporting will vary by participant. At the PI's discretion, only events and factors significant to the present study that are fully de-identified will be included in the dissemination of findings. Historic factors related to individual participant pain will be considered and can include past pain medication and radiation experience, or any diagnosis that contributes to radiation therapy pain.

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12.0 APPENDICES

Appendix A: ECOG Performance Status Scale

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).

2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead.

Appendix B. Strong and Moderate CYP3A4 Inhibitors

Strong CYP3A4 inhibitors allowed during study and include but are not limited to the following:

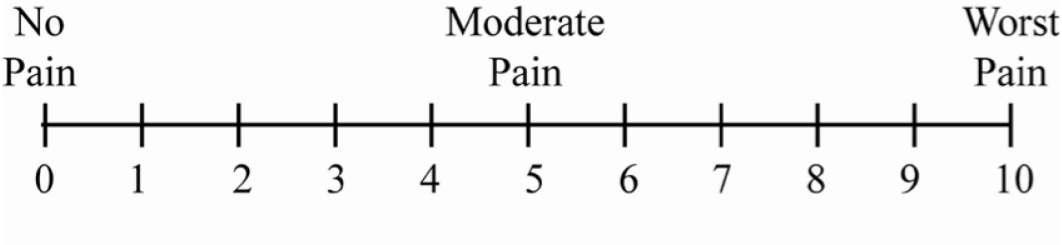
- Boceprevir
- Clarithromycin
- Conivaptan
- Grapefruit juice
- Indinavir
- Itraconazole
- Ketoconazole
- Lopinavir/ritonavir
- Mibefradil
- Nefazodone
- Nelfinavir
- Posaconazole
- Ritonavir,
- Saquinavir
- Telaprevir
- Telithromycin
- Voriconazole

Moderate CYP3A4 inhibitors are allowed during study and include but are not limited to the following:

- Amprenavir
- Aprepitant,
- Atazanavir,
- Ciprofloxacin,
- Darunavir/ritonavir,
- Diltiazem,
- Erythromycin,
- Fluconazole,
- Fosamprenavir,
- Grapefruit juice,
- Imatinib,
- Verapamil

Please refer to the U.S. Food and Drug Administration website, *Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers*, for additional information: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Appendix C. Numerical Rating Score (NRS) for Pain



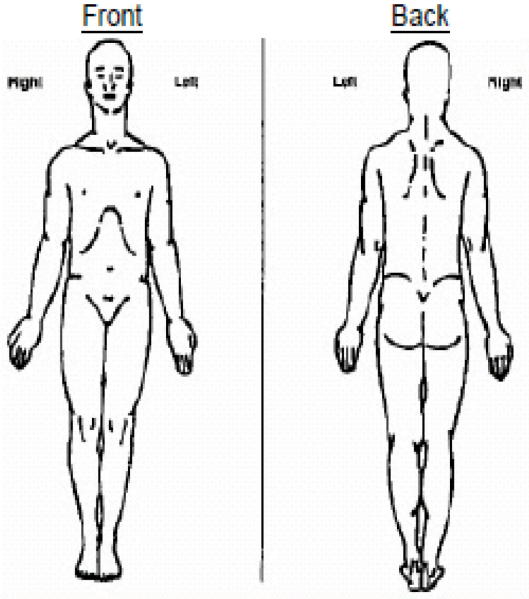
Appendix D. Brief Pain Inventory-short form (BPI-sf)

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

Page 1 of 2

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
No Relief										Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Does Not Interfere — Completely Interferes

B. Mood

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Does Not Interfere — Completely Interferes

C. Walking ability

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Does Not Interfere — Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Does Not Interfere — Completely Interferes

E. Relations with other people

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Does Not Interfere — Completely Interferes

F. Sleep

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Does Not Interfere — Completely Interferes

G. Enjoyment of life

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Does Not Interfere — Completely Interferes

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Appendix E. Medication Use Diary

Medication Use Diary

Protocol No.	Participant No.	Participant Initials
UCSD XXXXXX		

Instructions for completion:

- Please remember to complete this diary ***daily*** while participating in this study.
- Record each medication you are taking at home on a separate line. For each medication recorded, please list the date or dates that it was taken, how many times it is taken each day, the dose each time it is taken, and the reason why you are taking the medication.
- If there is any information that you do not know, please write "UNK" in the space provided.

Name of Medication	Date(s) Medication Taken (mm/dd/yy)	No. of times taken each day	Dose (each time it is taken)	Reason for Taking Medication

Please sign when the diary when all spaces are full and return to the study coordinator during your next clinic visit.

Participant Signature: _____ **Date:** _____

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Appendix F. Laxation Diary

Laxation Diary

Protocol No.	Participant No.	Participant Initials
UCSD XXXXXX		

Instructions for completion:

- Please remember to complete this diary ***daily*** while participating in this study.
- Record time of each bowel movement that you have throughout the day on a separate line, and circle "am" or "pm".
- At the end of each day, please record the total number of bowel movements for that day in the space provided.
- If you did not have any bowel movement throughout the day, please leave all spaces for time blank, and record "0" in the space for total number of bowel movements.

Date							
Time (hh:mm)	am pm	am pm	am pm	am pm	am pm	am pm	am pm
Time (hh:mm)	am pm	am pm	am pm	am pm	am pm	am pm	am pm
Time (hh:mm)	am pm	am pm	am pm	am pm	am pm	am pm	am pm
Time (hh:mm)	am pm	am pm	am pm	am pm	am pm	am pm	am pm
Time (hh:mm)	am pm	am pm	am pm	am pm	am pm	am pm	am pm
Time (hh:mm)	am pm	am pm	am pm	am pm	am pm	am pm	am pm
Time (hh:mm)	am pm	am pm	am pm	am pm	am pm	am pm	am pm
Time (hh:mm)	am pm	am pm	am pm	am pm	am pm	am pm	am pm
Total # bowel movements							

Please sign when the diary has been completed at the end of the study return to the study coordinator during your next clinic visit.

Participant Signature: _________________________ **Date:** ____________

version dated 29DEC16

Appendix G. Nausea/Vomiting Diary

Nausea and Vomiting Diary

Protocol No.	Participant No.	Participant Initials
UCSD XXXXXX		

Instructions for completion:

- Please remember to complete this diary ***daily*** while participating in this study.
- Record each episode of nausea, retching, vomiting or dry heaves that you have throughout the day on a separate line. For each episode recorded, please record the time of the episode and whether rescue medication was taken.
- At the end of each day, please record the total number of episodes for that day in the space provided.
- If you did not have any nausea, retching, vomiting or dry heaves throughout the day, please leave all spaces for type and time of episode and rescue medication blank, and record "0" in the space for total episodes.

Type of episode (*nausea, retching, vomiting, dry heaves*)	**Time of Episode**	**Rescue Medication Taken (yes/no)?** *If yes, record on the Medication Use Diary*
	am pm	
	am pm	
	am pm	
	am pm	
	am pm	
	am pm	
	am pm	
	am pm	
Total number of episodes in the last 24 hours?		_____

Please sign when the diary has been completed at the end of each day and return to the study coordinator during your next clinic visit.

Participant Signature: _____ **Date:** _____

version dated 29DEC16

Appendix H. Study Drug Diary

Study Drug Diary

Protocol No.	Participant No.	Participant Initials
UCSD XXXXXX		

Instructions for completion:

- Please complete this diary on ***each day that you take your Lazanda dose***. Enter the date and time you take Lazanda in the appropriate box. Circle "am" or "pm" next to the time for each dose.
- Please indicate the dose of Lazanda administered on each day: 1 spray in 1 nostril = 100 mcg, 1 spray in each nostril = 200 mcg, 2 sprays in each nostril = 400 mcg
- If you forget to take your dose of Lazanda before your daily radiation treatment, skip the dose for that day and resume taking Lazanda at your next scheduled radiation therapy visit. Please mark a line through the date and time for any day where a dose was missed.

Date (mm/dd/yy)	Time (hh:mm)	Dose (mcg)
	am pm	
	am pm	
	am pm	
	am pm	
	am pm	
	am pm	
	am pm	

Date (mm/dd/yy)	Time (hh:mm)	Dose (mcg)
	am pm	
	am pm	
	am pm	
	am pm	
	am pm	
	am pm	
	am pm	

Please sign when the diary has been completed at the end of the study and return to the study coordinator during your next clinic visit.

Participant Signature: _____ **Date:** _____

version dated 29DEC2016

Appendix I. NRS Scale Log

NRS Score Log

Protocol Number	Participant No.	Participant Initials
HRPP#XXXXXX		

Instructions for completion:

- Use the NRS score scale, where 0 is no pain, 5 is moderate pain and 10 is worst pain
- If the 100 mcg dose not achieve adequate pain control at the first assessment of the simulation visit, the subject will receive a second dose 2 hours later as per label until the optimal dose is obtained. If not practical the subject will delay or reschedule the next assessment of the simulation (within a 14 days period) or XRT delivery. **Mark N/A if a higher dose is not required.**
- Palliative radiation treatments usually last 15 minutes or less, are completed once a day, five days a week, up to 10 days in duration. **Mark N/A if fraction 6 to 10 are not required.**

Visit/Event		T (-)15: 15 minutes prior to laying down on traetment surface	T0 Laying down on treatment surface	T+15: 15 minutes after laying down on the treatment surface
Mock/ Baseline Visit				
Radiation Therapy Simulation	Lazanda 100mcg			
	Lazanda 200mcg			
	Lazanda 400mcg			
Radiation Therapy	Fraction 1			
	Fraction 2			
	Fraction 3			
	Fraction 4			
	Fraction 5			
	Fraction 6			
	Fraction 7			
	Fraction 8			
	Fraction 9			
	Fraction 10			