Protocol #: LCI-NOS-PAIN-001

TITLE: A PROSPECTIVE, PHARMACOGENOMIC-DRIVEN PILOT STUDY OF PAIN MANAGEMENT IN ONCOLOGY OUTPATIENTS

LAY TITLE: PAIN MANAGEMENT IN ONCOLOGY OUTPATIENTS

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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
ASCO	American Society of Clinical Oncology
BSA	Body Surface Area
COMT	Catechol-O-methyltransferase
CPIC	Clinical Pharmacogenetics Implementation Consortium
CTMS	Clinical Trials Management System
eCRF	Electronic Case Report Form
EM	Extensive Metabolizer
ESAS	Edmonton Symptom Assessment Scale
FDA	Food and Drug Administration
IM	Intermediate Metabolizer
IRB	Institutional Review Board
MEDD	Morphine Equivalent Daily Dose
NCCN	National Comprehensive Cancer Network
OPRM1	Opioid Receptor-like 1
PGx	Pharmacogenomic
PM	Poor Metabolizer
RICE	Rest, Ice, Compression, Elevation
UM	Ultra-rapid Metabolizer

SCHEMA

LCI-NOS-PAIN-001: A Prospective, Pharmacogenomic-Driven Pilot Study of Pain Management in Oncology Outpatients

S-I: Patel, J.

Objectives:

Primary: To determine the percentage of subjects achieving significant pain improvement over a one month period.

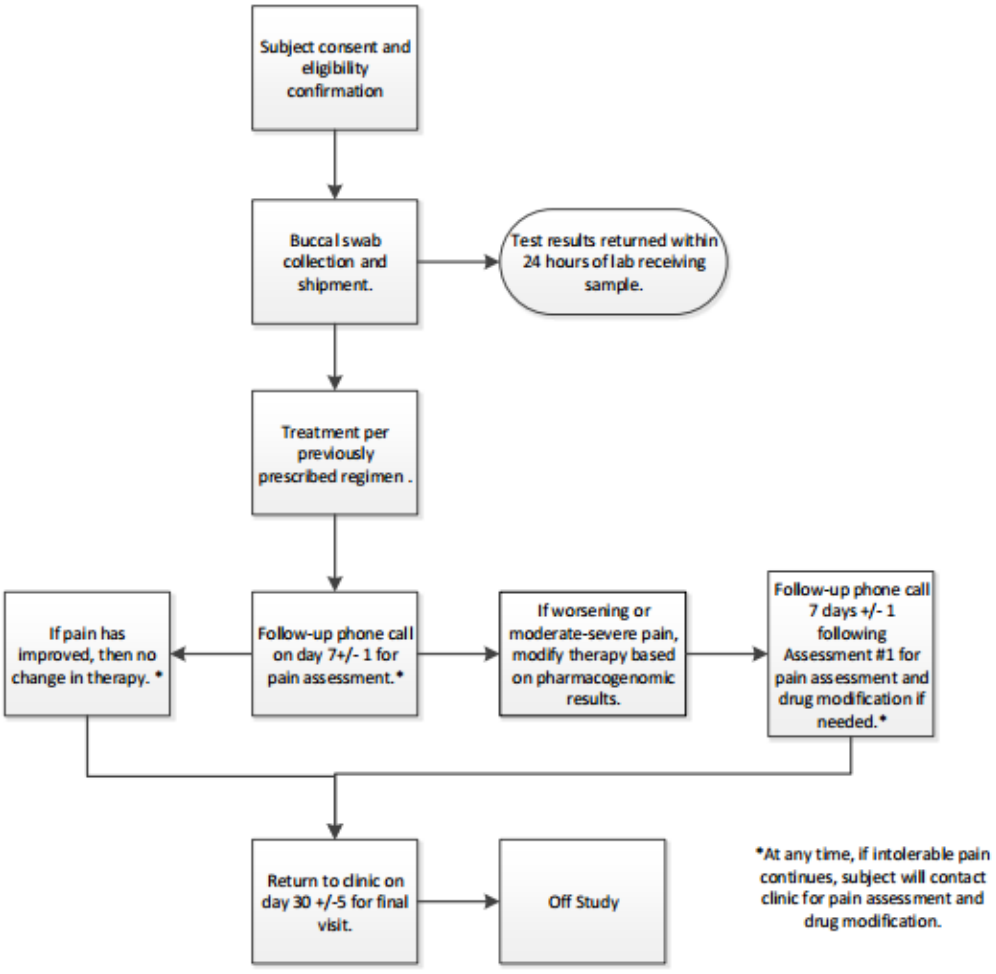
Secondary: 1) To determine success rate of achieving significant pain improvement after receiving pharmacogenomic-guided drug/dose modification. 2) To detect the frequency of actionable and potentially actionable genotypes. 3) To correlate morphine equivalent daily doses with pharmacogenomic results and pain response. 4) To determine the success rate of achieving a subject's personalized pain goal by one month. 5) To determine the use of incidental information.

Safety: 1) To identify rates of opioid-related adverse events.

Exploratory: 1) To evaluate selected secondary objectives on the subgroup of subjects enrolled after the expanded gene panel. 2) To develop a multigene model that may predict opioid response using pharmacogenomic response. 3) To determine whether caffeine consumption and CYP1A2 genotype correlates with pain response. 4) To measure subjects' perceptions of being bothered by pain treatment over the course of the study, using a 5 point rating subjective scale.

Inclusion Criteria:

- New malignant pain (≥ 2/10) as diagnosed and assessed using the Edmonton Symptom Assessment Scale.
- Any stage of cancer of any tumor location.
- At least 18 years of age.
- Either nociceptive or neuropathic pain.
- Able to understand and be willing to sign the study consent form.



PROTOCOL SUMMARY	
A. Study Title	A PROSPECTIVE, PHARMACOGENOMIC-DRIVEN PILOT STUDY OF PAIN MANAGEMENT IN ONCOLOGY OUTPATIENTS
B. Indication	Malignant pain
C. Clinical Phase	Pilot/Single-arm Phase II
D. Summary of Rationale	About half of all cancer patients seen in oncology clinics have pain at initial assessment; pain relief within a one-month period is seen in approximately one third of these patients and pain worsening in about one fifth. Risk factors for under-treatment of cancer pain include age older than 65 years, minority status, and inadequate pain assessment practices. There is a need for better methods of opioid drug/dose selection and identification of risk factors for worsening pain. Pharmacogenomic approaches offer insight into the genetic variables that impact the pharmacokinetic and pharmacodynamic behavior of opioids. Translating pharmacogenomic results into actionable prescribing decisions will ultimately enable a personalized approach to pain management, increasing the chance of significant pain improvement.
E. Objectives	Primary objective: To determine the percentage of subjects achieving significant pain improvement over a one month period (≥ 2 point decrease from baseline pain score on an 11-point scale [0-10]) in patients receiving pharmacogenomic testing. Secondary objectives: To determine the success rate of achieving significant pain improvement at Assessment #2 as measured from pain score at Assessment #1 in subjects who received a PGx-guided drug/dose modification at Assessment #1. To determine the success rate of achieving significant pain improvement at the Final Assessment as measured from pain score at Assessment #1 in subjects who received a PGx-guided drug/dose modification at Assessment #1. To determine the success rate of achieving significant pain improvement at Assessment #1 as measured from baseline pain score in all evaluable subjects. To determine the success rate of achieving significant pain improvement at Assessment #2 as measured from baseline pain score in evaluable subjects who complete Assessment #2, per protocol.

	To evaluate the proportion of gene mutations determined in the pharmacogenomic panel, "Pain Profile". To detect the frequency of "actionable genotypes" and "potentially actionable genotypes". To correlate morphine equivalent daily doses (MEDD) with pharmacogenomic results and pain response. To describe the rate of observing potential drug-gene interactions not related to pain medications. To determine subjects' "personalized pain goal" at baseline and measure the success rate of achieving his/her "personalized pain goal" at the Final Assessment. <u>Safety objectives:</u> To identify rates of opioid-related adverse events including, but not limited to, constipation, fatigue, nausea, vomiting, somnolence, dizziness, cognitive disturbance, dry mouth, shortness of breath, pruritus, and urticaria. To correlate rates of opioid-related adverse events with pain worsening and pharmacogenomic results. <u>Exploratory objective:</u> To evaluate selected secondary objectives on the subgroup of subjects enrolled after the expanded gene panel. To develop a model that may predict opioid response using pharmacogenomicresults and other factors associated with pain worsening. To determine whether caffeine consumption and CYP1A2 genotype correlate with pain response. To measure subjects' perceptions of being bothered by pain treatment over the course of the study, using a 5-point subjective rating scale.
F. Summary of Study Design	Cancer outpatients with uncontrolled malignant pain will be offered a pharmacogenomic panel through participation in the proposed study. All subjects will be assessed and prescribed a pain regimen as part of standard practice at the initial visit. Subjects who meet the eligibility criteria will be

	offered to participate in the clinical trial. Consented subjects will provide a buccal swab for pharmacogenomic testing and will be discharged on their initial opioid pain regimen. After the initial visit, subjects will be asked to rate their daily pain on a scale of 0-10 using a standardized, single question. A nurse or coordinator will follow up with the subject by telephone on day 7 +/- 1; this will be "Assessment #1". Subjects will be asked to report information about their pain scores, pain medication use, and caffeine intake, in addition to any bothersome symptoms. A Subject who continues to have "uncontrolled" pain, is experiencing bothersome symptoms, and/or requests for a drug/dose modification will have his/her drug/dose modified using the pharmacogenomic test results as a tool. If the subject has had significant pain improvement, stable mild pain and/or is satisfied with their level of pain at the assessment (regardless of pain score), he/she will be recommended to continue the current drug/dose and return to clinic on day 30 +/- 5 for the final follow up. Subjects will be told to call the clinic if their pain becomes intolerable or they experience bothersome symptoms after the first Assessment for further drug/dose modification, if needed prior to day 30 +/- 5. The nurse or coordinator will follow up with subjects receiving a drug/dose modification after another 7 days +/- 1; this will be considered "Assessment #2". Subjects who have now had significant pain improvement, stable mild pain, and/or are satisfied with their level of pain at the assessment (regardless of pain score) will continue on the same regimen. If the subjects' pain is still "uncontrolled", they are experiencing bothersome symptoms, and/or they request for a drug/dose modification, the clinical team will modify the drug/dose accordingly. Subjects will then be told to call the clinic if they continue to experience intolerable pain and/or bothersome symptoms; otherwise, all subjects will be seen in clinic on day 30 +/- 5 (the last day of study completion); this will be the "Final Assessment." If a subject experiences intolerable pain prior to any scheduled assessment, the subject will call the clinic immediately for appropriate drug/dose modification. The subject will administer the opioid regimen for at least 48 hours to allow drug effect to take place, prior to contacting the clinic for intolerable pain. If a subject is in contact with the LCI Palliative Clinic prior to "Assessment #1" or "Assessment #2", and reports uncontrolled pain or bothersome symptoms requiring a drug/dose modification or adjustment, the interaction will be considered "Assessment #1" or "Assessment #2", respectively. Subjects will be instructed to administer the pain medication(s) for at least 48 hours prior to calling the clinic to allow adequate time for drug effect to take place.
G. Sample	71 evaluable subjects
H. Dosage	Variable, depending on subject and genetic factors

I. Statistical analysis	The primary objective is to evaluate the percentage of subjects achieving at least a 2-point improvement in their self-reported pain at one month compared to their baseline pain score. It has been reported that, based on this same scale, approximately 30% of cancer patients receiving standard of care pain management experienced at least a 2-point improvement in pain score between visits. Assuming a one-sided alpha = 0.10 significance level, a sample size of 71 will provide at least 90% power to reject the null hypothesis, assuming the true pain improvement rate is 0.45. The study will enroll subjects until the evaluable population consists of 71 subjects.

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1. OBJECTIVES

1.1. Primary Objective

To determine the percentage of subjects achieving significant pain improvement over a one month period (defined as a ≥ 2 point decrease from baseline pain score on an 11-point scale [0-10]) in oncology outpatients receiving pharmacogenomic testing.

1.2. Secondary Objectives

a. To determine the success rate of achieving significant pain improvement *at "Assessment #2"* (i.e. after initial pharmacogenomic-driven therapy selection) as measured from pain score at Assessment #1 in subjects who received a PGx-guided drug/dose modification at Assessment #1.

b. To determine the success rate of achieving significant pain improvement *at the Final Assessment* as measured from pain score at Assessment #1 in subjects who received a PGx-guided drug/dose modification at Assessment #1.

c. To determine the success rate of achieving significant pain improvement at Assessment #1 as measured from baseline pain score in all evaluable subjects.

d. To determine the success rate of achieving significant pain improvement at Assessment #2 as measured from baseline pain score in evaluable subjects who complete Assessment #2, per protocol.

e. To evaluate the proportion of gene mutations determined in the pharmacogenomic panel, "Pain Profile".

f. To evaluate the frequency of "actionable genotypes" (i.e. presence of mutation(s)/genotype(s) that were used to guide a drug/dose modification) and "potentially actionable genotypes" (i.e. presence of mutation(s)/genotype(s) associated with drug the patient currently is on or presence of mutation(s)/genotype(s) associated with drug the patient is changed to, but the mutation(s)/genotype(s) were not used to guide drug/dose modification) at Assessments #1, #2 (if applicable), and at any unscheduled assessments.

g. To correlate morphine equivalent daily doses (MEDD) with pharmacogenomic results and pain response.

h. To describe the rate of observing potential drug-gene interactions not related to pain medications. (i.e. how often did the Investigator identify a drug-gene

interaction for non-pain related medications, regardless of whether or not a modification was made).

i. To determine subjects' "personalized pain goal" (the maximal intensity of pain from 0 to 10 that would still be considered comfortable for the subject) at baseline and measure the success rate of achieving his/her "personalized pain goal" at the Final Assessment.

1.3. Safety Objectives

a. To identify rates of opioid-related adverse events including, but not limited to, constipation, fatigue, nausea, vomiting, somnolence, dizziness, cognitive disturbance, dry mouth, shortness of breath, pruritus, and urticaria.
b. To correlate rates of opioid-related adverse events with pain worsening and pharmacogenomic results.

1.4. Exploratory Objectives

a. To evaluate selected secondary objectives on the subgroup of subjects enrolled after the expanded gene panel.
b. To develop a model that may predict opioid response using CYP2D6, CYP3A4, COMT, and OPRM1 status and other factors associated with pain control (i.e. baseline demographics, baseline pain, bother by adverse events, caffeine intake, other genetic variants etc.). A second model will be estimated using the subgroup of subjects enrolled after the expanded gene panel to assess the impact of the expanded gene panel in addition to the genes and other factors used in the first model.
c. To determine whether caffeine consumption and CYP1A2 genotype correlate with pain response.
d. To measure subjects' perceptions of being bothered by pain treatment over the course of the study, using a 5-point subjective rating scale.

2. BACKGROUND AND RATIONALE

2.1. Pain in Oncology Patients

Pain is one of the most persistent and burdensome symptoms in patients with cancer, affecting 49% to 57% of patients with curable cancer and 56% to 75% of patients with advanced disease. Even when treated, pain is often severe enough to impair patients' ability to function [1]. A meta-analysis of 52 pain studies showed that pain prevalence exceeds 50% for all cancer types. Of these patients, one-third graded their pain as moderate or severe [2]. Estimates of sub-therapeutic treatment of pain in cancer patients range from 25-43% worldwide [3], with approximately one-third of cancer

patients in the United States achieving significant pain improvement at one month [4]. Risk factors for under-treatment of cancer pain include age older than 65 years, minority status, misconceptions about analgesics and their adverse effects, as well as clinician knowledge deficits and inadequate pain assessment practices. Studies have also demonstrated a relationship between pain control and survival. In a study of 339 head and neck cancer patients, the 5-year survival rate was 81.8% for patients with low post-treatment pain and 65.1% for those with high pain [5]. In addition to its influence on survival and quality of life, the economic costs of chronic pain are enormous [6]. In fact, a study found that the annual cost of [cancer and non-cancer] pain (total financial cost, including health care cost and loss of productivity, ranged from $560-635 billion) was greater than the annual costs in 2010 dollars of heart disease ($309 billion), cancer ($243 billion), and diabetes ($188 billion) [7].

Published in 2014, the largest prospective evaluation of pain in ambulatory cancer patients in the United States sought to understand how cancer-related pain changes and what factors influence it [6]. Investigators analyzed a total of 2,761 patients who had pain scores reported at both the initial assessment and follow up (one month). Of the entire sample, 53% had no pain, 23.5% had mild pain, 10.3% had moderate pain, and 13.2% had severe pain. Of the patients presenting with any pain, 32.2% had reduced pain, 19.6% had worse pain, and 48.2% had stable pain at follow-up assessment. Of the entire sample, 54.9% of patients had adequate pain management at both visits, 11.4% had adequate pain management at initial visit but were undertreated at follow-up visit, 10.2% of patients were undertreated at initial visit but had adequate pain management at follow-up visit, and 11.7% of patients were undertreated at both visits. Of the patients presenting with any pain, 42.5% were at least moderately bothered by adverse effects related to treatment of pain (higher for those taking stronger opioids). In a multivariable logistic analysis, pain owing to cancer, neuropathic pain, moderate-to-severe constipation, comorbidity-related discomfort, lung cancer, taking fewer medicines, unemployment, and treatment in community institutions were associated with increased odds of worsening pain[6].

A Special Series of 14 articles published in May 2014 in the *Journal of Clinical Oncology* on "Pain in Patients with Cancer" acknowledged that untreated or undertreated pain is common in cancer patients, with little evidence of recent improvements. This special issue was assembled with the hope of enhancing clinicians' understanding of cancer pain and treatment, and provides practical methods to managing malignant pain such as the use of a multidisciplinary approach involving non-pharmacologic interventions (education, psychosocial support, physical therapy, etc.). However, the influence of pharmacogenomic variables on pain management was not discussed, likely due to the paucity of prospective clinical data that exists.

2.2. Pharmacogenomics and opioids

CYP2D6 is the primary metabolic enzyme responsible for the activation of weak opioids (codeine, tramadol, oxycodone and hydrocodone) into stronger opioids (morphine, o-desmethyltramadol, oxymorphone and hydromorphone, respectively); however, it is important to note that oxycodone and hydrocodone parent metabolites still carry significant opioid activity compared to parent codeine and tramadol. More than 100 CYP2D6 alleles have been identified, with *3, *4, and *5 accounting for approximately 95% of the poor metabolizer (PM) phenotype. The most common intermediate metabolizer (IM) phenotypes are *10 and *17. Additionally, multiple copies of a functional allele may result in the ultra-rapid metabolizer (UM) phenotype (most often occurring with *1 or *2 duplications). Patients harboring the *1 and/or *2 alleles are termed extensive metabolizers (EM; normal genotype). Allele frequencies vary by ethnicity; Caucasians have a higher frequency of the *4 allele (18-23%), the African American population have a higher frequency of the *17 allele (15-34%), and the Japanese population have a higher frequency of the *10 allele (39-41%) [8].

Codeine and tramadol rely almost exclusively on CYP2D6 for activation to their active metabolites, morphine, and O-desmethyltramadol, respectively. The clinical analgesic effect of codeine is mainly attributed to its conversion to morphine, which has a 200 times higher affinity and 50 times higher intrinsic activity at the mu-opioid receptor than codeine itself [9]. Case reports of codeine fatalities in CYP2D6 UMs [10-15] resulted in a black box warning being issued in 2013, stating that codeine use in certain children with the UM phenotype may result in life-threatening adverse events or death. As a result, institutions such as St. Jude Children's Hospital require preemptive CYP2D6 genotyping prior to codeine administration. Similarly, a case report of tramadol-induced respiratory depression was reported in a UM patient who also had renal impairment [16]. Alternatively, it has been demonstrated that the analgesic activity of tramadol in PM patients is significantly reduced [16-19]. In a prospective study of nearly 300 patients recovering from abdominal surgery, the percentage of non-responders was significantly higher in the PM group (46.7%) compared with the EM group (21.6%; p=0.005)[19].

Oxycodone and hydrocodone are metabolized by CYP2D6 to more potent metabolites, oxymorphone, and hydromorphone, respectively, and by CYP3A4 to inactive metabolites, noroxycodone, and norhydrocodone [20]. In one study, CYP2D6 PMs required significantly larger cumulative oxycodone doses for equianalgesic effect compared to EMs (25 mg vs. 16 mg; P=0.005) [21]. Similarly, a study showed that PMs achieved 8-fold lower hydromorphone concentrations versus UMs, which significantly correlated with pain relief [20]. Another study demonstrated that CYP2D6 UMs experienced 40% higher pain tolerance thresholds compared to EMs,

while PMs had a 20-30-fold lower pain tolerance compared to EM/IMs [22]. Although no studies have investigated the association between CYP3A4 polymorphisms and oxycodone or hydrocodone response, drug-interaction studies have demonstrated that CYP3A4 inhibition increases exposure and pharmacodynamic effects of oxycodone [23]. Studies have confirmed that the CYP3A4*22 allele (frequency in Caucasian population is 5-7%) results in significantly lower enzyme activity, impairing the metabolism of common CYP3A4-metabolized drugs [24]. While the change in opioid levels due to the use of competing CYP450 drugs is an iatrogenic effect, a similar mechanism is at the root of natural polymorphisms that give rise to the varying metabolic capacity of opioids that utilize this pathway. Drug-gene and drug-drug interactions may overlap, resulting in additive effects on drug disposition and ultimately therapeutic response and/or toxicity.

The efficacy of opioid analgesia can be enhanced by the co-administration of catecholamines, which are involved in the modulation of pain. Catechol-O-methyltransferase (COMT) is responsible for the inactivation of catecholamines (dopamine, adrenaline and norepinephrine). As a result, genetic variability in COMT can contribute to pain sensitivity. It has been shown that a common variant allele (1947G>A) (allele frequency 48%) results in a three- to four-fold reduction in COMT enzyme activity [25]. A study of 207 Caucasian cancer patients demonstrated that patients with the GG genotype required significantly more morphine (155 mg/24 hrs) compared to AG (117 mg/24 hrs) and AA genotypes (95 mg/ 24 hrs)[26]. Another study in 197 Caucasian cancer patients found that certain haplotypes within the COMT gene influence the cumulative morphine dose needed [27].

Lastly, the mu-opioid receptor, the primary site of action of opioids, is encoded by the gene opioid receptor-like 1 (OPRM1). The OPRM1 118A>G polymorphism (allele frequency 8-17%) results in less effective opioid analgesia, as demonstrated with cancer patients with the GG genotype requiring higher morphine doses for pain relief compared to AA patients [28]. A study showed that patients undergoing total knee arthroplasty with the GG genotype consumed approximately 60% more morphine than patients who were heterozygous or homozygous wild-type [29].

Organizations, such as the Clinical Pharmacogenetics Implementation Consortium (CPIC)[30], provide pharmacogenomic-based guidelines on dosing recommendations for codeine, while the Dutch Pharmacogenetics Working Group[31] provides guidelines for codeine, oxycodone, and tramadol (amongst other classes of drugs metabolized by the CYP2D6 pathway, such as antidepressants).

2.3. Study Rationale

There is an evident unmet clinical need for optimal methods of personalizing pain management. Current standard of care for pain management is highly empirical, drug and dose selection is often based on subjective measurements, and continuous dose modifications are required in at least half of all patients.

The existing literature regarding opioid pharmacogenomics has been correlative in nature. The paucity of interventional trials conducted in clinical practice has resulted in the lack of routine clinical use of these tests, particularly in cancer patients. To our knowledge, this pilot trial will be the first prospective, interventional study to investigate the clinical application of a multigene pharmacogenomic panel, or "Pain Profile" provided by XGene Diagnostics to guide opioid drug and dose modifications. After study activation, this "Pain Profile" was expanded by XGene Diagnostics to include additional genes not in the original panel, here referenced as "expanded gene panel." Given the number of pain medications and dosages available coupled with the large variability in equianalgesic dosing, our proposed method provides an advantage over existing methodologies by using an informed approach to pharmacotherapy selection based on patient-specific genetic factors that influence drug disposition and action, potentially allowing for enhanced pain control. In the same manner a clinician modifies therapy based on pain score, drug interactions, lab values, tolerability, and other clinical factors, pharmacogenomic information is an additional tool that can be used to further personalize drug and dose selection. By incorporating subjects' genotype into medication management, in addition to the use of a validated pain assessment tool (Edmonton Symptom Assessment Scale [ESAS]) which is already integrated into our electronic medical record, our approach reduces the subjectivity inherent in the nature of the pain phenotype. Given the lack of prospective studies, our interventional trial is imperative to allow better interpretation of the clinical actionability of these pharmacogenomic variants and how they influence opioid response.

Additionally, given that caffeine consumption has been demonstrated to influence pain response [32], we hypothesize that pharmacogenomic variations in the drug metabolizing enzyme of caffeine, CYP1A2, in addition to caffeine consumption, may influence pain response through modulation of caffeine levels. We will explore this association as an exploratory endpoint.

The results of this study will allow clinicians in our palliative medicine clinic to better understand the clinical utility of applying pharmacogenomic information to personalize pain medication management. Given that approximately 50-60 cancer patients are referred to the palliative medicine clinic per month (the majority of whose

chief complaint is malignant pain), we will be able to rapidly assess the feasibility of our approach in a pilot setting (expected study duration is approximately 24 months). If this proof of concept is met, we plan to conduct a randomized study to validate our approach versus standard of care. The results of these studies will help to confirm or nullify the clinical utility and applicability of using pharmacogenomic testing to guide pain management in ambulatory cancer patients, an important and lingering question amongst oncology professionals. If successful in meeting the primary endpoints, these studies may help define a paradigm in which pharmacogenomic testing is routinely used in clinical practice to optimize pain management in cancer patients.

3. SUBJECT SELECTION

3.1. Accrual

Accrual is expected to be 71 evaluable subjects, those enrolled subjects who complete the pain question as part of the Edmonton Symptom Assessment Scale at both the initial visit and on the final visit, over an enrollment period of approximately 24 months. Subjects will be recruited from the LCI Palliative Care Clinic.

3.2. Inclusion Criteria

Subjects must meet <u>all</u> of the following criteria:

- Presence of uncontrolled *malignant* pain (score of ≥ 2 on an 11point scale [0-10]) as diagnosed and assessed by the Investigator, using the Edmonton Symptom Assessment Scale (ESAS) (Appendix B)
- Documentation of any stage of cancer of any tumor location (solid or hematological)
- At least 18 years of age
- Either nociceptive or neuropathic painAnticipated to begin treatment with at least one opioid analgesic for treatment of malignant pain, or continue treatment with an opioid analgesic if opioid-tolerantAble to understand and be willing to sign the study consent form

3.3. Exclusion Criteria

Subjects must not meet <u>any</u> of the following criteria:

- Inpatient service at baseline visit
- Significant dysphagia and inability to swallow oral medications as determined by the Investigator

- Active or recent (within one year) drug and/or alcohol abuse as determined by the Investigator
- Significant baseline cognitive impairment, as determined by the Investigator
- Known (anaphylactic) hypersensitivity to any opioid
- Severe oral mucositis that would impair proper buccal testing as determined by the Investigator
- Receiving concurrent rehabilitation medicine care, nociception modulation (e.g. electrical stimulation), use of modalities with physiologic effects that indirectly influence nociception (e.g. light, laser therapy), or any other non-pharmacologic approaches to malignant pain management other than exercise and rest, ice, compression, and elevation (RICE)
- Presence of major psychiatric disorders as determined by the Investigator
- Receiving active treatment or prophylaxis for epilepsy
- Unable or unwilling to sign the study consent form

3.4. Subject Withdrawal

Subjects **must** be withdrawn from the study (treatment and procedures) for the following reasons:

- Subject withdraws consent from study treatment and study procedures. A subject will be removed from the trial at his/her own request. At any time during and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantages as a result.
- If, in the Investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- Study samples for pharmacogenomic testing are lost or non-evaluable.
- Severe opioid-related toxicity requiring inpatient hospitalization
- Death

Subjects **may** be withdrawn from the study for the following reasons:

- The subject is non-compliant with the study treatment, procedures, or both, where non-compliance is defined as lack of drug administration for any reason other than tolerability
- Subject is lost to follow-up and/or is unable to be contacted for Assessment #1 and/or #2 during the time window indicated in the protocol.
- Development of a concurrent illness or situation which would, in the judgment of the Investigator, significantly affect assessments of clinical status and trial endpoints.

- Use, or suspicion of use, of illicit drugs or substances (self-reported) that may, in the opinion of the Investigator, have a reasonable chance of contributing to non-compliance, opioid abuse, drug toxicity, and/or otherwise skewing the trial result
- Any other (non-disease related) reason, at the Investigator's discretion
- Pharmacogenomic test results are not returned prior to the subject needing a drug/dose modification.
- Subject is unable to return to clinic within 5 days before or after day 30 (day 30 +/- 5).

Any subject removed from the trial will remain under medical supervision per standard of care procedures until discharge or transfer is medically acceptable.

In all cases, the reason for withdrawal must be recorded in the CTMS and in the research record.

3.5. Screen Failures

A subject who, for any reason (e.g. failure to satisfy the selection criteria or withdraws consent), terminates their participation in the study before providing a buccal swab sample is regarded as a "screen failure".

All screen failures will be recorded in the Clinical Trial Management System (CTMS).

3.6. Replacements

Subjects who withdraw consent after providing a buccal swab sample will not be replaced. Screen failures may be replaced.

4. INVESTIGATIONAL PLAN

4.1. Milestone Date Definitions

Eligibility date: the date when the last procedure occurred that confirmed subject eligibility.
Enrollment date: the date of buccal swab collection.
Treatment Discontinuation date: the date the subject is taken off their prescribed pain medications, whether it be doctor-alone or PGX-guided. This is prior to the Off Study date. If the subject continues their prescribed pain medication after completing study procedures, the Treatment Discontinuation date will be the same as the Off Study date.

Off Study date: the day after the Final Assessment Day 30 +/- 5 or sooner if subject is withdrawn from the study.

4.2. Overall Study Design and Plan

This is a prospective, single arm, Phase II interventional study involving the use of pharmacogenomics to guide pain management in oncology outpatients with pain. All subjects will be assessed and diagnosed using the Edmonton Symptom Assessment Scale (ESAS) at baseline and prescribed an opioid pain regimen per standard practice. Following consent and eligibility confirmation, all subjects will submit a specimen (buccal swab) for pharmacogenomic testing, the results of which will be used to help determine their appropriate pain medication/dose modification in the event their initial regimen does not result in pain improvement. All drug/dose modifications will be within standard guideline recommendations, such as those set forth by the National Comprehensive Cancer Network Assessments and follow-up will be done according to the Study Calendar.

4.3. Enrollment

The Investigators will identify potential subjects suitable for the study and will notify the Sponsor-Investigator and/or Protocol Coordinator of the potential enrollment. Written informed consent will be obtained prior to enrollment. The following documents will be obtained/completed:

- Consent form signed by the subject
- Authorization for the Release of Medical Records form signed by the subject
- Lab Requisition Form (XGene Diagnostics)

Following informed consent and eligibility check per standard operating procedures, subjects will be registered and assigned a Study ID number. The Study ID will be a four digit number sequentially assigned to the subject, where 1001 will be the Study ID number assigned to the first subject.

4.4. Baseline

Cancer outpatients referred to the palliative care clinic with uncontrolled malignant pain (pain score ≥ 2 on an 11 point scale [0-10]) will be assessed and prescribed an opioid pain regimen as part of standard practice. Subjects will be assessed using ESAS and treated by their Clinician (MD or NP) Investigator according to standard of care treatment pathways developed by the LCI Palliative Medicine Section at baseline. The treatment pathways have been developed using NCCN and ASCO Guidelines, in addition to a review of the best available literature.

Subjects who consent and are considered eligible will provide a buccal sample for pharmacogenomic testing. The buccal specimen for sample analysis, completed laboratory requisition form, and copy of the subject's medication list will be mailed to XGene Diagnostics. Subjects will also be given a tool to aid in recording pain drug compliance, caffeine intake, and any other pain medications taken as well as a Bothersome Symptom Log to complete at home. The Bothersome Symptom Log and recording tool will be provided to the subject upon discharge from the Baseline visit (multiple copies will be provided in case the subject loses one or more forms). **Only subjects who do not experience significant pain improvement and who receive a new pain regimen at Assessment #1 will be asked to report information about their pain scores, pain medication use, and caffeine intake at Assessment #2 (all subjects will be asked to report this information at Assessment #1).** If the subject has experienced pain improvement, has stable mild pain, or requests no drug/dose modification (regardless of pain score) at Assessment #1, he/she will not require an Assessment #2. All subjects will be asked to complete the Bothersome Symptom log as needed throughout the study period. Baseline bothersome symptoms and adverse events will be recorded at the Baseline visit.

The Investigator will document the subject's personalized pain goal at Baseline, defined as the maximal intensity of pain which the subject deems "comfortable."

The cutoff points for categories of pain severity will be determined using Serlin criteria [36]. Subjects' pain ratings of 1-3 will be coded as mild, 4-5 as moderate, and 6-10 as severe pain at both initial and follow-up assessments. Performance status will be assessed using Eastern Cooperative Oncology Group (ECOG) standards.

Other study procedures as indicated on the Study Calendar will also be completed at Baseline.

4.5. Treatment

Drug administration is variable, depending on drug regimen. Opioids of consideration may include codeine, tramadol, oxycodone, hydrocodone, morphine, oxycontin, MS contin, hydromorphone, fentanyl, or methadone. All drugs are FDA approved, and will be prescribed in the outpatient setting. Dosages and titrations are within guidelines set forth by the National Comprehensive Cancer Network (**http://www.nccn.org/professionals/clinician_gls/f_guidelines.asp**).

Upon receiving the initial prescription for their opioid pain regimen and completing the buccal swab (Baseline visit), subjects will be informed to fill their prescription at a pharmacy that same day. A delay in filling the prescription will not be considered a

protocol violation. Subjects will be asked to rate their pain daily on a scale of 0-10 using the same standard pain question from ESAS (Appendix B) and report their pain medication use at the next assessment.

Subjects will also be asked to report other pain medications or treatments for pain and caffeine intake at Assessments 1 and 2. Caffeine consumption will be measured as the total consumption of all sources of caffeine daily. Subjects will be asked to indicate their primary source(s) of caffeine. In the event that a subject consumes >1 source of caffeine, the exploratory analysis will assume 1 cup of coffee = 1 soda = 1 energy drink = 1 caffeine pill, etc.

Subjects will complete a Bothersome Symptom Log in the event they experience any bothersome symptoms throughout the study period. Subjects will call the clinic if they continue to have intolerable pain or experience bothersome symptoms prior to day 7 +/- 1. This intervention will be considered Assessment #1. Subjects will be instructed at the Baseline visit to take their pain medication(s) as prescribed for at least 48 hours prior to calling the clinic to allow adequate time for drug effect to take place. The subject will be contacted by a research designee via telephone on day 7 +/- 1 for follow-up using the phone call script, if the subject has not already contacted the clinic. The interaction with the subject, whether on day 7 +/- 1 or prior, is defined as "Assessment #1" per the Study Calendar in Section 6.

4.5.1. Assessment #1:

The clinic nurse or research designee will transcribe the information the subject provides. The relevant information (medication, dose, number of pills taken, pain score, and caffeine intake) will be included on the supplementary *Study Data Sheet for Assessments 1 [and 2]*. The Assessment #1 call will take place on day 7 +/-1, unless the subject is in contact with the LCI Palliative Clinic prior to day 7 +/-1 reporting uncontrolled pain or bothersome symptoms requiring a drug/dose modification or adjustment. If the subject experienced any bothersome symptoms and/or adverse events, they will also be recorded at this time. All information obtained during the Assessments will be provided to the multidisciplinary team, including the PharmD and subject's Investigator.

Situations in which there is reason to doubt the validity of the data shared by the subject at their assessment, will prompt a discussion between the Sponsor-Investigator and Protocol Coordinator to consider whether the subject should be withdrawn from the study. These situations do not mandate immediate removal of the subject from the study as certain endpoints may still be evaluable.

If the subject accidentally or unknowingly calls another physician for therapy modification and a drug/dose change is made, the Sponsor-Investigator and Protocol Coordinator will determine whether the subject should be withdrawn from the study; however, this situation does not mandate immediate removal of the subject from the study as certain endpoints may still be evaluable.

The change in pain severity from baseline to Assessment #1 will be calculated for all evaluable subjects by computing the difference between pain score at baseline and pain score at Assessment #1. Pain worsening will be defined as ≥ 2 point **increase** in pain score from baseline on an 11 point scale (0-10), pain improvement as ≥ 2 point **decline** in pain score from baseline, and stable pain will be ≤ 1 point increase or decrease from baseline. Uncontrolled pain will be defined as either pain worsening or stable moderate-to-severe pain (4-10) and will constitute a drug/dose modification.

<u>If the subject has experienced significant pain improvement, mild pain, and/or feels like their pain is adequately treated at Assessment #1:</u>

Subject will continue their prescribed opioid regimen at the same drug and dose and will return to clinic on day 30 +/- 5 for the Final Assessment. If the subject experiences initial pain improvement, but has subsequent pain worsening or experiences bothersome symptoms prior to day 30 +/- 5, they will be requested to call the clinic immediately for drug/dose modification, using pharmacogenomic results, if applicable.

<u>If the subject has pain worsening, stable moderate-to-severe pain, request for further drug/dose modification, and/or has bothersome symptoms (or specifically requests for therapy modification at clinician's discretion) at Assessment #1:</u>

Pharmacogenomic test results, in addition to a review of drug interactions and clinical factors, will be used to guide drug and dose modification. A treatment algorithm has been developed as a starting point to initiate a multidisciplinary discussion of treatment options based on pharmacogenomic test results. This pharmacogenomic-driven treatment algorithm was developed based on opioid metabolism and currently available literature regarding pharmacogenomics and response. There will be no requirement to abide by this set of proposed guidelines as each case will be different based on pain score, clinical factors, drug interactions, and other subject specific variables. A multidisciplinary team including physicians, nurse practitioners and pharmacists (one of which has

particular training and expertise in pharmacogenomics) will evaluate each case to decide on the most appropriate course of treatment.

If at any point the subject requests for or against a medication/dose change, the Investigator will respect this request regardless of the subject's pain score and/or pharmacogenomic test results, and in his/her best clinical judgment may prescribe or not prescribe a medication or dose adjustment. This will not be considered a protocol violation and a discussion will be made between the Sponsor-Investigator and Protocol Coordinator as to whether this subject should be potentially withdrawn. In the event a medication change is made, the subject must return to the clinic to pick up the new prescription. If the subject requires a change in the number or frequency of pills to take, the directions may be provided over the phone and will be appropriately documented.

Subjects will call the clinic if they continue to have intolerable pain prior to the 7th day after initiating the new opioid regimen. Subjects will be instructed to administer the new opioid regimen for at least 48 hours prior to calling the clinic to allow adequate time for drug effect to take place. Otherwise, the subject will be contacted 7 days +/- 1 after Assessment #1 by a research designee using the phone call script. This interaction with the subject is defined as "Assessment #2".

Study procedures as indicated on the Study Calendar will be completed at Assessment #1.

4.5.2. Assessment #2:

Subjects will only have Assessment #2 if a modification to their pain regimen occurred at Assessment #1.

The change in pain severity from Assessment #1 to Assessment #2 will be calculated for subjects receiving a PGx-guided drug/dose modification at Assessment #1 by computing the difference between pain score at Assessment #1 and pain score at Assessment #2. Additionally, the change in pain severity from baseline to Assessment #2 will be calculated for evaluable subjects who complete Assessment #2, per protocol, by computing the difference between pain score at baseline and pain score at Assessment #2. Pain worsening will be defined as ≥ 2 point **increase** in pain score on an 11 point scale (0-10), pain improvement as ≥ 2 point **decline** in pain score, and stable pain will be ≤ 1 point increase or decrease in pain score. Uncontrolled pain will be defined as either pain worsening or

stable moderate-to-severe pain (4-10) and will constitute a drug/dose modification.

The Assessment #2 call will take place for applicable subjects 7 days +/-1 after Assessment #1, unless the subject is in contact with the LCI Palliative Clinic prior to 7 days +/-1 reporting uncontrolled pain or bothersome symptoms requiring a drug/dose modification or adjustment. The clinic nurse or research designee will transcribe the information shared by the subject (medication, dose, number of pills taken, pain score, and caffeine intake) and relay this information to the multidisciplinary team as well as add the results to the subject's research chart. If the subject experienced any bothersome symptoms and/or adverse events, this will also be recorded. Subjects who experience pain worsening, stable moderate-to-severe pain, bothersome symptoms, or request a drug/dose modification may have their drug/dose modified per Investigator discretion. A new prescription will be provided, if needed. Subjects will be informed to call the clinic if they continue to experience intolerable pain and/or bothersome symptoms on the new regimen for a subsequent drug/dose modification; otherwise the subject will return to clinic on day 30 +/- 5 for the Final Assessment.

There is no limit on the number of medication and/or dose modifications that can be made throughout the study period, and subsequent modifications after Assessment #2 will be per Investigator discretion.

Subjects who have had significant pain improvement, mild pain, no bothersome symptoms and/or feel like their pain is adequately treated at Assessment #2 will continue on the same drug and dose and will return to clinic on day 30 +/- 5 for the Final Assessment. Mutation(s)/genotype(s) considered "Actionable" at Assessment #1 or Assessment #2 will not be considered "Potentially Actionable" at Assessment #2 or thereafter for the purposes of the study.

Study procedures as indicated on the Study Calendar will be completed at Assessment #2.

4.5.3. Unscheduled Visit(s)

Subsequent to Assessment #1 or #2, if the patient experiences pain worsening prior to the Final Assessment, phone contact will be made with the clinic to allow the Investigator to make a drug/dose modification, as needed. The Investigator will use pharmacogenomic test results to make a drug/dose modification, when appropriate. The subject may need to come in to the office to receive the new or

modified prescription. The date of the unscheduled visit, pain score during the assessment, subsequent medication/dose change, and evaluation of actionable and potentially actionable genotypes will be documented.

4.5.4. Final Assessment

All subjects will have a Final Assessment on day 30 +/- 5 regardless of whether a drug modification was previously made or not. Subjects will be seen on day 30 +/- 5 and will be re-assessed using ESAS. If a subject is unable to return to clinic within the window, the pain question from ESAS may be collected via phone as per Assessment 1 or 2 procedure. Remaining Final Assessment procedures will be completed when the subject returns to clinic.

The change in pain severity from Baseline to Final Assessment will be calculated for all subjects by computing the difference between initial baseline pain score and pain score at final assessment. Pain worsening will be defined as ≥ 2 point **increase** in pain score from baseline on an 11 point scale (0-10), pain improvement as ≥ 2 point **decline** in pain score from baseline, and stable pain will be ≤ 1 point increase or decrease from baseline. Uncontrolled pain will be defined as either pain worsening or stable moderate-to-severe pain (4-10) and will constitute a drug/dose modification.

In addition, the change in pain severity from Assessment #1 to Assessment #2 (in those completing Assessment #2) and from Assessment #1 to Final Assessment will be calculated for subjects receiving a PGx-guided drug/dose modification at Assessment #1 by computing the difference between pain score at Assessment 1 and pain score at second or final assessment, respectively. Pain worsening will be defined as ≥ 2 point **increase** in pain score from Assessment #1 on an 11 point scale (0-10), pain improvement as ≥ 2 point **decline** in pain score from Assessment #1, and stable pain will be ≤ 1 point increase or decrease from Assessment #1. Uncontrolled pain will be defined as either pain worsening or stable moderate-to-severe pain (4-10) and will constitute a drug/dose modification.

The Investigator will determine the success of achieving the subject's personalized pain goal at this time.

The morphine equivalent daily dose (MEDD) will be calculated and recorded at the Final Assessment by converting the subject's total daily opioid consumption at the Final Assessment to morphine equivalent doses using the following

website: http://www.globalrph.com/narcoticonv.htm widely used across many health systems for drug/dose conversions and fully referenced. If the subject consumes a different amount of opioid each day, the average daily consumption over the previous week will be calculated and recorded.

Subjects will be asked to describe their perceptions of being bothered by pain treatment overall throughout the course of the one-month period, which will be defined as "bothersome symptoms" and measure on the following 5-point rating scale: "1 - Not at all", "2 - A little bit", "3 – Moderately", "4 - Quite a bit", "5 - Extremely". If a subject is unable to return to clinic within the window, the subject's "bothersome symptoms" question may be collected via phone.

Bothersome symptoms and/or adverse events experienced by the subject will be assessed. Other study procedures as indicated on the Study Calendar will also be completed at the Final Assessment.

4.6. Off Study

Subjects will be considered Off Study on the day after their Final Assessment Day 30 +/- 5 or sooner if any criteria requiring subject withdrawal apply. The Off Study date will be recorded in the CTMS.

Adverse events ongoing at the Final Assessment will be managed according to standard of care procedures since subjects may continue on pain regimen and/or undergo changes in their pain regimen after completing all study procedures.

5. STUDY PROCEDURES

The following study procedures are outlined on the Study Calendar.

5.1. Informed Consent

Written informed consent will be obtained from each subject prior to undergoing any protocol-specific evaluations or procedures and prior to initiating treatment. Additionally, all subjects will provide authorization for the release of their medical records for research purposes.

5.2. Demographics and Medical/Treatment History

Demographics and medical/treatment history will be collected at the Baseline visit. Significant medical history findings, as determined by the Clinician Investigator, which occurred prior to the subject signing the study consent, will be documented in

the medical record. Relevant medical and treatment history include, but are not limited to, active medication list, alcohol/tobacco/drug use, prior drug or alcohol rehabilitation, surgical history, past medical history and family history.

5.3. Office Visit

Physical exam and evaluation by body system, height (baseline only), weight, and body surface area (BSA) will be documented in the electronic medical record during the Baseline and Final Assessment visits. Vital signs will also be recorded in the electronic medical record at the Baseline and Final Assessment visits. ECOG performance status will be assessed at the Baseline and Final visit. The Edmonton Symptom Assessment Scale (ESAS) evaluation will be completed at the Baseline visit and at the Final Assessment visit. Subjects will also be assessed for delirium/confusion and active constipation at the Baseline visit and at the Final Assessment Visit. Their personalized pain goal will be determined and recorded at the Baseline visit. Office visits will occur according to the Study Calendar in Section 6.

5.4. Concomitant Medications

Concomitant medications (active and past medication history within previous two weeks of consent, including prescription, herbal and over the counter medications) will be collected per standard clinic procedure for medical and treatment purposes. Any known opioid history will also be noted.

Given that several of the opioids are metabolized by CYP2D6 (but not all) and partially by CYP3A4, potential drug–interactions exist. Precautions should be taken, at the Investigator's discretion, if subjects must receive concomitant medications which are strong CYP2D6 inhibitors and CYP3A4 inhibitors/inducers (examples listed below). Close monitoring of interacting drugs and/or appropriate drug/dose modifications are indicated per Investigator discretion.

Examples of strong CYP2D6 inhibitors (use with caution):

- Bupropion
- Fluoxetine
- Paroxetine
- Quinidine
- Methadone

Examples of moderate CYP2D6 inhibitors (use with caution):

- Duloxetine

- Cinacalcet
- Terbinafine
- Sertraline

Examples of strong CYP3A4 inhibitors (use with caution):

- HIV protease inhibitors
- Clarithromycin
- Grapefruit juice
- Itraconazole
- Ketoconazole
- Nefazodone
- Posaconazole
- Voriconazole

Examples of strong CYP3A4 inducers (use with caution):

- Carbamazepine
- Phenytoin
- Rifampin
- St. John's Wort

5.5. Buccal Collection, Shipping, and Analysis

Collection:
Enrolled subjects will provide a buccal swab for pharmacogenomic testing using a specimen kit from XGene Diagnostics at the Baseline visit (after confirmation of study eligibility) using the supplementary *Buccal Swab Collection Instructions*.

Shipping:
The shipping materials are pre-paid and supplied by XGene Diagnostics on an as needed basis. Once samples have been obtained and packaged, they will be shipped ambient overnight to XGene Diagnostics. The laboratory does not operate on Saturdays or holidays.

Ship to:
X-Gene Diagnostics
5330 Spectrum Drive, Suite K Frederick, MD 21703

Analysis:
Specimen analysis will be conducted per standard procedures atXGene Diagnostics (Appendix A). Test results will be available on a HIPAA compliant web database,

DataPharm (www.xgenedx.com/datapharm), approximately 24 hours after receipt of the specimen at XGene Diagnostics and will be accessible by all Investigators.

Results will be recorded for all subjects, regardless of whether or not the results are used to guide therapy. The pharmacogenomic panel ("Pain Profile") tests may include but is not limited to the following genes: CYP3A5, CYP2B6, CYP2D6, CYP3A4, OPRM1, COMT, CYP2C9, VKORC1, CYP2C19 and CYP1A2. Genes previously reported to be related to opioid use are CYP2D6, CYP3A4, CYP2B6, CYP3A5, OPRM1 and COMT. The genetic test results for these six genes will be used to guide opioid therapy, if applicable. Pharmacogenomic results may also be used to modify other commonly used drugs not relating to pain management, pending subject consent. Regardless, the number of times a potential drug-gene interaction not relating to pain medications are identified will be recorded as a secondary objective. The results for the entire panel of genes may or may not be released to the subject, depending on the subject's request.

5.6. Toxicity Assessment

All adverse events (AEs) and serious adverse events related to the subject's prescribed opioid pain regimen will be monitored and documented (regardless of grade) and reported to the sponsor on an ongoing basis beginning at the Baseline visit and until the subject is off study. The AEs will be documented in the research record and recorded on the eCRF.

Adverse events will be graded according to CTCAE version 4.0 and categorized as "unrelated", "unlikely related", "possibly related", "probably related", or "definitely related" to the subject's pain medication by the Investigator. **All AEs will be recorded per standard procedures. However, only AEs deemed "possibly related", "probably related", and "definitely related" by the Investigator will be included in the study data set.** Investigators will refer to the medication package inserts for the expected side effects. As with any drug, there is always the potential for unexpected AEs, including hypersensitivity reactions.

5.7. Bothersome Symptoms Log Completion

Subjects will track and record their side effects on their Bothersome Symptom Log beginning at Baseline and report these during Assessment #1, Assessment #2 (if applicable), and at the Final Assessment. Subjects will be asked to include the start date, symptoms description, stop/resolve date, frequency of the symptom, severity of the symptom, what relieves the symptom and what makes the symptom worse.

Instructions on how to complete the Log will be provided to the subject. Bothersome symptom information provided by the subjects will be used by the Investigator to assign a toxicity grade and attribution. In the event that the bothersome symptom is related to the subject's prescribed opioid pain regimen, the bothersome symptom will also be recorded as an adverse event and/or serious adverse event.

At the Final Assessment, subjects will rate their overall bothersome symptoms on a subjective scale of 1 to 5 as indicated in Section 4.5.4. The score at the Final Assessment will be recorded in the eCRF.

A subject's failure to complete the Bothersome Symptom Log is not considered a protocol deviation. However, the subject may be withdrawn from the study if failure to complete the Log is categorized as non-compliance per the Investigator.

5.8. Subject Reported Assessment Information

At Assessments 1 and 2, enrolled subjects will be asked to share their medication use, daily pain scores, caffeine intake and additional pain medications taken with the research designee. Subjects will be asked to rate his/her pain symptoms "at their worst" in the previous 24 hours on a scale ranging from 0 ("not present") to 10 ("as bad as you can imagine"). Subjects will be instructed to rate their pain daily at 9PM (or prior to going to sleep). In the event that a subject does not report their daily pain scores upon the Assessment, the subject will be asked to rate their pain at the time of assessment to determine whether their pain has improved, worsened, or has remained the same.

All subjects will be asked to report this information from Baseline visit through the Assessment #1 time point or up to 7 days +/- 1, whichever occurs first. Only subjects who have uncontrolled pain/bothersome symptoms at Assessment #1, per the Investigator, protocol and/or subject assessment, and who receive a new pain regimen will be asked to report this information through the Assessment #2 time point or up to 7 days +/- 1 from Assessment #1, whichever occurs first. Subjects may reference their own notes or the tool provided at Baseline for this information. After Assessment #2, subjects will not be asked to report this information.

5.9. Morphine Equivalent Daily Dose Calculation

The morphine equivalent daily dose (MEDD) will be calculated at the Final Assessment and recorded in the eCRF.

6. STUDY CALENDAR

	Baseline (Day 0)	Assessment #1 (Day 7, +/- 1 day)[a]	Assessment #2 (7 days +/- 1 after Assessment #1)[a,b]	Unscheduled Visits[c]	Final Assessment (Day 30, +/- 5 days)	
Informed Consent	X					OFF STUDY
Medical &Treatment History	X					
Office Visit	X				X	
ECOG Performance Status	X				X	
Concomitant Medications	X					
Buccal Collection	X					
Toxicity Assessment	X	X	X	X	X	
MEDD					X	
Bothersome Symptoms Log	X	X	X	X	X	
ESAS	X	X[d]	X[d]	X[d]	X[e]	

[a] Completed via telephone using the phone call script. Assessment #1 and #2 may occur prior to day 7 +/-1 and day 14 +/-1, respectively, if the subject continues to experience pain/bothersome symptoms and is in contact with the clinic prior to this time.

[b] Only subjects who have uncontrolled pain/bothersome symptoms at Assessment #1 AND who receive a new pain regimen will complete Assessment #2.

[c] A visit or call with a subject outside of protocol defined Assessment window in which the subject reports uncontrolled pain or bothersome symptoms, whereby a drug/dose modification is necessary. Presence of "actionable" or "potentially actionable" mutation(s)/genotype(s) may or may not guide modification. An office visit may be required if the subject needs a new prescription. Otherwise, the visit will be completed over the phone.

[d] Only the pain question from ESAS will be asked at Assessment #1, Assessment #2 and/or an Unscheduled Visit.

[e] Pain question from ESAS may be completed via telephone.

7. STUDY TREATMENT-RELATED ADVERSE EVENTS

7.1. Serious Adverse Events (SAE) Related to Pain Regimen

Serious adverse events related to strong opioids at high doses include respiratory depression, myoclonus, and severe cognitive dysfunction (frequency <1% with proper titration)[34]. Pain is the physiological antagonist to the central depressant effects of opioids. Clinically important respiratory depression is rare in cancer patients because the dose of the opioid is balanced by the underlying pain. Subjects who become very sedated by the medication may, however, develop respiratory depression. This may occur during the initial titration or because of metabolic dysfunction. Respiratory depression can be reversed immediately by the intravenous administration of 0.2-0.4 mg of naloxone, an opioid antagonist. In subjects who are taking drugs with a long plasma half-life, such as methadone, it may be necessary to administer naloxone every 2-3 hours.

All SAEs (including event name, grade, start/stop dates and attribution) will be documented in the subject research record and in the eCRF. The Investigator is responsible for verifying and providing source documentation for all SAEs and assigning the attribution for each event for all subjects enrolled on the study.

Note: Subjects may experience SAEs related to their cancer or cancer treatments. These SAEs (e.g. laboratory abnormalities, hospitalizations, secondary malignancies, etc.) should be recorded in the subject research record and managed according to standard of care procedures but should **not** be identified as SAEs for the purposes of this study, reported to the sponsor, or included in the dataset. Deaths while on study or within 30 days of the off study date (regardless of expectedness or relatedness) are the **only** exception to this criteria. Subject deaths occurring on study or within 30 days of the off treatment date **will** be considered SAEs for this study and **will** be reported to the sponsor and included in the dataset.

7.2. Most Common Adverse Events (AE) Related to Pain Regimen

The following toxicities commonly occur in subjects taking opioids:

- Constipation and/or bowel obstruction
- Nausea
- Vomiting
- Drowsiness
- Confusion
- Histamine release resulting in pruritus, bronchoconstriction, etc.

Investigators will refer to the medication package inserts for the expected side effects. As with any drug, there is always the potential for unexpected AEs, including hypersensitivity reactions.

Adverse events will be managed according to Investigator discretion and standard of care procedures. LCI treatment guidelines may be utilized as a resource to treat adverse events such as constipation and nausea/vomiting.

7.3. Adverse Event (AE) Grading

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE grading. All Levine Cancer Institute staff will have access to a copy of the CTCAE version 4.0.

Grade refers to the severity (intensity) of the AE:

CTCAE Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention is not indicated.

CTCAE Grade 2: moderate; minimal, local, or noninvasive intervention is indicated; limiting to age-appropriate instrumental activities of daily living (ADL; instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

CTCAE Grade 3: severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization is indicated; disabling; limiting to self-care ADL (self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

CTCAE Grade 4: life-threatening consequences; urgent intervention is indicated.

CTCAE Grade 5: death due to an AE.

7.4. Adverse Event Attribution Assignment

Attribution is based on the question of whether there was a “reasonable causal relationship” to the subject’s prescribed opioid pain medication while on study as determined by the Investigator. AEs are considered to be “unrelated” or “related” to the pain medication according to the definitions in Section 9.3.

8. DATA AND SAFETY MONITORING PLAN

8.1. Safety Monitoring

This protocol will be monitored according to the processes in effect for all Levine Cancer Institute investigator- initiated studies and the protocol-specific monitoring plan, and will abide by standard operating procedures set forth by both the Carolinas Healthcare System Office of Clinical and Translational Research and the Levine Cancer Institute Clinical Trials Office. It is the responsibility of the Sponsor-Investigator to monitor the safety data for this study. The Sponsor-Investigator, Statistician, Protocol Coordinator, and other team members as needed will meet regularly to monitor subject consents, enrollment and retention, safety data for all subjects [including adverse events (AE's) for all grades and attributions, serious adverse events (SAE's)], prescribed opioid regimen administration, and validity/integrity of the data. Documentation of these meetings will be kept with study records. SAEs will be reported to the IRB per their requirements. Major protocol deviations that result in a threat to subject safety or the integrity of the study will be reported to the IRB per their requirements. The Sponsor-Investigator will submit data to the LCI Data and Safety Monitoring Committee according to the overarching LCI Data and Safety Monitoring Plan.

As part of the trial, subjects will be assessed at least 3 times within a one month period after the initial visit. At these times, the multidisciplinary team involving a physician, nurse practitioner, pharmacist, and/or research designee will evaluate the subject for symptoms of opioid toxicity (these assessments will be completed by the research designee over the phone, who will then update the clinical team). If the subject experiences any opioid-related severe toxicity, he/she will be admitted to the hospital for in-patient services and will be withdrawn from the study. Given the short duration of the study and the extended approved usage of opioids, safety issues apart from standard side effect management involving primarily constipation and nausea are not expected.

8.2. Data Quality Assurance

This study will be organized, performed, and reported in compliance with the study protocol, standard operating procedures (SOPs) of the Levine Cancer Institute and Carolinas Medical Center Office of Clinical and Translational Research, and other applicable regulations and guidelines (e.g. GCP).

Subject data will be monitored by Levine Cancer Institute Research Monitors routinely for data quality. This monitoring will be done by comparing source documentation to the eCRFs. Any variation between the two data sets will be discussed with the Protocol Coordinator, Sponsor-Investigator, and/or appropriate research personnel.

The study database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be generated and addressed by the appropriate study team member, Protocol Coordinator and/or Sponsor- Investigator. Only authorized personnel will make corrections to the study database and all corrections will be documented in an electronic audit trail.

8.3. Communication Between Investigational Sites

Investigational sites will be required to report applicable AEs, SAEs, deviations or any other problem that could affect the validity/integrity of the study data to the Sponsor-Investigator. All investigational sites will report AEs using the eCRFs, and SAEs using the SAE reporting function in the CTMS to the Sponsor. AEs will be reported within 10 business days of the investigator learning of the event. SAEs will be reported within 24 hours of the investigator learning of the event. Drug administration or any other problem should be communicated to the Protocol Coordinator and/or Sponsor-Investigator in writing as soon as possible but within 2 business days of learning of the event.

9. SAFETY DATA COLLECTION, RECORDING AND REPORTING

All subjects who receive at least one dose of the prescribed opioid regimen will be valid for the safety analysis. All observations pertinent to the safety of the prescribed opioid regimen will be recorded and included in the final report.

Safety variables include AEs and SAEs (whether related to the pain regimen or not) which will be assessed according to the Study Calendar. AEs will be evaluated continuously throughout the study. Safety, tolerability, relationship to the prescribed opioid regimen, and intensity will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

9.1. Unanticipated Problem (UAP) Definition

An unanticipated problem is any event, experience, issue, instance, problem, or outcome meeting all 3 of the following criteria:

- Unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol –related documents AND the characteristics of the subject population being studied.

- Possibly, probably, or definitely related to participation in the research. This means that there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research study.
- The event, experience, issue, instance, problem or outcome suggests that the research places the subject or others at greater risk of harm that was previously known or recognized.

9.2. Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug. Pre-existing conditions that increase in frequency or severity or change in nature during, or as a consequence of use of a drug in human clinical trials are also considered AEs.

Any continuing medical condition with an onset date before the first date of prescribed opioid regimen administration should be considered pre-existing and should be documented at Baseline.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE.

An AE does **not** include:

• Relapse or progression of the underlying malignant disease;
• Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is the adverse event;
• Overdose of either pain medication or concomitant medication without any signs or symptoms unless the subject is hospitalized for observation; and
• Toxicities which can be attributed to the subject's cancer, cancer therapies, comorbidities, or concomitant medications other than the prescribed opioid regimen prescribed as part of participation on this study.

An AE for the study is defined as a toxicity which is deemed possibly, probably, or definitely related to the subject's prescribed opioid regimen by the Investigator. However, only AEs attributed to the subject's prescribed opioid regimen will be recorded in the eCRF and included in the study dataset.

9.3. Adverse Event Attribution

The relationship to the prescribed opioid regimen should be assessed using the following definitions:

Not Related: Evidence exists that the AE has an etiology other than the prescribed opioid regimen (e.g., pre-existing condition, underlying disease, intercurrent illness, cancer therapies, or concomitant medications). This includes events that are considered unrelated or unlikely related to the prescribed opioid regimen.

Related: A temporal relationship exists between the event onset and administration of the prescribed opioid regimen. It cannot be readily explained by the subject's clinical state, intercurrent illness, cancer therapies, or concomitant therapies (other than the pain medication). In the case of cessation or reduction of the dose of pain medication, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective pain medication should not be considered causally related in the context of AE reporting. This includes events that are considered possibly, probably, or definitely related to the prescribed opioid regimen.

Final attribution of AEs should be stated and recorded as follows (choose only one):

Definite – The AE is clearly related to the prescribed opioid regimen.
Probable – The AE is likely related to the prescribed opioid regimen.
Possible – The AE may be related to the prescribed opioid regimen.
Unlikely – The AE is doubtfully related to the prescribed opioid regimen.
Unrelated – The AE is clearly NOT related to the prescribed opioid regimen.

Adverse events (including event name, grade, start/stop date and attribution) will be documented in the research record and recorded on the eCRF for this protocol.

The Investigator is responsible for verifying and providing source documentation for adverse events and assigning the attribution for each event for all subjects enrolled on the study.

9.4. "Unexpected" Definition

An AE is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g. package insert/summary of product characteristics).

9.5. "Serious" and "Life-Threatening" Definitions

An AE or SAE is to be considered serious if the Investigator or Sponsor-Investigator deem it as such and the event results in any of the following outcomes:

- Death;
- Life-threatening situation (subject is at immediate risk of death);
- Inpatient hospitalization or prolongation of an existing hospitalization (excluding those for treatment of cancer, palliative or hospice care, or placement of an indwelling catheter, unless associated with other serious events);
- Persistent or significant disability/incapacity;
- Other: Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm;
    - Blood dyscrasias or convulsions that do not result in hospitalization
    - Development of drug dependency or drug abuse.

An AE or SAE is to be considered life-threatening if the Investigator or Sponsor-Investigator deems it as such and the event poses an immediate threat of death.

9.6. Serious Adverse Event (SAE) Definition

Adverse events may also be considered serious adverse events. **SAEs for this study are defined as medical events that are related to the prescribed opioid regimen (suspected adverse reactions), serious (meeting the definitions in Section 9.5), and unexpected.** Any important medical event, if deemed appropriate by the Sponsor-Investigator, can and should be reported as an SAE to the Sponsor, IRB, and other applicable entities per their requirements.

SAEs will be captured from the time of subject enrollment until the Final Assessment. SAEs will be followed according to standard of care procedures until clinical recovery is complete or until there has been acceptable resolution of the event. This may at times cause the follow-up period of SAEs to be greater than 30 days. The above referenced 30 day time period applies even if the subject is taken off study during this time period. Similarly, the Sponsor-Investigator is responsible for following the subject during the required follow-up period even if the subject lives elsewhere or has been released from his/her care and is being treated under another service at LCI.

Planned hospitalizations and the development of new cancers should not be indicated as SAEs for this study and should not be reported to the sponsor, IRB, or other applicable entities.

Deaths:

While there is no additional protocol mandated follow-up after the subject is considered Off Study, deaths occurring greater than 30 days of the protocol-defined Off Study date thought to be possibly, probably, or definitely related to the prescribed opioid regimen must be reported to the sponsor, IRB, and other applicable entities within 24 hours of knowledge of the event.

All SAEs (including event name, grade, start/stop date, and attribution) will be documented in the medical record and/or research chart and recorded in the study dataset.

The Investigator is responsible for verifying and providing source documentation for all SAEs and assigning the attribution for each event for all subjects enrolled on the study.

SAEs are not expected for this study. An example of a rare potential SAE for this study is an anaphylactic reaction possibly, probably, or definitely related to pain medication.

9.7. Safety Reporting to the IRB

All safety events occurring during the conduct of a protocol and meeting the definition of an UAP or SAE will be reported to the IRB within 10 working days of the Sponsor-Investigator learning of the event.

Protocol deviations involving the informed consent process or subject safety will be reported promptly to the Sponsor-Investigator and IRB but no later than 10 working days of the Investigator learning of the event.

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size

The study will enroll to target 71 evaluable subjects for the final analysis. The primary objective is to evaluate the percentage of subjects achieving at least a 2-point improvement in their self-reported pain at one month compared to their baseline pain score. The self-reported pain score is based on the standardized pain question ranging from 0 (pain not present) to 10 (pain as bad as you can imagine) that is included in the

Edmonton Symptom Assessment Scale (ESAS). It has been reported that, based on this same scale, approximately 30% of cancer patients receiving standard of care pain management experienced at least a 2-point improvement in pain score between visits [5]. A single-stage design will be used to test the hypothesis that the pain improvement rate is less than or equal to 0.30. If at least 27 of the 71 subjects experience at least a 2-point improvement in pain on day 30 +/- 5, the null hypothesis will be rejected (based on an exact binomial test) and the pharmacogenomic-guided therapy for pain management may be considered for further evaluation. Assuming a one-sided alpha = 0.10 significance level, this sample size will provide at approximately 90% power to reject the null hypothesis, assuming the true pain improvement rate is 0.45.

10.2. Endpoint Definitions

10.2.1. Primary Endpoint

The primary endpoint for this study is a binary variable that will be determined for each subject indicating whether or not they experienced at least a 2-point improvement in pain on day 30 +/- 5.

10.2.2. Secondary Endpoints

A secondary endpoint will be calculated for each subject as an ordered categorical variable indicating at least a 2-point improvement in pain score, stable pain (no more than a 1-point change in score), or at least a 2-point worsening in pain score between baseline and the final assessment.

A secondary endpoint for this study is a binary variable that will be determined for each subject in the subset of subjects receiving a PGx-guided drug/dose modification at Assessment #1 indicating whether or not they experienced at least a 2-point improvement in pain as calculated between reported pain scores at “Assessment #1” and “Assessment #2”. Additionally, a secondary endpoint will be calculated for subjects receiving a PGx-guided drug/dose modification at Assessment #1 as an ordered categorical variable indicating at least a 2-point improvement in pain score, stable pain (no more than a 1-point change in pain score), or at least a 2-point worsening in pain score within this interval.

A secondary endpoint for this study is a binary variable that will be determined for each subject in the subset of subjects receiving a PGx-guided drug/dose modification at Assessment #1 indicating whether or not they

experienced at least a 2-point improvement in pain as calculated between reported pain scores at "Assessment #1" and Final Assessment. Additionally, a secondary endpoint will be calculated for subjects receiving a PGx-guided drug/dose modification at Assessment #1 as an ordered categorical variable indicating at least a 2-point improvement in pain score, stable pain (no more than a 1-point change in pain score), or at least a 2-point worsening in pain score within this interval.

A secondary endpoint for this study is a binary variable that will be determined for each subject indicating whether or not they experienced at least a 2-point improvement in pain as calculated between reported pain scores at baseline and Assessment #1. Additionally, a secondary endpoint will be calculated as an ordered categorical variable indicating at least a 2-point improvement in pain score, stable pain (no more than a 1-point change in pain score), or at least a 2-point worsening in pain score within this interval.

A secondary endpoint for this study is a binary variable that will be determined for each subject completing Assessment #2, per protocol, indicating whether or not they experienced at least a 2-point improvement in pain as calculated between reported pain scores at baseline and Assessment #2. Additionally, a secondary endpoint will be calculated as an ordered categorical variable indicating at least a 2-point improvement in pain score, stable pain (no more than a 1-point change in pain score), or at least a 2-point worsening in pain score within this interval.

Other secondary endpoints will include binary and count variables indicating the presence and frequency of "actionable genotypes" (i.e. mutation(s)/genotype(s) that were present and used to guide drug/dose modifications) and "potentially actionable genotypes" (i.e. presence of mutation(s)/genotype(s) associated with drug the subject currently is on or presence of mutation(s)/genotype(s) associated with drug the subject is changed to, but the mutation(s)/genotype(s) were not used to guide a drug/dose modification) for each subject, during Assessment 1, Assessment 2, or any unscheduled visit.

Binary variables will be calculated for each subject and for each gene provided in the pharmacogenomic test results indicating whether or not the genotype is a mutation.

Outcomes from the pharmacogenomic panel, "Pain Profile", and derived morphine equivalent daily doses will also be reported as a secondary endpoint. The MEDD conversion website: http://www.globalrph.com/narcoticonv.htm will be used to convert the average milligrams of opioid consumed daily just prior to the Final Assessment to morphine equivalent daily doses.

A secondary endpoint will be reported as a binary variable indicating whether or not the subject achieves their personalized pain goal (the maximal intensity of pain from 0 to 10 that would still be considered comfortable for the subject) recorded at baseline at the Final Assessment.

10.2.3. Safety Endpoints

Safety endpoints will include opioid-related adverse events (based on CTCAE Version 4.0) and serious adverse events.

10.2.4 Exploratory Endpoints

Average daily caffeine product consumption will be calculated and recorded for each subject as a continuous variable and exploratory endpoint using the information recorded at Assessment #1 and Assessment #2 for those subjects who have an Assessment #2. This measure will be considered both separately and in conjunction with CYP1A2 genotype as correlates with pain response.

A scale of bothersome symptoms related to treatment of pain or other symptoms is reported as a 5-point rating scale ("Not at all", "A little bit", "Moderately", "Quite a bit", "Extremely"). Outcomes for the subjects enrolled will be recorded as an ordered categorical variable and exploratory endpoint at the Final Assessment.

10.3. Analysis Populations

The primary efficacy analysis will be conducted on the population of enrolled subjects who complete the pain question as part of the Edmonton Symptom Assessment Scale at both the initial visit and on the final visit (i.e., the evaluable population). Safety analyses will be conducted on all enrolled subjects. Secondary analyses concerning changes in pain scores from Assessment 1 to Assessment 2 will be conducted on the subgroup of subjects receiving a PGx-guided drug/dose modification at Assessment #1. Secondary analysis concerning changes in pain score from baseline to Assessment #1 will be conducted in all evaluable subjects completing Assessment #1. Secondary analysis concerning changes in pain score

from baseline to Assessment #2 will be conducted in all evaluable subjects completing Assessment #2, per protocol. Secondary analysis concerning the frequency of actionable and 'potentially actionable' genotypes as well as the prevalence of gene mutations will be conducted on the population of subjects receiving pharmacogenomic test results. Aforementioned secondary analyses concerning frequency of genotypes and the prevalence of genes mutations will be evaluated for the original gene panel on the entire cohort of subjects receiving pharmacogenomics results and secondly evaluated for the expanded genes on the cohort of subjects receiving pharmacogenomics results for the expanded gene panel. Other secondary analyses will be conducted on the population of enrolled subjects who are not withdrawn from the study secondary to a protocol violation or the Investigator's discretion. The date of the buccal swab collection will be the enrollment date. Subjects with a baseline pain score of 9 or 10 will be excluded from the analyses of the pain worsening binary variable and the ordered categorical variable described above (because these subjects cannot show a 2-point worsening).

10.4. Analysis Methods

10.4.1. Subject Disposition

An accounting of all enrolled subjects will be provided at the end of the study. This will include a breakdown of subjects who consented, who provided a buccal swab, who completed each assessment, who died on study, who were lost to follow-up during the on study period and/or withdrew consent.

10.4.2. Baseline Subject and Disease Characteristics

A summary of subject demographics (age, race, gender) and disease-related characteristics (as described in Section 5.3) will be completed and subject medical history will be assessed.

10.4.3. Efficacy Analyses

10.4.3.1. Primary Analysis

The frequency and proportion of subjects experiencing at least a 2-point improvement in pain score at Day 30 +/- 5 will be calculated, along with a 95% Clopper Pearson confidence interval. A one-sided exact binomial test of proportions, with $\alpha = 0.10$, will be carried out, testing the null hypothesis that the pain improvement rate is less than

or equal to 0.30.

10.4.3.2. Secondary Analyses

Similar analyses of the pain improvement rate as described in Section 10.4.3.1 will be conducted on the subset of subjects who receive a drug/dose modification at Assessment #1 between two differing intervals: difference in pain scores from Assessment #1 to Assessment #2 and difference in pain scores from Assessment #1 to Final Assessment.

The frequency and distribution of "actionable genotypes" and "potentially actionable genotypes" from the pharmacogenomic panel, "Pain Profile", will be summarized and described.

The frequency and distribution of gene mutations for each gene provided in the pharmacogenomic panel, "Pain Profile", will be summarized and described.

Logistic regression models will be used to model the probability of pain improvement as a function of morphine equivalent daily doses. A cumulative logistic regression model will be used to model the 3-level ordered categorical variable describing pain improvement (described in Section 10.2.2) as a function of morphine equivalent daily doses. Additionally, linear regression models will be used to determine if morphine equivalent daily doses (the response variable) are associated with the pharmacogenomic parameters.

The frequency and proportion of subjects achieving their "personalized pain goals" (described in Section 10.2.2) at the Final Assessment will be summarized and described.

10.4.4. Safety Analyses

Incident rates for adverse events and SAEs will be summarized. Logistic regression models will be used to model the probability of pain worsening as a function of selected adverse events and pharmacogenomics results.

10.4.5. Exploratory Analyses

Logistic regression models will be used to model the probability of pain improvement as a function of CYP2D6, CYP3A4, COMT, and OPRM1 gene status. Additional logistic regression models will be estimated using the subgroup of subjects enrolled after the expanded gene panel to assess the impact of the expanded genes in addition to the genes and other factors used in the aforementioned models. Univariate models will be used to identify genes that are individually predictive and multivariate models including backward elimination and forward selection will be used to identify genes that are independently predictive of response. Additionally, other baseline subject, disease, pain, and bother by adverse event characteristics will be correlated with outcomes.

Logistic regression models will be used to model the probability of pain improvement both univariately as a function of average daily caffeine product consumption or CYP1A2 genotype and bivariately as a function of both average daily caffeine product consumption and CYP1A2 genotype.

Subjects' perceptions of being bothered by pain treatment over the course of the study is recorded using a 5-point rating subjective scale ('Not at all', 'A little bit', 'Moderately', 'Quite a bit', 'Extremely'). It has been reported that, based on this same scale, approximately 58% of patients reported some degree of bother by adverse events related to treatment of pain or other symptoms and approximately 30% of patients reported at least moderate bother by adverse events related to treatment of pain or other symptoms. The proportions and 95% Clopper-Pearson confidence intervals of patients reporting any degree of bother and at least moderate degree of bother will be calculated. A one-sided exact binomial test of proportions, with $\alpha = 0.10$, will be carried out, testing the null hypothesis that the proportion of subjects reporting some degree of bother by adverse events related to treatment of pain or other symptoms is less than or equal to 0.60. A one-sided exact binomial test of proportions, with $\alpha = 0.10$, will be carried out, testing the null hypothesis that the proportion of subjects reporting at least moderate bother by adverse events related to treatment of pain or other symptoms is 0.30.

10.5. Interim Analyses

No interim analyses are planned for this study.

11. STUDY COMPLETION AND TERMINATION

11.1. Completion

The study will be considered complete when one or more of the following conditions are met:

- All subjects have completed all study visits.
- All subjects have discontinued participation in the study.
- The IRB, LCI DSMC, or Sponsor-Investigator discontinues the study for any reason.
- The Sponsor-Investigator defines an administrative or clinical cut-off date.

11.2. Termination

The study will be terminated when one of the following conditions occurs:

If the risk-benefit ratio becomes unacceptable owing to, for example:

- Results of any interim analysis.
- Results of any parallel clinical studies.
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The Sponsor-Investigator has the right to close the study at any investigational site at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected investigational sites must be informed as applicable according to regulation.
- In case of a partial study closure, ongoing subjects, including those in follow-up, must be taken care of in an ethical manner.

Details for individual subject withdrawal can be found in Section 3.4.

12. RETENTION OF RECORDS

Essential documentation, including all IRB correspondence, will be retained for at least 2 years after the study is completed. Documentation will be readily available upon request.

13. ETHICAL AND LEGAL ISSUES

13.1. Ethical and Legal Conduct of the Study

The procedures outlined in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor-Investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate agencies (e.g. DSMC, IRB) will be obtained for all participating investigational sites before the start of the study, according to GCP, local laws, regulations, and organizations.

Strict adherence to all specifications laid out in this protocol is required for all aspects of study conduct; the Investigators may not modify or alter the procedures described in this protocol. Any deviations from the protocol must be explained and documented by the Investigator.

Modifications to the study protocol may be made by the Sponsor-Investigator in the form of a protocol amendment and will not be implemented until after documented approval from the IRB.

The Sponsor-Investigator is responsible for the conduct of the study at all the investigational sites in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Sponsor-Investigator is responsible for overseeing the treatment of all study subjects. The Sponsor-Investigator must assure that all study site personnel, including Sub-Investigators and other study staff members, adhere to the study protocol and applicable regulations and guidelines regarding the study both during and after study completion.

The Sponsor-Investigator will be responsible for assuring that all the required data will be collected and properly documented.

13.2. Confidentiality

All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publically available.

13.3. National Protocol Registration

The Sponsor-Investigator will ensure that the information regarding the study be publically available on the internet at www.clinicaltrials.gov.

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APPENDICES

A. Genotyping information

Pharmacogenomic testing will be conducted at XGene Diagnostics. Specimens will be analyzed for gene mutations by real-time polymerase chain reaction (PCR) (TaqMan SNP Genotyping, Thermo Fisher) developed by X-Gene, Inc. All assays were validated pursuant to the 1988 Clinical Laboratory Improvement Amendment (CLIA) standards by XGene Diagnostics. Performance characteristics were validated by the X-Gene Laboratory with analytical specificity and sensitivity of >99% for detection of all variants listed. The FDA has neither cleared nor approved these assays, nor is FDA pre-market review required. XGene Diagnostics is certified under the Federal 1988 CLIA legislation to perform high complexity clinical laboratory testing and is inspected and accredited by the College of American Pathologists. All pharmacogenetic test results will be available 24 hours after the sample has been received at the laboratory of XGene Diagnostics. Results will be uploaded to a HIPAA compliant web database called DataPharm. Interpretation and commentary are provided to the clinician for educational and consultation purposes only. Diagnosis and treatment decisions are the sole responsibility of the clinician.

B. Edmonton Symptom Assessment System (integrated into electronic medical record)

	0	1	2	3	4	5	6	7	8	9	10	Comment
Pain												
Fatigue												
Nausea												
Depression												
Anxiety												
Drowsy												
Appetite												
Well Being												
SOB												
Other symptom												