ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A221504

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PILOT STUDY OF AN ORAL, SELECTIVE PERIPHERAL OPIOID RECEPTOR ANTAGONIST IN ADVANCED NON-SMALL CELL LUNG CANCER

Industry-supplied agent: Naloxegol (IND: exempt)

ClinicalTrials.gov Identifier: NCT03087708

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Study Resources:

Expedited Adverse Event Reporting
[redacted]

Medidata Rave® iMedidata portal
[redacted]

OPEN (Oncology Patient Enrollment Network)
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Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox [redacted]
Questions regarding specimens/specimen submissions:	Alliance Biorepository at Mayo Clinic

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at [redacted] and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN can be accessed at [redacted] Contact the CTSU Help Desk with any OPEN-related questions at [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website [redacted]. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
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For clinical questions (i.e., patient eligibility or treatment-related) see the Protocol Contacts, Page 2.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – [redacted]. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU website is located at [redacted]		

A Randomized, Double-Blind, Placebo-Controlled Pilot Study of an Oral, Selective Peripheral Opioid Receptor Antagonist in Advanced Non-Small Cell Lung Cancer

Eligibility Criteria (see Section 3.2)

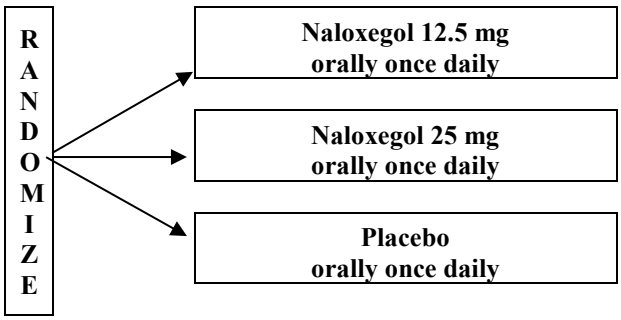
Advanced (stage IIIB or IV) non-small cell lung cancer. See 3.2.1
No known presence of known EGFR or EML4-ALK driver mutations in the tumor
Started first-line systemic therapy of the investigator's choice within 12 weeks prior to registration, or planning to initiate first-line systemic therapy of the investigator's choice within 4 weeks after registration. . See 3.2.3.
No prior systemic therapy for advanced NSCLC (other than current treatment). See 3.2.4.
No current or prolonged recent use of mixed opioid agonists/antagonists or other opioid antagonists. See 3.2.5
No methadone within 4 weeks prior to registration.
Patients must have used opioid medication(s) for pain at some time in the 4 weeks prior to registration. See 3.2.7.
Expected survival > 3 months.
No concurrently active second invasive malignancies except non-melanoma skin cancer. See 3.2.9.
No history of gastrointestinal obstruction or conditions that increase the risk of gastrointestinal obstruction, perforation, bleeding or impairment of the gastrointestinal wall. No abdominal surgery within 60 days of registration.
No acute gastrointestinal conditions. See 3.2.11
No conditions that may compromise blood-brain barrier permeability. See 3.2.12
No history of myocardial infarction ≤ 6 months prior to registration. See 3.2.13.
No severe hepatic impairment (Child-Pugh class C), or acute liver disease.
No known serious or severe hypersensitivity reaction to naloxegol or any of its excipients
No concurrent use of moderate/strong CYP3A4 inhibitors, strong CYP3A4 inducers, or other opioid antagonists or mixed agonists/antagonists. See 3.2.16.
Not pregnant and not nursing. See 3.2.17.
Age ≥ 18 years
ECOG Performance Status 0-2

Required Initial Laboratory Values

Absolute neutrophil count (ANC)	≥ 1500/mm^3
Platelet Count	≥ 100,000/mm^3
Calc. Creatinine Clearance (see Alliance website)	≥ 60 mL/min*
Total Bilirubin	≤ 1.2 x ULN**
AST and ALT	≤ 2.5 x ULN

* Calculated using the Cockcroft-Gault formula
**Unless due to Gilbert's disease

Schema
1 Cycle = 3 weeks during the first year of treatment
1 Cycle = 3 months during the second year of treatment



Treatment is to continue for up to 2 years, but it can be discontinued for unacceptable adverse events. Clinic visits will take place at 3 and 6 weeks and then every 6 weeks for 1 year following the start of treatment. Patients will then be followed every 3 months until 2 years after the start of treatment.

Administration of standard opioids and other analgesics to control pain adequately will be permitted in all patients at the discretion of the treating physician.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

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1.0 BACKGROUND

1.1 Rationale for Proposed Study

Opioid medications are the mainstay of treatment for severe, chronic cancer pain. The analgesic activity of opioids is mediated via central mu opioid receptors (MORs) in the central nervous system (CNS). However, MORs are also present on endothelial cells[1] and in human tumors (peripheral MORs), including lung[2-4] and prostate[5] cancer. Compelling pre-clinical studies indicate that expression and activation of peripheral MORs are associated with tumor progression in animal models. Recent clinical studies raise the possibility that opioid exposure is also associated with tumor progression in patients with various malignancies including lung cancer. See section 1.7. In patients with advanced malignancies, symptoms related to progression of cancer and its treatments, as well the adverse effects of commonly used opioids, all contribute to impair the health-related quality of life (HRQoL).

In view of the above, our long-term goal is to develop a novel, non-chemotherapeutic intervention blocking the activation of *peripheral* opioid receptors that contributes to tumor progression and adverse effects of opioids may improve the HRQoL of patients with advanced malignancies, and may also improve disease outcomes. Towards this eventual goal, we will perform this pilot study to first determine the feasibility and safety of long-term administration of an orally available, FDA-approved, peripherally acting mu opioid receptor antagonist (PAMORA) in a patient population receiving standard systemic therapy for advanced, incurable lung cancer. We hope to eventually study this agent in a more advanced phase clinical trial.

1.2 Rationale for selecting lung cancer

Worldwide, lung carcinoma is the most common malignancy and the leading cause of cancer deaths. The global incidence of lung cancer was estimated to be 1.8 million cases/year in 2012, resulting in nearly 1.6 million deaths/year (nearly 20% of all cancer deaths).[6] In the United States, the incidence of lung cancer is projected to be 224,390 new cases in 2016, which will lead to approximately 158,000 deaths (26.5% of all cancer deaths).[7] The majority (≥ 80%) of lung cancers are non-small cell lung cancer (NSCLC), of which adenocarcinoma is the most common subtype.

Advanced malignancies, including NSCLC, are often accompanied by pain. Approximately 2/3 of patients with advanced malignancies experience pain, with 50% experiencing at least moderate pain; lung cancer ranks third highest for pain prevalence among all malignancies.[8]

Malignancy options that were considered for the current study included (a) patients with various advanced malignancies, or (b) patients with a single tumor type (non-small cell lung cancer, pancreatic, breast or prostate cancer). Including patients with diverse malignancies would accelerate accrual and generalization of the results, but we were concerned that heterogeneity in this patient population and their cancer treatments would have an insurmountable impact on statistical analysis of adverse effects and activity. Advanced pancreatic cancer is common, often presents with inoperable/incurable disease in which survival is relatively short, and is associated with severe, refractory pain. However, there is a lack of basic, pre-clinical or clinical data relevant to the current concept. Breast and prostate cancer were not considered as the optimal malignancies to study because long survival of patients with both of those malignancies will require very prolonged follow-up to detect possible benefit.

The clinical course and prognosis of the various subtypes of NSCLC including adenocarcinoma, large cell carcinoma and squamous cell carcinoma are similar (overall response rate of ~30%, time to progression of 4-6 months, 1-year survival of 30-40% and 2 year survival of 10-15%). Impairment of HRQoL (the primary endpoint of this study) is therefore likely to occur at similar time points in patients with adenocarcinoma as in patients with other subtypes of NSCLC.

Several groups (including ours) have reported that pain/opioids/peripheral opioid receptor activation is associated with poorer outcomes (including shorter survival) in cohorts of NSCLC patients including both adenocarcinoma and other subtypes.[24, 47, 48, 49, 58, 59, 93] We and others have also reported that similar effects occur in diverse malignancies, including those of the prostate, breast, pancreas, esophagus, stomach, colon.[5, 48, 53-59, 94, 95] Therefore, the evidence indicates that the association of peripheral opioid receptor activation with poorer clinical outcomes is likely to be a phenomenon that occurs in many common malignancies, and is not restricted to adenocarcinoma of the lung.

When this study was initially designed, the standard systemic therapy for adenocarcinoma of the lung was a combination of a platinum (cisplatin or carboplatin) and pemetrexed, so we accordingly restricted eligibility to adenocarcinoma alone. However, the field has advanced rapidly, and current standard therapy for adenocarcinoma as well as other subtypes of NSCLC includes immune checkpoint inhibitor alone (e.g. pembrolizumab) for all subtypes of NSCLC where tumor PD-L1 expression is ≥50%, and a combination of immune checkpoint inhibitor therapy with platinum-based chemotherapy in all subtypes of NSCLC where tumor PD-L1 expression is ≥1%. While pemetrexed itself is not recommended for patients with squamous cell carcinoma, the other commonly used standard platinum-based regimens are all Category 1 options common to adenocarcinoma and squamous cell carcinoma (e.g. those including paclitaxel, docetaxel, etoposide or gemcitabine: NCCN Guidelines version 6.2018 for Non-Small Cell Lung Cancer). For the above reasons, we believe that it is no longer necessary to restrict eligibility to adenocarcinoma of the lung, and that patients with other subtypes of NSCLC receiving standard first-line systemic therapy should also be eligible.

We therefore elected to limit this study to patients with advanced NSCLC, because (a) it is a very common tumor type, (b) patients often present with advanced (incurable) disease associated with relatively short survival, (c) there is extensive basic and pre-clinical data available regarding opioid receptor expression and activity that provides a solid scientific basis for this study, as well as retrospective clinical data showing association of opioid exposure with poorer clinical outcomes, and (d) tumor progression (that usually occurs within 5-8 months of starting first-line chemotherapy[9]) impairs HRQoL.[10-12] For the above reasons, we expect to reach the primary endpoints relatively quickly in this pilot study. See section 1.7.

1.3 Rationale for selecting feasibility and safety as the primary endpoint:

In an initial pilot study, it is most important to determine if (a) a sufficiently high accrual rate will be achieved in a diverse multi-center setting to make it possible to successfully undertake a larger, more definitive study, (b) the majority of patients will be able to continue taking the study drug together with systemic therapy for an extended period, (c) the study drug is associated with an acceptably low rate of severe (grade III or higher) side effects in this setting, and (d) there is any signal that administration of the study drug may be associated with unexpected adverse clinical outcomes when given together with systemic therapy.

Of note, several pre-clinical studies from study team and others demonstrating that PAMORAs **inhibit** morphine-induced upregulation of angiogenesis and multi-drug resistance to chemotherapy[13-14] provide reassurance that the study drug is not likely to adversely affect the efficacy of systemic therapy.

1.4 Rationale for estimating change in HRQoL in the current study

Tumor progression is known to impair, and effective chemotherapy is known to improve, HRQoL in advanced NSCLC.[11-12] Early initiation of non-chemotherapeutic interventions (e.g., palliative care) in patients with advanced NSCLC further improves HRQoL, irrespective of anti-cancer therapies.[15]

The HRQoL of patients with advanced malignancies is adversely affected by pain and other symptoms due to tumor progression as well as by the adverse peripheral effects of opioid analgesics, including constipation, nausea, vomiting, xerostomia and drowsiness.[16] Recent studies further suggest that opioid-associated tumor progression may be an additional factor that impairs HRQoL.

In patients with advanced non-squamous NSCLC (adenocarcinoma), pemetrexed-based chemotherapy achieves a median progression-free survival (PFS) of 5.3 (95% CI: 4.8-5.7) months, with a median overall survival (OS) of 12.6 months; approximately 75% patients remain alive at 6 months.[17] Pemetrexed-based induction chemotherapy followed by maintenance pemetrexed achieves a median PFS of 4.4 (95% CI: 4.1-5.7) months from randomization to maintenance pemetrexed,[18] or 7.5 (95% CI: 6.9-8.6) months from the start of initial induction chemotherapy.[9]

Overall HRQoL (total FACT-L score) and the trial outcome index (TOI) of patients with advanced NSCLC treated with standard induction chemotherapy declines significantly by 6 months.[19] A more recent HRQoL analysis of patients receiving pemetrexed maintenance chemotherapy for NSCLC found that the time to worsening of symptoms (TWS) for pain occurred at a median of 6.1 (95% CI: 4.6 – 9.6) months and TWS for overall HRQoL occurred at a median of 5.8 (95% CI: 4.4 – 8.4) months from randomization to maintenance pemetrexed (please see figure 1).[10] Of note, there was a rapid decline in HRQoL within the first few months of starting maintenance pemetrexed (i.e., after 3 months of prior induction chemotherapy).

In the above study, there was a highly significant correlation between TWS of pain or HRQoL and progression-free survival and overall survival ($P < 0.0001$) for all comparisons, indicating that worsening of pain and HRQoL coincide with disease progression and death.[10] The Food and Drug Administration (FDA) and the American Society of Clinical Oncology (ASCO) have opined that determining the effect of treatment on symptoms and HRQoL is of major importance in advanced NSCLC.[20,21] Accordingly, HRQoL has been used as a primary endpoint in recent phase III trials comparing pemetrexed based chemotherapy with other regimens in NSCLC.[22,23]

For the above reasons, HRQoL may therefore serve as the "best" overall measure of potential benefit of the study drug with respect to mitigation of opioid-induced tumor progression as well as mitigation of the peripheral adverse effect of opioids. In view of the expected PFS, OS and time to decline in HRQoL in advanced NSCLC (detailed above), we propose to estimate the difference in HRQoL at 6 months in this pilot study, to inform the design of the subsequent phase II or III studies. Patients may experience objective progression of disease by this time,[9,18] but naloxegol/placebo will be continued for up to 2 years, and data will continue to be collected regarding the safety and potential efficacy of the study drug during this time, even in patients who progress on first line therapy. See Section 1.7. The Alliance has considerable experience in ensuring continued data collection by mail or phone in patients who become unable to come to clinic visits because of clinical deterioration, so we expect the drop-out rates for HRQoL data collection to be relatively low for the proposed duration.

1.5 Rationale for selecting baseline levels/presence/absence of pain, opioid use and peripheral adverse effects of opioids:

Inclusion/exclusion criteria regarding pain and opioid use prior to registration/initiation of study:

We considered various options, including (a) limiting the study to patients with minimal pre-study pain and little/no opioid use, (b) limiting the study to patients with high levels of pain and extensive opioid use, or (c) not requiring patients to be experiencing a specific level of pain, but only requiring patients to have needed opioid medication(s) for pain within 4 weeks of registration.

Option (a) would minimize the theoretical likelihood that pain/opioids would have impacted on tumor biology prior to initiation of study drug, but might delay detection of improvement in HRQoL endpoints.

Option (b) would increase likelihood of early detection of improvement in HRQoL, but would also increase likelihood of GI side effects of the study drug (due to a rapid reversal of constipation). Such patients may also be too ill to stay on the study for sufficient length of time and experience short survival, compromising their contribution to provide adequate longer-term data on the endpoints being studied. Furthermore, potential benefit of study drug may not be seen because pain/opioids may already have induced tumor angiogenesis/signaling pathways causing tumor progression.

Considering all these aspects, we initially selected option (c) because it was suggested by reviewers, that we do this when an early version of this protocol concept was reviewed, it might achieve the best possible balance between testing the underlying pathophysiological phenomena, facilitate rapid enrollment, allow for widest possible applicability of the results, and allow detection of improvement in HRQoL during the planned duration of the study (please see section on HRQoL above, and Figure 1 for the basis for this expectation), since patients would have started requiring opioid medications for pain control already. We did not expect this criterion to create a significant barrier to enrollment, since, in our recent study[24] the majority of patients with advanced NSCLC had required opioids prior to initiation of chemotherapy.

Inclusion/exclusion criteria regarding opioid-induced adverse effects prior to registration/initiation of study:

The study design includes specifically and prospectively assessing the separate impact of naloxegol on constipation (using a validated opioid-induced constipation [OIC] instrument) and other side effects of opioids (using Linear Analogue Self-Assessment [LASA] and Patient-Reported Outcome - Common Terminology Criteria for Adverse Events [PRO-CTCAE] items) as they may arise over time, so that the results of this pilot study will provide an exploratory assessment of the effect of naloxegol on diverse side effects of opioids in cancer patients, and directly inform the design of a future definitive study. While the patients who we enter on this trial may not have a large number of symptoms or a poor HRQoL at baseline, we fully expect that HRQoL will decrease over time as the lung cancer disease becomes more prominent. Thus, we will have patients who could give a positive HRQoL signal due to beneficial effects on cancer-related symptoms, and perhaps also on peripheral adverse effects of opioids as they arise in patients who require escalating opioid doses with cancer progression (see section on HRQoL above, and Figure 1).

1.6 Rationale for a 3-arm study design including placebo and 2 dose arms of study drug:

Why a pilot study is needed:

Data are not available on long-term administration of naloxegol in patients with advanced malignancies receiving chemotherapy.

Specifically, what is not known is: (a) if a sufficiently high accrual rate will be achieved to a study of a PAMORA in patients with advanced malignancy, (b) what proportion of patients can take the study drug together with chemotherapy or other first-line systemic therapy, (c) the length of time patients can stay on the study drug together with systemic therapy, (d) the frequency of severe adverse effects of the study drug, and rate of discontinuation, when given with systemic therapy (d) if there is any signal that the study drug may be associated with unexpected clinical outcomes when given together with systemic therapy, (e) the length of time patients will be compliant with completing HRQoL and other questionnaires in this setting, and (f) if PAMORAs will improve HRQoL, as HRQoL has not been directly assessed in the retrospective clinical studies of PAMORAs thus far.

It will be advisable to ascertain the feasibility and safety of administering naloxegol at selected doses in patients receiving systemic therapy for advanced NSCLC, before committing greater resources and a larger number of patients to a phase II or III study. We propose to conduct a pilot, placebo-controlled trial of two FDA-approved doses of naloxegol. This pilot trial will test the feasibility of the study design, provide reassurance regarding the tolerability and safety with systemic therapy of at least one of the two doses of naloxegol in this patient population, and perhaps provide a signal regarding efficacy, to inform the design of a subsequent definitive study. Further, the effect of PAMORA medications (e.g. naloxegol) on HRQoL in cancer patients needs to be evaluated prospectively, which we propose to *initiate* in this pilot study.

Use of placebo: A placebo design is essential to provide a control arm for comparison of potential adverse effects and possible activity (difference in HRQoL between the study drug arms and placebo) of the study drug, although it will increase the sample size.

Use of a 3-arm design: The commonly used phase I type study design (sequential testing of escalating doses of study drug) will not be optimal for the current study because (a) it will not permit inclusion of a placebo arm, and (b) it will not lend itself well to assessment of [i] relative safety in patients receiving systemic therapy, i.e., relative frequency of systemic therapy side effects and discontinuation in patients receiving systemic therapy without vs with naloxegol, or [ii] efficacy of the study drug with respect to improvement in HRQoL. We therefore elected to use a study design that allows randomization to placebo or one of two doses of the study drug. We have used this design previously.[29,30]

We propose to test two doses of the study drug to increase the likelihood of identifying an "optimal" dose, and reduce the likelihood of missing an activity signal because of insufficient dosing (if dosing is based on prior studies where amelioration of opioid-induced constipation was the primary endpoint). We recognize that testing two doses will increase the sample size, and the higher dose may be associated with more adverse effects. Using a placebo and 2 doses of the study drug will still be possible with a sample size of ~200 patients, which is feasible in this setting.

We considered several approaches regarding the number of doses (1, 2 or 3) of the study drug to test, before selecting the current 2-dose design:

Testing <u>one</u> dose will require the smallest sample size. However, it may miss potential activity of naloxegol on inhibiting morphine-induced tumor progression, since the currently approved lower dose (12.5 mg/day) is based on activity in ameliorating opioid-induced constipation. Mechanisms such as higher levels of drug efflux from malignant cells may require a higher dose for optimal activity against tumor progression.

Testing three doses will increase the likelihood of identifying an "optimal" dose, and reduce the likelihood of missing an activity signal because of insufficient dosing (if dosing is based on prior studies where amelioration of opioid-induced constipation was the primary endpoint). However, this will considerably increase sample size, and a dose higher than the FDA-approved doses may be associated with more adverse effects.

We therefore elected to test two FDA-approved doses of naloxegol, to achieve the best possible balance between improving the chances of identifying possible activity against tumor progression, while maintaining tolerability/safety and limiting the total sample size.

1.7 Basic and pre-clinical studies

Studies in animal models

Pre-clinical studies from our group and others have shown that morphine and other opioids, in clinically relevant doses, promote cancer growth and metastasis by stimulating pro-angiogenic, survival- and growth- promoting signaling in endothelium.[1,31,32] We also showed that chronic morphine treatment stimulates angiogenesis, tumor growth and metastasis, and impairs survival, in mouse models of breast cancer.[1,31] In a mouse model that spontaneously develops breast cancer and mimics the evolutionary spectrum of human breast cancer, we found that morphine activates mast cells and lymphangiogenesis in the tumors, while promoting tumor progression and shortening survival.[33] The relevance of this finding is further supported by observations from our laboratory and others that the opioid receptor antagonists, including naloxone, inhibit breast cancer growth in rodents.[1,34-37] However, naloxone cannot be used clinically in this context because it antagonizes the analgesic effect of opioids.

Studies in lung cancer

Our group has shown that MORs and receptor tyrosine kinases (RTKs) are expressed and co-localized in advanced lung cancer, and that morphine induces RTK activation and signaling, leading to growth and spread of lung cancer cells.[2] These human lung cancer cells, as well as primary lung adenocarcinomas showed significantly increased expression of MOR (mu opioid receptors) as compared to control Beas-2B cells and normal lung tissue. Concurrently, complementary studies by members of our study team demonstrated that MOR silencing of Lewis lung carcinoma cells (LLC) led to decreased metastasis in mice, and that MOR knockout mice did not develop significant LLC tumor growth as compared to wild type mice.[4] Importantly, pharmacological treatment with methylnaltrexone (a PAMORA) inhibited LLC invasion in soft agar and LLC tumor volume and metastasis in mice.[4] Subsequent studies by our study team showed that overexpression of MOR in human lung cancers promotes tumor growth and metastases in xenografts in mice.[38] More recently we showed that morphine, acting via MOR, upregulates multi-drug resistance to chemotherapeutic agents in human NSCLC cells; this effect is blocked by the PAMORA methylnaltrexone.[13] Together, these preclinical data provide compelling evidence for the role of MOR in lung cancer progression and metastasis; and amelioration of lung cancer progression and metastasis with strategies utilizing inhibition of MOR including antagonism with a PAMORA.

Taken together, these pre-clinical studies provide strong evidence that in animal models of several malignancies, activation of peripheral MORs (on endothelial cells and tumors, not in the CNS), by clinically used opioid medications, promotes tumor progression via several different mechanisms including Stat3, MAPK/ERK and Akt phosphorylation, nitric oxide synthesis, COX-2 activation, PGE2 production, cross-activation of EGFR and VEGF-R2, substance P (SP) and mast cell activation.[14,31-33,38-42] Notably, these mechanisms play a central role in cancer progression as well as nociception. More recently, Suzuki et al. have shown that the peripheral opioid receptor antagonist methylnaltrexone augments the antineoplastic activity of the

chemotherapeutic agent docetaxel and improves survival in a mouse xenograft model of human gastric cancer.[43]

Human studies

In a retrospective study involving patients with advanced prostate cancer receiving androgen deprivation therapy, we found that greater opioid requirement and higher levels of MOR expression in the tumor specimen are independently associated with shorter progression-free survival and overall survival.[5] More recently, Halabi et al. confirmed and extended our findings to patients with advanced prostate cancer receiving first-line docetaxel-based chemotherapy on CALGB study 90401 and the ENTHUSE-33 trial, reporting that opioid use is an independent prognostic factor for survival.[44]

In a retrospective NSCLC study, we examined if long-term opioid requirement, independently of chronic pain, is associated with survival.[24] We analyzed 209 patients diagnosed with stage IIIB/IV NSCLC and treated with standard chemotherapy. The effects of pain, opioid requirement, and known prognostic variables on outcomes were analyzed in univariable and multivariable models. Both the severity of chronic pain and greater opioid requirement after starting chemotherapy were strongly associated with shorter OS by univariate analysis. The survival of patients experiencing lower levels of chronic pain and requiring lower doses of opioids (LPLO group) was markedly longer than the survival of patients experiencing higher levels of chronic pain and/or requiring higher doses of opioids in the period from starting chemotherapy until death/last follow up (median overall survival, 16.4 vs ~7 months, $p \leq 0.001$). Remarkably, the level of pain experienced and opioid analgesics required during the first 3 months after diagnosis were strongly predictive of survival. Patients in the LPLO group during the first 3 months after starting chemotherapy had nearly 12 months longer median survival compared to the other 3 groups: 17.9 months vs. 5.7 months (severe pain but low opioid requirement), 6.5 months (low pain but high opioid requirement), and 6.2 months (severe pain and high opioid requirement), log-rank $p = 0.002$. In multivariable models, longer survival in the LPLO group was sustained after adjustment for known prognostic factors including age, stage and performance status. In various malignancies, at least 3 prospective studies suggest that endogenous or pharmacological opioids may promote cancer progression in patients with astrocytomas,[45] pancreatic cancer[46] and various advanced solid tumors.[47]

More recently, we found that opioid exposure during the first 3 months after first treatment in 1,386 patients with stage IV non-hematologic malignancies (largest subgroup [~ 40%] lung cancer) was independently predictive of overall survival ($P < 0.0001$).[48]

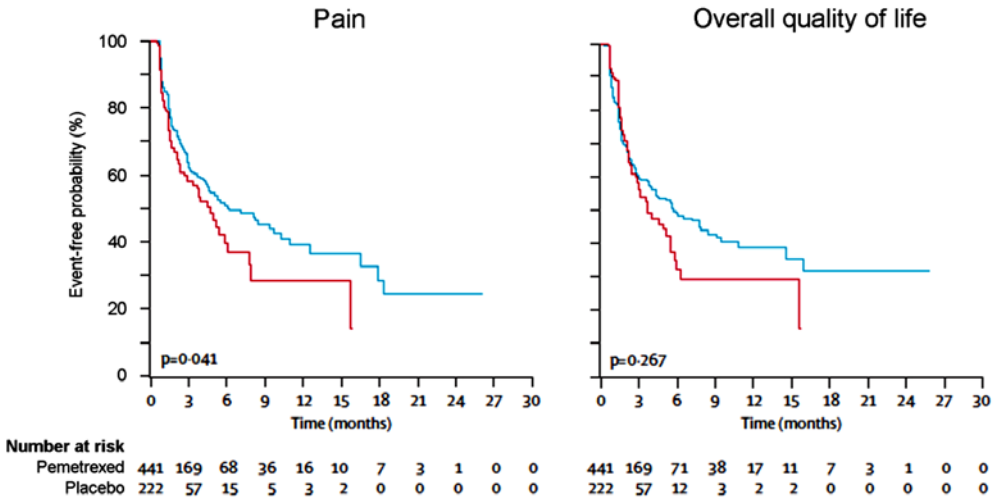
Several additional retrospective clinical studies from our group and others have reported that (1) human lung cancers express opioid receptors,[3] (2) opioid receptor expression is greater in metastatic lesions compared to the primary tumor,[49] and (3) opioid exposure is associated with tumor progression/recurrence and shorter survival.[50,51]

Importantly, a recent study showed that administration of a PAMORA to patients with advanced malignancies was associated with a significantly lower rate of tumor progression compared to placebo (13.8% vs 25.4% respectively; $P = 0.03$).[52]

Further, pain itself increases the levels of circulating endogenous opioids (e.g. endorphins). It is therefore possible that even in patients who are not receiving pharmacological opioid medications, elevated levels of endogenous opioids may themselves activate peripheral MORs and cross-activate signaling pathways that influence tumor progression. This mechanism may be responsible for the known adverse prognostic effect of pain in malignancies including prostate cancer,[53-57] NSCLC[58] and other malignancies.[59]

The above observations raise the possibility that inhibiting the activity of opioids on peripheral opioid receptors by a PAMORA medication may improve HRQoL by mitigating both the symptoms related to tumor progression and the peripheral adverse effects of opioids.

Figure 1



Panels from Fig. 1 in Belani et al. 2012,[10] showing the time to worsening (TWS) of pain and overall quality of life (QoL) in patients with advanced NSCLC receiving maintenance pemetrexed (blue/lighter lines) or placebo (red/darker lines). In these figures, TWS is shown from the date of randomization to maintenance pemetrexed or placebo. Randomization to maintenance was preceded by platinum-based induction chemotherapy given over approximately 3 months.

TWS for pain occurred at a median of 6.1 (95% CI: 4.6 – 9.6) months and TWS for overall QoL occurred at a median of 5.8 (95% CI: 4.4 – 8.4) months in patients receiving maintenance pemetrexed. The corresponding durations were 4.6 (95% CI: 3.3 – 6.0) and 3.7 (3.0 – 5.5) months respectively in patients on the placebo arm who did not receive maintenance pemetrexed.

1.8 Naloxegol and other PAMORAs

Clinically, PAMORAs are well known to ameliorate opioid-induced constipation mediated by peripheral opioid receptors, without compromising the analgesic effect of opioids mediated by central opioid receptors.[13] In short-term studies in healthy volunteers, these drugs also reduce morphine-induced peripheral adverse effects including nausea, pruritis and flushing, as well as a composite score of these and other adverse effects.[25,26] The PAMORA methylnaltrexone is effective in relieving opioid-induced constipation in terminally ill patients with diverse advanced malignancies, and intermediate-term (up to 4 months) administration is well tolerated without inducing opioid withdrawal or worsening of pain.[61,62] A recent post-hoc analysis suggests that PAMORAs may also ameliorate tumor progression in humans.[52]

Of the PAMORAs, **naloxegol** (PEGylated naloxone; Movantik®) is the only **oral** agent approved by the FDA for **prolonged** treatment of opioid-induced constipation in non-cancer patients.[27] Naloxegol needs to be administered only once a day by mouth, does not adversely affect the analgesic effects of opioids, and is generally well tolerated with adverse effects largely

limited to mild-moderate and transient gastrointestinal symptoms.[27,28] It has been administered in long-term studies in 537 patients for ≥ 6 months and in 320 patients for ≥ 12 months.[28] Importantly, naloxegol does not influence cardiac repolarization or prolong the QTc interval.[63] Adverse events leading to discontinuation of naloxegol occurred in 10.5% of 804 non-cancer patients in a long-term (52 week) study, primarily due to gastrointestinal events (diarrhea, abdominal pain, nausea/vomiting).[64] It does not carry a risk for dependency/abuse and has recently been determined to not be a controlled substance.[65] Thus, what is known about naloxegol is that: (a) It is an orally administered PAMORA that inhibits peripheral opioid receptors, and (b) It is safe and effective in relieving opioid-induced constipation in non-cancer patients.

1.9 Study Hypotheses

Primary hypothesis: Long-term administration of naloxegol is feasible and safe in patients receiving first line systemic therapy for advanced malignancy (NSCLC).

Secondary hypothesis: Activation of peripheral opioid receptors promotes cancer progression and mediates the distressing side effects of opioid medications, together leading to worsening of disease-related symptoms and impairment of HRQoL. Selective inhibition of peripheral opioid receptors will improve HRQoL by ameliorating **both** these undesirable effects of opioid receptor activation (tumor progression and peripheral adverse effects), without compromising analgesia (which is mediated by central opioid receptors, i.e. in the CNS).

1.10 How this pilot study will provide essential data for a future, more definitive study, and its possible design:

Information that needs to be generated from the currently proposed pilot study in order to proceed to a phase II or III trial: (a) best dose of naloxegol to use, (b) tolerability/safety and feasibility information, (c) ideally, suggestions of efficacy pertaining to HRQoL (from inhibition of tumor progression and amelioration of opioid peripheral adverse effects).

(a) It is possible that the optimal dose of naloxegol for relieving constipation may be different from the dose that effectively inhibits opioid receptors in advanced NSCLC. If both FDA-approved doses of naloxegol induce an equally significant beneficial effect, we will choose the lower (12.5 mg/day) dose for a subsequent study. If the higher dose (25 mg/day) demonstrates greater efficacy without causing a significant increase in toxicity, we will select that dose.

(b) Since this will be a pilot study of a relatively recently approved medication, we chose to include a co-primary endpoint of safety and feasibility. Acceptable levels of the feasibility endpoints (accrual rate ≥ 80% of target and ≥ 80% of patients alive at 6 months remaining on study for at least 6 months) are specified in the study design (below). The duration of treatment with the study drug/placebo will be 2 years, since the primary endpoints will be reached by this time and because this period will be beyond the expected median survival of 13-17 months for the study population.

(c) Naloxegol is likely to influence HRQoL by reducing the adverse peripheral effects of opioid analgesics, particularly constipation, and perhaps nausea, vomiting or other adverse effects. We therefore expect that physical well-being and functional well-being will be most likely to be improved by use of this drug. HRQoL may be further improved if tumor progression is slowed, and therefore all aspects of HRQoL could be positively affected. In this study, we therefore want to observe that administration of naloxegol is associated with a generally accepted magnitude of clinically meaningful improvement (change in TOI score at 6 months[11]; FACT-L; Appendix VI) that naloxegol improves HRQoL items listed in Appendix V (e.g. dry mouth, urinary symptoms, increased sweating, or vomiting etc.,) more than placebo, and that naloxegol results in less constipation than placebo (Appendix III).

The design of a future phase II or III study will largely depend on the above aspects. Endpoints of major importance for such larger, definitive studies will include HRQoL, PFS, OS, and safety profile.

2.0 OBJECTIVES

2.1 Primary objective

To determine feasibility and safety of long-term administration of two doses of a peripheral opioid receptor antagonist in patients with advanced NSCLC receiving first-line systemic therapy.

2.2 Secondary objective(s)

2.2.1 To explore whether patients randomized to one or both of the two study drug arms have less decline in HRQoL than patients randomized to placebo.

2.2.2 To estimate the difference in the pain levels and opioid/non-opioid analgesic requirements between patients receiving naloxegol or placebo.

2.2.3 To estimate the difference in the adverse peripheral effects of opioids (e.g. constipation, nausea/emesis, dry mouth and urinary retention) between patients receiving naloxegol or placebo.

2.2.4 To explore whether there is a signal that naloxegol may be associated with longer PFS and OS.

2.2.5 To evaluate the difference in discontinuation rate of systemic therapy due to AEs and deaths attributable to systemic therapy.

2.3 Correlative science objective

2.3.1 To examine if MOR expression or activation is a prognostic marker in advanced NSCLC, and whether its expression/activation can be used to guide pain management**.** (Specific biomarkers to be examined are listed in Section 14.1.3)

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a “currently active” second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a “currently active” malignancy if they have completed therapy and are free of disease for ≥ 3 years.

- Patients who cannot swallow oral formulations of the agent(s).

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom). Women of childbearing potential must use two forms of barrier contraception for the duration of the study and for 12 weeks (3 months) post-treatment. Sexually active male patients must use a double-barrier contraception (condom with spermicide) from the first dose of study drug until (12 weeks) after the last dose. Women of childbearing potential must have a negative pregnancy test ≤ 7 days prior to registration.

Concurrent enrollment to therapeutic clinical trials: In general, per Alliance policies, concurrent registration to other clinical trials using investigational treatments is not allowed. However, for this study concurrent registration on other lung cancer trials is allowed, provided the patient meets all eligibility criteria listed in Section 3.2. Contact the Alliance A221504 Study Chair and Protocol Coordinator to verify that concurrent enrollment is appropriate for the patient.

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

___ **3.2.1 Documentation of Disease:**

Histologic Documentation: Advanced (stage IIIB or IV) non-small cell lung cancer diagnosed by biopsy of the primary or metastatic site. (AJCC 7.0.[92])

___ **3.2.2 No known presence of known EGFR or EML4-ALK driver mutations in the tumor.**

___ **3.2.3 Started first-line systemic therapy of the investigator's choice within 12 weeks prior to registration, or planning to initiate first-line systemic therapy of the investigator's choice within 4 weeks after registration.** No planned initiation of definitive (potentially curative) concurrent chemo-radiation.

___ **3.2.4 No prior systemic therapy for advanced NSCLC, including chemotherapy, targeted therapy or immunotherapy (other than current treatment).** Prior palliative radiation permitted; prior adjuvant systemic therapy /radiation is permitted.

___ **3.2.5 No more than 7 days of prior use of mixed opioid agonist/opioid antagonists or other opioid antagonists within 4 weeks before registration (See list of drugs in section 7.3).** Patients should not receive such medications after registration and for the entire duration of study treatment**.**

___ **3.2.6 No methadone within 4 weeks prior to registration.**

___ **3.2.7 Patients must have used opioid medication(s) for pain at some time in the 4 weeks prior to registration. Current use of opioids (at the time of registration) and/or later during the course of the study is permitted but not required.**

___ **3.2.8 Expected survival > 3 months.**

___ **3.2.9 No concurrently active second invasive malignancies except non-melanoma skin cancer.** (See Section 3.1 for definitions**).**

___ **3.2.10 No history of gastrointestinal obstruction, or conditions that increase the risk of gastrointestinal obstruction, perforation, bleeding or impairment of the gastrointestinal wall. No abdominal surgery within 60 days of registration.**

___ **3.2.11 No acute gastrointestinal conditions, such as**: obstruction, fecal impaction, obstipation, acute surgical abdomen, ongoing need for manual maneuvers to induce bowel movements (such as digital evacuation).

___ **3.2.12 No conditions that may compromise blood-brain barrier permeability** (e.g., multiple sclerosis, recent brain trauma, Alzheimer's disease, or uncontrolled seizures).

- No symptomatic and untreated brain metastases. Patients will be eligible for study if radiation therapy for brain metastases was completed at least 7 days prior to registration.
- Patients having received stereotactic radiation will be eligible if the radiation was completed at least 7 days prior to registration.
- Patients having undergone surgical resection of brain metastases will be eligible after they have healed and recovered from the surgical intervention sufficiently to start systemic treatment for NSCLC, as determined by a neurosurgeon.
- No known leptomeningeal carcinomatosis.

___ **3.2.13 No history of myocardial infarction ≤ 6 months prior to registration. No current symptomatic congestive heart failure, uncontrolled angina or uncontrolled cardiac arrhythmias.**

___ **3.2.14 No severe hepatic impairment (Child-Pugh class C) or acute liver disease.**

___ **3.2.15 No known serious or severe hypersensitivity reaction to naloxegol or any of its excipients.** See list of excipients in Section 10.1.

___ **3.2.16 No concurrent use of moderate/strong CYP3A4 inhibitors, or strong CYP3A4 inducers.** (See Sections 8.1.5 and 8.1.6)

___ **3.2.17 Not pregnant and not nursing,** because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.

Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 7 days prior to registration is required. A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ **3.2.18 Age ≥ 18 years**

___ **3.2.19 ECOG Performance Status 0-2**

___ **3.2.20 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Platelet Count	≥ 100,000/mm^3
Calc. Creatinine Clearance	≥ 60 mL/min *
Total Bilirubin	≤ 1.2 x upper limit of normal (ULN)**
AST and ALT	≤ 2.5 x upper limit of normal (ULN)

* Calculated using the Cockcroft-Gault formula
**Unless due to Gilbert's disease

4.0 PATIENT REGISTRATION

4.1 CTEP / DCP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at [redacted]. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at [redacted]

RCR utilizes five person registration types.

IVR—MD, DO, or international equivalent;

NPIVR—advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);

AP—clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);

Associate (A)—other clinical site staff involved in the conduct of NCI-sponsored trials; and

Associate Basic (AB)—individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance).

Additional information is located on the CTEP website at [redacted] For questions, please contact the **RCR Help Desk** by email at [redacted]

Registration requires the submission of:

Human Subject Protection (HSP) training certificate

4.2 CTSU Site Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling [redacted]

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

4.2.1 Additional site registration requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.2 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website [redacted] using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of your screen
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select *Alliance*, and protocol number [*A221504*].
- Click on Documents, select Site Registration, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website → Regulatory → Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at [redacted] in order to receive further instruction and support.

4.2.4 Checking Your Site's Registration Status

You can verify your site's registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website;
- Click on *Regulatory* at the top of your screen;
- Click on *Site Registration*;
- Enter your 5-character CTEP Institution Code and click on Go.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration Requirements

- **Informed consent:** the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.
- **Patient completed booklets:** Patient questionnaire booklets are to be ordered prior to the registration of any patients. Patient completed booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the A221504 CTSU site) and submitting it through the CTSU regulatory portal. Samples of the booklets are found in Appendices I, and IV-VI, which are to be used for reference and IRB submission only. They are not to be used for patient completion.

4.4 Patient Registration/Randomization Procedures

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at [redacted] or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at [redacted]. For any additional questions, contact the CTSU Help Desk at [redacted]

To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol-specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website a [redacted] For any additional questions contact the CTSU Help Desk at [redacted].

4.5 Registration to Correlative and Companion Studies

4.5.1 Registration to Substudies described in Section 14.0

There is 1 substudy within Alliance A221504. This correlative science study must be offered to all patients enrolled on Alliance A221504 (although patients may opt to not participate). This substudy does not require separate IRB approval. The substudy included within Alliance A221504 is:

- Biological/physiological endpoints, biological mechanism of action, and biomarkers that would predict response/risk to the study drug, Alliance A221504-ST1.

If a patient answers "yes" to "I agree to have my specimen collected and I agree that my specimen sample(s) and related information may be used for the laboratory study described above," they have consented to participate in the substudy described in Section 14. The patient should be registered to Alliance A221504-ST1 at the same time they are registered to the treatment trial (A221504). Samples should be submitted per Section 6.2.

4.6 Stratification Factors

4.6.1 Planned use of bevacizumab (for first-line treatment regimen or maintenance): Yes vs. No

4.6.2 ECOG performance score: 0 – 1 vs. 2

4.7 Procedures for Double-Blinding the Treatment Assignment

After the treatment assignment has been ascertained in the OPEN application, the patient's study medication code number will be displayed on the confirmation of registration screen. If the code number is not displayed, contact the Registration Office at [redacted] or [redacted]

The medication code number of the treatment bottles assigned to the patient will be recorded on the Drug Order Form by institutional staff.

5.0 STUDY CALENDAR

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Pre-Study Testing Intervals

- To be completed ≤ 7 DAYS before registration: Pregnancy test.
- To be completed ≤ 14 DAYS before registration: All laboratory studies, history and physical.

•	Prior to Registration	Prior to the start of treatment*	Every 6 weeks (+/- 7 days) until 1 year after start of treatment**	Every 3 months (+/- 7 days) from 1 year to 2 years after the start of treatment
Tests & Observations				
History and physical, weight, PS	X (1)			
Adverse Event Assessment		X	A	X
PRO-CTCAE (Appendix V)		X	B	X
Urinary Hesitancy Question (Appdx V)		X	B	X
FACT-L (Appendix VI)		X	X (3)	X
Bowel Function Diary (Appendix IV)		X	B	X
Pain and Pain Med Diary (Appdx I)		X	B	X
Patient Medication Diary (See Appdx II)			X (4)	X (4)
Laboratory Studies				
Complete Blood Count, Differential	X	X	C	
Serum/plasma Creatinine	X	X	C	
AST, ALT, Alk. Phos., total bilirubin	X	X	C	
Sodium and potassium	X	X	C	
Serum or Urine HCG	X (2)			
Correlative studies: For patients who consent to participate				
Tissue	(see Section 6.2)			
Blood sample	(see Section 6.2)			

* Labs completed prior to registration may be used for prior to the start of treatment tests if obtained ≤ 14 days prior to treatment.

** While it is expected that patients will visit the clinic at least every 6 weeks, the cycle length for reporting treatment and adverse events is every 3 weeks.

1 The history and physical exam should specifically include information regarding smoking status, weight loss, stage of lung cancer, and presence/absence of known brain metastases.

2 For women of childbearing potential (see Section 3.3). Must be done ≤ 7 days prior to registration.

3 To be collected on Weeks 3 and 6 (Cycles 1 and 2), then every 6 weeks (i.e., Week 12/Cycle 4, Week 18/Cycle 6, Week 24/Cycle 8, etc.).

4 To be provided to patients for site and patient convenience only.

A Every 3 weeks. For patients who are not scheduled to visit the clinic every 3 weeks, adverse event assessment should be done by telephone.

B Every 3 weeks. For patients who are not scheduled to visit the clinic every 3 weeks, booklets may be given to the patient to complete at home and return to the clinic by mail or at the next clinic visit.

C To be collected on Weeks 3 and 6 only.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data submission schedule

A Schedule of Forms is available on the Alliance study webpage, within the Case Report Forms section. The Schedule of Forms is also available on the CTSU site within the study-specific Education and Promotion folder, and is named Time & Events.

6.1.2 Medidata Rave

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to [redacted] for registration types and documentation required.
    - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type;
    - To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR; and
    - To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login [redacted] using their CTEP-IAM username and password, and click on the accept link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at [redacted] or by contacting the CTSU Help Desk at [redacted] or by e-mail at [redacted]

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients (see Section 4.3). Samples of questionnaire booklets are available in Appendices IV-VI for reference and IRB submission only. They are not to be used for patient completion. Booklets must be given to patients to complete and patients

should be instructed to return the booklets to site staff either in person or by mail and site staff will enter patient and caregiver responses into Rave.

6.1.3 Supporting documentation

This study requires supporting documentation for diagnosis, anti-cancer treatment administered (systemic therapy and/or radiation), response, progression and survival. Supporting documentation will include pathology and radiology reports and must be submitted at the following time points:

Baseline: Pathology and radiology reports and clinic notes

At Progression and response: Radiology reports and clinic notes, based on standard RECIST criteria.

All supporting documentation should be de-identified according to institutional standards prior to upload into RAVE.

6.1.4 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

6.2 Specimen collection and submission

For patients registered to substudy A221504-ST1: All participating institutions must ask patients for their consent to participate in the correlative sub-studies planned for Alliance A221504-ST1, although patient participation is optional. Biomarker studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 14.0. For patients who consent to participate, tissue and blood will be collected at the following time points for these studies:

	At Registration	**3 weeks (+/-7 days) after start of study medication**	**6 weeks (+/-7 days) after start of study medication**	**Storage/ Shipping conditions**	**Submit to:**
For patients registered to A221504-ST1, submit the following: (optional)					
Diagnostic tumor tissue block (biopsy or surgery) (1)	X			Ambient	Alliance Biorepository at Mayo Clinic FFPE Tissue
Number and volume of tubes to draw					
Whole blood (2) (EDTA/lavender top) (see Section 6.2.3)	1 x 5 mL	1 x 5 mL	1 x 5 mL	pack/ship plasma on dry ice over night	Alliance Biorepository at Mayo Clinic BAP Freezer
Whole blood (2) (Heparin/green top) (see Section 6.2.3)	1 x 5 mL	1 x 5 mL	1 x 5 mL	pack/ship plasma on dry ice over night	Alliance Biorepository at Mayo Clinic BAP Freezer

(1) Tissue to be used for biomarker analyses described in Section 14.1. See Section 6.2.2 for alternative submission.

(2) Plasma from whole blood to be used for biomarker analyses described in Section 14.1. See Section 6.2.3 for processing instructions and Appendix VIII.

6.2.1 Specimen submission using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: [redacted] using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS webpage to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted] For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted]

Sample collection kits must be ordered thought BIOMS. Please log into BioMS, and click on "Kit Requests" to order blood specimen kits.

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (A221504), Alliance patient number, patient's initials, date and type of specimen collected (e.g., serum, whole blood). See Section 6.2.2.

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Ship specimens on Monday through Friday only. Shipping by overnight service to assure receipt is encouraged.

6.2.2 Collection and Submission of Diagnostic Tumor Tissue

For patients who consent to participate, tumor blocks will be used for the analyses described in Section 14.1.

Paraffin blocks of diagnostic tumor tissue (from primary or metastatic site) should be sent to the Alliance Biorepository at Mayo Clinic FFPE Tissue.

The Alliance has instituted special considerations for the small percentage of hospitals whose policy prohibits long-term storage of blocks, and the smaller percentage of hospitals whose policies prohibit release of any block. If, due to institutional policy, a block cannot be sent then please send slides of diagnostic tumor tissue.

The goal of the Alliance Biorepository is to provide investigators with quality histology sections for their research while maintaining the integrity of the tissue. For these reasons it is preferred that the Alliance Biorepository bank the block until the study investigator requests thin sections. Please contact the Alliance Biorepository if additional assurances with your hospital pathology department are required.

If an institution is unable to provide a tissue block, please submit either of the following:

10 unstained PLUS-charged glass slides (or as many as possible if fewer than 10) of 4-6 micron thick sections from:

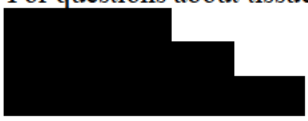
- The most recent diagnostic biopsy confirming advanced (stage IIIB/IV) non-small cell carcinoma of the lung **OR**
- A diagnostic biopsy (or surgery) performed previously, if the patient was previously diagnosed and/or treated for the same malignancy (i.e., early stage non-small cell carcinoma of the lung) and has now progressed or relapsed **OR**
- A fine needle aspiration (FNA) or cell block, if only a FNA or bronchoscopic washings were performed (or found to contain diagnostic material).

Label the unstained slides with Alliance patient ID number, accession number, and order of sections via institution's standard method for labeling clinical slides or using a permanent marker. **Please DO NOT use sticky labels.**

Tissue sample should be sent within 7 days after registration. A de-identified surgical pathology report should be sent with tumor tissues (blocks or unstained slides). Usually, this is generated by obscuring all PHI (names and dates) with white-out or a black magic marker, labeling each page of the report with the Alliance patient ID, and photocopying the report.

ALL tumor specimens should be sent to the following address:

For questions about tissue submission contact:



6.2.3 Blood sample submission

For patients who consent to participate, plasma from whole blood samples will be used for the biomarker analyses described in Section 14.1.

To obtain plasma, collect 5 mL of peripheral venous blood in one lavender top tube (K2EDTA anti-coagulant) and another 5 mL of peripheral venous blood in one green top (heparin) tube at the time of **registration**, **3 weeks (+/-7 days) after initiation of study medication and 6 weeks (+/-7 days) after initiation of study medication**.

Processing of blood drawn in lavender top EDTA tube:

First, label two or three cryovials* for each blood sample, per labeling instructions.

Then draw 5 ml blood into a Lavender Top Vacutainer EDTA tube.

Gently invert the tube 8-10 times immediately after collection of blood.

Centrifuge the blood to separate plasma, per institutional standard operating procedure.

Remove plasma and transfer to a clean 5 ml centrifuge tube.

Repeat the centrifuge step.

Immediately aliquot ~1 ml plasma in each pre-labeled cryovial.

Snap freeze the cryovials as soon as possible, then store at –70°C until shipment. If –70°C or colder freezer is not available, temporary storage on dry ice or at –20°C prior to shipment is acceptable for up to approximately 48 hours. Ship on dry ice to the Alliance Biorepository.

Processing of blood drawn in green top heparin tube:

First, label three cryovials* for each blood sample, per labeling instructions.

Then draw 5 ml blood into a Green Top Vacutainer heparin tube.

Gently invert the tube 8-10 times immediately after collection of blood.

Centrifuge the blood to separate plasma per institutional standard operating procedure.

Remove plasma and transfer to a clean 5 ml centrifuge tube.

Repeat the centrifuge step.

Immediately aliquot ~1 ml plasma in each pre-labeled cryovial.

Snap freeze the cryovials as soon as possible, then store at –70°C until shipment. If –70°C or colder freezer is not available, temporary storage on dry ice or at –20°C prior to shipment is acceptable for up to approximately 48 hours.

Ship on dry ice to the Alliance Biorepository.

Label samples with the following identification:

1) Procurement date and time
2) Alliance patient number
3) Patient initials
4) Alliance study number (i.e., A221504-ST1)
5) EDTA plasma or heparin plasma

*Cryovial Choices: Some examples of acceptable 1-1.2 mL cryovials are: Nalgene® Cryogenic Tubes, Brand® Cryogenic Tubes, Corning® Cryogenic Vials, Nunc® CryoTubes.

Blood submission for patients who agree to participate:

Shipment on Monday through Friday by overnight service to assure receipt is encouraged. Do not ship specimens on Saturdays. Samples should be sent accordingly within 30 days from the date of collection. Ship samples to the following address:

[redacted]

For questions about blood submission contact:

[redacted]

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 7 days of registration.

Naloxegol or matching placebo will be administered continuously during the study period. Cycle length will be every 3 weeks during the first year of treatment. Cycle length will be every 3 months during the second year of treatment. Protocol treatment will be continued for up to 2 years, but it will be discontinued for unacceptable adverse effects or withdrawal of consent. Naloxegol/placebo will NOT be discontinued for disease progression.

7.1 Naloxegol/ Placebo

Naloxegol or placebo will be administered once daily as two tablets, as specified in the table below. Each patient randomized to receive naloxegol/placebo will receive one bottle of naloxegol/placebo 12.5 mg tablets and one bottle of naloxegol/placebo 25 mg tablets to be administered together once per day in 3-week cycles. Patients should note that 12.5 and 25 mg tablets will look different from each other, minimizing the risk that patients will accidentally take two tablets from the same bottle. Patients should take one tablet from each bottle at the same time each day 1 hour before eating or 2 hours after a meal.

Bottle 1 Dose	Bottle 2 Dose	Total Naloxegol Dose	Route	Day
12.5 mg Naloxegol	25 mg Placebo	12.5 mg	PO	Daily
12.5 mg Placebo	25 mg Naloxegol	25 mg	PO	Daily
12.5 mg Placebo	25 mg Placebo	0 mg	PO	Daily

Patients will discontinue all maintenance laxatives/stool softeners/fiber therapy the day (at least 24 hours) prior to initiation of naloxegol/placebo. Laxatives/stool softeners/fiber can be restarted and used as needed if constipation persists for three or more days after starting naloxegol/placebo.

Advanced lung cancer is considered to be incurable, and patients with progressive disease often experience increasing pain that requires treatment with escalating doses of opioids. Since the objective of this study is to examine whether naloxegol can mitigate the adverse effects of opioids, the study drug should be continued for as long as possible for up to 2 years.

Recommendations for missed doses: If a patient vomits, there is a possibility that some of the dose may already have been absorbed. Another dose must NOT be administered the same day. The patient should take the following day's dose at the correct time on the next day.

Similarly, if a patient has forgotten a dose, it may be reasonable for them to take it if only a few hours have elapsed since the scheduled time, but skip that day's dose if it has been many hours.

7.2 First-line systemic therapy.

The choice of first-line systemic therapy, number of cycles to be administered, and whether or not maintenance treatment is used, will be at the discretion of the treating physician. Systemic therapy may include chemotherapy with/without immunotherapy (e.g. pembrolizumab) or anti-angiogenic agents (e.g. bevacizumab), immunotherapy alone, or other agents.

7.3 Opioids

The use of standard opioids (and other analgesics) to control pain adequately will be permitted at the discretion of the treating physician.

While patients are receiving naloxegol/placebo, the use of mixed opioid agonists/antagonists or other opioid antagonists **will not be permitted** (e.g. pentazocine, buprenorphine, nalbuphine, naloxone and other naloxone containing products such as oxycodone/naloxone combinations [e.g., Targin®], naltrexone and other naltrexone containing products such as morphine/naltrexone combinations [e.g., Embeda®], methylnaltrexone [Relistor®], or alvimopan [Entereg®]). Patients who have used such drugs in the past will not be eligible for this study.

Additionally, since patients receiving methadone may experience a higher frequency of GI adverse effects possibly related to opioid withdrawal upon administration of naloxegol, the use of methadone while patients are receiving naloxegol/placebo **will not be permitted**. Patients who have used methadone in the past 4 weeks prior to registration will not be eligible for this study.

8.0 DOSE AND TREATMENT MODIFICATIONS & UNBLINDING

8.1 Ancillary therapy, concomitant medications, and supportive care

Use of mixed opioid agonists/antagonists or other peripheral opioid antagonists will not be permitted as long as patients are taking the study medication/placebo on this trial. Administration of standard opioids and other analgesics to control pain adequately will be permitted at the discretion of the treating physician. Pain levels and actual opioid and non-opioid analgesic use will be recorded using patient diaries.

8.1.1 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as

antidiarrheals, analgesics, and/or antiemetics received while on naloxegol/placebo will be recorded in the medical records.

8.1.2 Antiemetics, including aprepitant or fosaprepitant, may be used at the discretion of the treating physician.

8.1.3 Diarrhea management is per the discretion of the treating physician. Diarrhea could be managed conservatively with medications such as loperamide.

Patients with severe diarrhea should be assessed for intravenous hydration and correction of electrolyte imbalances.

8.1.4 Palliative radiation therapy may be administered at any time as needed, including whole-brain and/or stereotactic irradiation given for documented CNS disease. Continue protocol treatment (naloxegol or placebo) during irradiation.

8.1.5 CYP3A4 Inhibitors

Chronic concomitant treatment with moderate or strong inhibitors of CYP3A4 is not allowed during this trial. The following drugs are EXAMPLES of strong inhibitors of CYP3A4 and are not allowed during treatment with naloxegol.

- Indinavir
- Clarithromycin
- Ketoconazole
- Cannabinoids

The following drugs are EXAMPLES of moderate inhibitors of CYP3A4 and are not allowed during treatment with naloxegol*:

- Diltiazem
- Erythromycin
- Verapamil~~l~~
- Grapefruit juice
- Fluconazole

Because lists of these agents are constantly changing, please consult an updated list and review any drugs being taken by the patients for their potential to inhibit CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

* While Aprepitant is a moderate inhibitor of CYP3A4 its short-term use (up to 3 days) as an antiemetic with each cycle of chemotherapy will be allowed.

8.1.6 CYP3A4 Inducers

Chronic concomitant treatment with strong inducers of CYP3A4 is not allowed during this trial. The following drugs are EXAMPLES of strong inducers of CYP3A4 and are not allowed during treatment with naloxegol.

- Rifampin
- Carbamazepine

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.2 Dose Modifications

CTEP-AERS reporting may be required for some adverse events (See Section 9.0). PRO-CTCAE data should not be used for determining dose modifications.

8.2.1 Abdominal Pain

If patients develop unusually severe, persistent or worsening ≥ grade 2 abdominal pain or other symptoms/signs of GI perforation or obstruction, naloxegol/placebo will be temporarily held and patients will be advised to obtain urgent medical attention.

8.2.2 Hepatotoxicity

For grade 2 or higher (ALT or AST > 3 x ULN) hepatotoxicity, patients will be evaluated clinically.

Naloxegol/placebo will be temporarily held for patients who develop any of the following:

- Grade 2 ALT or AST > 3-5 x ULN AND any of the following:
  - Grade 2 or higher total bilirubin (> 1.5 x ULN)
  - Grade 2 or higher INR (> 1.5)
  - Symptoms including fatigue, nausea, vomiting, right upper quadrant pain/tenderness, fever, rash, and/or eosinophilia.
- Grade 3 or higher ALT or AST (> 5 x ULN)

Naloxegol/placebo may be resumed for patients who recover to ≤ grade 2 ALT or AST (≤ 5 x ULN), ≤ grade 1 bilirubin and INR, and have no symptoms or signs of liver dysfunction.

All patients developing liver dysfunction should be monitored clinically and with serial laboratory tests, as clinically appropriate.

8.2.3 Diarrhea, nausea or vomiting

An assessment of whether these symptoms are related to systemic therapy or to naloxegol/placebo must be made.

For grade 2 or higher nausea, vomiting or diarrhea, believed to be at least possibly related to the study drug, naloxegol/placebo will be held temporarily. Naloxegol/placebo may be resumed with the original treatment schedule once these symptoms have improved to grade 1 or better.

At the treating physician's discretion, anti-diarrheal and anti-emetics can be used prophylactically to prevent another episode of grade 2-4 symptoms. If grade 2 or higher

nausea, vomiting or diarrhea believed to be at least possibly related to naloxegol/placebo recurs, then naloxegol/placebo will be permanently discontinued.

8.2.4 Other adverse events

Naloxegol/placebo will be temporarily held for any hematological or non-hematological toxicity believed to be possibly/probably/definitely related to the study drug and grade 2-4 in severity. Naloxegol/placebo will be resumed with the original treatment schedule once toxicity has improved to grade ≤ 1. If toxicity of grade 2-4 recurs, the naloxegol/placebo will be permanently discontinued.

Patients will be taken off protocol treatment if they are unable to resume naloxegol/placebo for ≥ 4 weeks because of persistent grade 2-4 toxicity that is possibly/probably/definitely related to the study drug/placebo.

If patients develop symptomatic brain metastases during the study (while patients are taking the study drug), it will be recommended that the study drug be temporarily withheld until 7 days after the end of radiation therapy, or until after recovery from brain surgery/resection of brain metastases.

If patients develop leptomeningeal carcinomatosis during the study, the study drug will be discontinued permanently.

8.2.5 Pregnancy: Naloxegol/placebo will be discontinued immediately and permanently for any patient who becomes pregnant during the treatment period of the study.

8.2.6 Chemotherapy

Dose adjustments and cycle delays for the individual chemotherapeutic agents used will be per institutional guidelines/practice and the package inserts.

8.3 Unblinding Procedures

Unblinding can be done only in cases of an emergency. Follow the directions below to unblind patient treatment. Please note that if a treatment assignment is unblinded, the patient must discontinue protocol therapy.

Emergency Unblinding Procedures:

Examples of emergencies include 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose. Expected adverse events are listed in the "Toxicities" section below.

Contact the Alliance Executive Officer on call by calling 773-702-6800, pressing 1 to speak with an operator, and then asking for pager ID 8625 to return the call.

The institution must provide the following information to the Alliance Executive Officer:

- Alliance study ID (i.e., "A221504")
- Alliance patient ID number (e.g., "999999")
- Patient initials (e.g., "L, FM")
- Institution name
- Name and telephone number of treating physician
- Name and contact information of person requesting the unblinding procedure
- Name and contact information of person to inform of treatment assignment
- Reason for emergency unblinding

Please remember that an emergency unblinding request may be authorized only by an Alliance Executive Officer, and emergency unblinding applies only if unblinding would influence management of the medical situation.

After the Executive Officer deems unblinding is warranted, the treatment assignment will be provided to the contact person at the treating site.

Procedures for unblinding after completion of treatment with naloxegol/placebo

Study participants can be unblinded after 2 years of treatment with naloxegol/placebo and all appropriate study forms have been completed.

To receive patient treatment assignment in either of these cases, contact the Alliance Registration Office at [redacted] during regular business hours.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. However, CTCAE v5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018. The CTCAE is available at [redacted]. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

NOTE: PRO-CTCAE data should not be used for determining attribution, or reporting of adverse events.

9.1 Routine adverse event reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, the Adverse Event Solicited form is used for routine AE reporting in Rave.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment by CTCAE, PRO-CTCAE, or both.

CTCAE v4.0 Term	PRO-CTCAE v1.0 Term	CTCAE v4.0 System Organ Class (SOC)
Abdominal pain	Abdominal Pain	Gastrointestinal Disorders
Headache	Headache	Nervous system disorders
Hyperhidrosis	Increased Sweating	Skin and subcutaneous tissue disorders
Diarrhea	Diarrhea	Gastrointestinal Disorders
Nausea	Nausea	Gastrointestinal Disorders
Flatulence	Gas	Gastrointestinal Disorders
Vomiting	Vomiting	Gastrointestinal Disorders
Gastric perforation		Gastrointestinal Disorders

Small intestinal perforation		Gastrointestinal Disorders
Colonic perforation		Gastrointestinal Disorders
Rectal perforation		Gastrointestinal Disorders
Opioid withdrawal		State presence or absence
Dry mouth	Dry Mouth	Gastrointestinal Disorders

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

***Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)**

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Alliance Central Protocol Operations Program, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: [redacted]. All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

PRO-CTCAE data should not be used for determining attribution, or reporting of serious adverse events.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE ≤ 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	• Grade 1 Timeframes	• Grade 2 Timeframes	• Grade 3 Timeframes	• Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- Grade 3/4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.
- Reporting of cases of secondary AML/MDS is to be done using the NCI/CTEP Secondary AML/MDS Report Form. New primary malignancies should be reported using Form Notice of New Primary.
- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors.

Secondary Malignancy:

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

- Treatment expected adverse events include those listed in Section 10.0 and in the package insert.
- CTEP-AERS reports should be submitted electronically.

Pregnancy loss

- Pregnancy loss is defined in CTCAE as "Death in utero."
- Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.
- A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEPAERS recognizes this event as a patient death.
- When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and submitted, along with any additional medical information (form is available on the CTEP website at [redacted]). The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

10.0 DRUG INFORMATION

10.1 Naloxegol (IND Exempt)

Naloxegol is an FDA approved medication that has recently been removed from the list of controlled substances.[65] Naloxegol is a PEGylated derivative of the opioid antagonist naloxone. Naloxegol contains naloxegol oxalate as the active ingredient. Naloxegol is an antagonist of opioid binding at the mu-opioid receptor which functions as a peripherally-acting mu-opioid receptor antagonist (PAMORA) in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids. The PEG moiety reduces its passive permeability. It is a substrate for the P-glycoprotein transporter (P-gp). Due to reduced permeability and increased P-gp mediated efflux across the blood-brain barrier, CNS penetration is negligible. Naloxegol therefore does not antagonize centrally mediated opioid analgesia.

No antidote is known for naloxegol. Dialysis was ineffective as a means of elimination in a clinical study in patients with renal failure. Patients who have received an overdose of the study drug should be monitored closely for potential evidence of opioid withdrawal symptoms such as chills, rhinorrhea, diaphoresis or reversal of central analgesic effect. Treatment should be based on the degree of opioid withdrawal symptoms, including changes in blood pressure and heart rate, and on the need for analgesia.

Procurement

Naloxegol will be provided by Astra Zeneca and distributed by the Alliance Research Base Pharmacy. The pharmacy will deliver patient-specific supplies of 18 tablets per bottle, and patients will be provided with a 3 month supply of five bottles containing 12.5 mg tablets and another five bottles containing 25 mg tablets at a time. **Sites should not repackage bottles within the kit, and drug should be dispensed in the original bottles.**

Each site is responsible to monitor their supplies and order additional bottles as required. At the end of the trial, any expired or remaining supplies should be destroyed according to institutional procedure.

Patient-specific supplies of naloxegol/placebo will be ordered by the registering institution after each patient is enrolled to the study.

Fax the Alliance A221504 Drug Order Form to:

The Alliance A221504 Drug Order Form is available on the A221504 study page of the Alliance and CTSU Web sites.
Note: Please note that sites in North Carolina should order drug as described above, but study drug will be shipped by Fisher Clinical Services.

IND Status

The FDA has determined that Naloxegol is IND exempt for this study.

Neither the investigator nor sponsor intends to seek a new indication for use or to support any other significant change in the labeling or product advertising for naloxegol. This investigation will use an approved route of administration and dosage of naloxegol and has no factors that increase the risk of the product. This investigation will be in compliance with 21CFR parts 56, 50, and 312.7 and neither the investigator nor sponsor will promote or represent that naloxegol is safe or effective for the context that is under investigation in this study. This investigation will not commercially distribute or test market the study agent, and will not unnecessarily prolong an investigation.

Formulation

Naloxegol film-coated tablets for oral use contain 14.2 mg and 28.5 mg of naloxegol oxalate, respectively equivalent to 12.5 mg and 25 mg of naloxegol. Excipients in the tablet core are: mannitol, cellulose microcrystalling, croscarmellose sodium, magnesium stearate, and propyl gallate. Excipients in the tablet coat are: hypromellose, titanium dioxide, polyethylene glycol, iron oxide red, and iron oxide black.

Naloxegol tablets are packaged in 18-count, high-density polyethylene (HDPE) bottles, with induction seal and HDPE child-resistant cap, and will include a desiccant pack. Please refer to the clinical label for the current shelf-life and in-use period.

Storage and Stability

The study drug should be stored at 20-25°C (68-77°F). Each lot of the study drug (and each bottle of naloxegol/placebo tablets)will have the expiration date specified on it.

Preparation & Administration

Naloxegol/placebo will be supplied as two bottles for each patient, one containing 12.5 mg tablets and the other containing 25 mg tablets. The 12.5 and 25 mg tablets will look different from each other, minimizing the risk that patients will accidentally take two tablets from the same bottle. Patients should take one 12.5 mg and one 25 mg tablet of naloxegol/placebo orally at the same time each day 1 hour before eating or 2 hours after a meal. Both tablets should be taken at the same time. Patients should be advised to swallow tablets whole, and not crush or chew them.

Patients should avoid consumption of grapefruit or grapefruit juice.

Drug Interactions

Concomitant use of naloxegol is not recommended with the following classes of medications:

Strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole [except topical use], cyclosporine, indinavir, nelfinavir, ritonavir, itraconazole, verapamil)

Moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, verapamil)

Strong CYP3A4 inducers (e.g., rifampin)

Opioid antagonists and mixed agonists/antagonists. EXAMPLES of such medications include: pentazocine, buprenorphine, nalbuphine, naloxone and other naloxone containing products such as oxycodone/naloxone combinations [e.g., Targin®], naltrexone and other naltrexone containing products such as morphine/naltrexone combinations [e.g., Embeda®], methylnaltrexone [Relistor®], or alvimopan [Entereg®]).

Pharmacokinetics

Absorption: rapid. With a high fat meal, C_{max} and AUC increase by 30% and 45% respectively.

Distribution: V_d 968-2140 L.
Protein binding: Low at approximately 4.2%.

Metabolism: Primarily hepatic via CYP3A4.

Half-life: 6-11 hours.

Excretion: primarily fecal (68%, approximately 16% as unchanged drug); urinary (16%, <6% as unchanged drug).

Adverse Events

Warnings/Precautions*:*

Gastrointestinal Perforation: Gastrointestinal perforation has been reported with another peripherally acting opioid antagonist in patients with conditions associated with compromised structural integrity of the gastrointestinal tract wall. Monitor for the development of severe, persistent or worsening abdominal pain; discontinue study drug and obtain urgent medical evaluation of patients who develop this symptom.

Opioid Withdrawal: Hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning have occurred in patients treated with naloxegol. Patients receiving methadone have a higher frequency of gastrointestinal adverse reactions possibly related to opioid withdrawal, compared to patients receiving other opioids. Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal or reduced analgesia. Monitor for symptoms of opioid withdrawal, particularly in such patients.

Adverse events:
>10%:
GI: Abdominal pain

1%-10%:
Central Nervous System: Headache
Dermatologic: Hyperhidrosis
GI: Diarrhea, nausea, flatulence, vomiting

Table 1 lists adverse reactions in pooled data from clinical studies in non-cancer patients receiving naloxegol for opioid-induced constipation, and occurring in ≥ 3% of patients receiving 12.5 mg or 25 mg naloxegol and at an incidence greater than placebo.

Adverse reaction	Naloxegol 25 mg (n = 446)	Naloxegol 12.5 mg (n = 441)	Placebo (n = 444)
Abdominal pain	21%	12%	7%
Diarrhea	9%	6%	5%
Nausea	8%	7%	5%
Flatulence	6%	3%	3%
Vomiting	5%	3%	4%
Headache	4%	4%	3%
Hyperhidrosis	3%	<1%	<1%

Nursing Guidelines

Upon starting the study, the patient and caregiver should be shown the two different naloxegol/placebo bottles and different colors of pills with instructions to take one tablet from each bottle daily; repeat demonstration from the patient or caretaker is recommended. Patient should be reminded to take naloxegol/placebo at least one hour before a meal or at least two hours afterwards. Grapefruit and grapefruit juice should be avoided while on naloxegol/placebo.

The patient medication diary should be explained to the patient and caregiver with instructions to note time/date of administration of naloxegol/placebo each day. The level and incidence of pain should be noted on the Pain and Pain Medication Diary using a scale of 0-10.

Patients should be instructed to call the site coordinator whenever a new drug is ordered, especially if the provider is outside of the cancer center and not fully aware of the study requirements and limitations. In the event of hospital admission, the study coordinator should monitor any new drugs to avoid undesirable interactions.

Patients should be instructed to call the site coordinator with any concerns. Ideally, a 24-hour number should be provided to the patient.

In the event that a 3-week interval visit is missed by the patient, the site coordinator can call the patient and obtain responses to the questionnaire(s) items OR discuss mailing the self-reported questionnaires with a stamped, returned envelope for return.

10.2 Placebo

A matching placebo will be provided by Astra Zeneca. It will match the active naloxegol 12.5 and 25 mg tablets in size, shape and color. The placebo tablets contain mannitol, microcrystalline cellulose and magnesium stearate. The coating material contains hypromellose, iron oxide/ferric oxide (red, black and yellow), macrogols/polyethylene glycol and titanium dioxide.

11.0 HEALTH OUTCOMES MEASURES

Each questionnaire administered in this study is described below. These self-reported questionnaires are expected to take less than 15 minutes for completion and be minimally burdensome. In the event that the patient is unable to complete the questionnaires, the local study coordinator may help the patient. Patients appreciate being asked about their symptoms on such questionnaires, and usually do not find them difficult or inconvenient to fill out.[74]

11.1 FACT-L

The FACT-L[75] includes the FACT-G [version 4.0], developed by Cella et al[76] as an overall cancer-specific HRQoL questionnaire, with a 9-item subscale concerning specific lung cancer issues. The FACT-G consists of a self-report 28-item HRQoL measure grouped into four subscales: physical well-being (PWB), social/family well-being (SFWB), emotional well-being

(EWB), and functional well-being (FWB). Most items are rated on a 5-point Likert scale, from 0, 'not at all' to 4, 'very much'. When the Lung Cancer Subscale (LCS) is added to FACT-G, 9 additional items focus on symptoms and issues more specific to lung cancer patients. The FACT-L will be scored according to the published scoring algorithm and following endpoints computed at each time point: FACT-L (PWB + SFWB + EWB + FWB + LCS), Trial Outcome Index (TOI; PWB + FWB + LCS), PWB, SFWB, EWB, FWB, and LCS. Higher scores indicate better HRQoL. Minimum clinically meaningful change in TOI and LCS scores have been determined[11] and will be used as a guide to assess the effect observed in this trial. See Section 13.0 and Appendix VI.

The focus of the secondary objective is to estimate the difference in HRQoL (TOI, FACT-L) improvement at 6 months from baseline between the study drug and placebo. However, collecting HRQoL data beyond 6 months (until the end of the 2 year study period) will allow us to explore the effect of treatment on long-term HRQoL. HRQoL data collected beyond 6 months will be summarized and compared, using similar methods described for change in HRQoL at 6 months (See Section 13.4.2). This exploratory analysis may inform the design of future randomized long-term studies.

11.2 PRO-CTCAEs and urinary hesitancy question

The standard mechanism for reporting toxicities in cancer research has been clinician-only reporting using items from the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAEs). Recently, the NCI has developed a patient-reported version of the CTCAE called the Patient-Reported Outcome-CTCAE (PRO-CTCAE). The PRO-CTCAE is a library of questions asking patients about specific symptomatic adverse events associated with cancer therapy, such as constipation or nausea. In multiple studies, PRO-CTCAE measures have improved the predictive accuracy of clinician CTCAE reporting. In a prospective study including lung cancer patients PRO measurements of toxicities better reflected patients' underlying state and functional status than clinicians' evaluations.[77]

For this study, we will use selected PRO-CTCAE items to assess the following symptoms: abdominal pain (3 PRO-CTCAE questions), headache (3 PRO-CTCAE questions), hyperhidrosis (sweating, 2 PRO-CTCAE questions), diarrhea (1 PRO-CTCAE question), nausea (2 PRO-CTCAE questions), flatulence (gas; 1 PRO-CTCAE question), vomiting (2 PRO-CTCAE questions) and dry mouth (1 PRO-CTCAE question). These items will be included in the questionnaires that patients complete at the same time as CTCAE assessments and a urinary hesitancy question, every 3 weeks for the first year, then every 3 months during year 2. The urinary hesitancy question (a visual analogue scale from 0-10 with 0 representing no symptom and 10 representing a symptom as bad as imaginable) is necessary because there are no PRO-CTCAE items that measure this symptom adequately. Summary statistics will be generated regarding change in PRO-CTCAE responses and change in urinary hesitancy scores over time in the three arms of the study. See Appendix V.

11.3 Bowel function-diary (BF-Diary)

Constipation will be assessed using modified versions of modules 1 and 2 of the bowel function-diary (BF-Diary)[78] prior to start of treatment and every 3 weeks (+/-7 days). See Section 5.0 and Appendix IV.

11.4 Pain and analgesic use

Pain and analgesic use will be assessed via a self-report daily medication/pain diary that patients will be asked to complete every day at home and bring to all study-related visits. See Section 5.0. See Appendix I.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Treatment

12.1.1 Patients are expected to receive the naloxegol/placebo for up to 2 years, in the absence of unacceptable toxicity or withdrawal of consent. Naloxegol/placebo will NOT be discontinued for disease progression. After 2 years of protocol treatment, patients may be unblinded per Section 8.3 and initiate open-label naloxegol treatment at the discretion of the treating physician.

12.1.2 Discontinuation of study agent: If the patient discontinues naloxegol/placebo, he/she should be followed for disease progression and survival by telephone or clinic visit every 3 months until 2 years after the date of registration. Submission of QOL booklets after discontinuation of naloxegol/placebo is not required.

12.2 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

A study patient who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

For all study patients who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Baseline and off-treatment notice data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

12.3 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Overview

This is a randomized, double blind, placebo-controlled, three-arm pilot study primarily designed to determine the safety and feasibility of the PAMORA naloxegol and to determine the optimal

of two FDA-approved doses of the study drug. Patients will be randomized at a 1:1:1 ratio to either one of the two doses of naloxegol or placebo.

13.2 Sample Size, Accrual Time and Study Duration

13.2.1 Sample Size

As this is a pilot study to assess feasibility and safety, it is not powered to test specific hypothesis. We plan to enroll a total of 204 patients, 68 patients per arm. Assuming approximately 10% of patients will be ineligible due to cancellation or major violations leading to a total 184 patients (61 per arm) evaluable for the primary endpoints of feasibility and safety. Among patients with advanced NSCLC, 0%, 25% and 33% of those receiving < 6, 6 – 8, and > 8 cycles discontinued pemetrexed + carboplatin induction chemotherapy for toxicity, respectively.[79] In phase III studies, deaths attributable to drug toxicity occurred in 1% and 0.3% patients during the induction and maintenance therapy phases, respectively.[17,18] About 75% of all patients who start pemetrexed-based chemotherapy for NSCLC are expected to be alive at 6 months.[17] Thus, we would like to observe that ≥ 80% of 75%, corresponding to ≥ 60% of all patients enrolled, continue on naloxegol/placebo for at least 6 months (the time point on which the change in Trial Outcome Index (TOI) of the FACT-L [secondary endpoint] will also be calculated). We will evaluate the safety of the naloxegol/placebo in NSCLC patients receiving systemic therapy by looking at the incidence of adverse events according to CTCAE criteria, including potentially expected and unexpected toxicities, and study drug vs placebo discontinuation rates, between the study arms.

Although the study is not powered to test specific hypotheses regarding HRQoL, the focus of the secondary objective of the study is to estimate the difference in HRQoL improvement at 6 months from baseline between the study treatment and placebo. Assuming 75% of patients will be alive at 6 months and 80% of these patients will return completed forms, we expect 111 patients (37 per arm) to be evaluable for this endpoint. The margin of error of a 90% two-sided confidence interval with this sample size is .38 SD. Cella et al.[11] reported that, in patients with advanced NSCLC receiving standard chemotherapy, the minimal Clinically Meaningful Change (CMC) size was 5-6 points (effect size, 0.14 – 0.45 SD) on the TOI and 2-3 points (effect size, 0.23 – 0.66 SD) on the LCS of the FACT-L, which correlated closely with changes in the disease status (objective response vs progression; early vs late progression). Using the SD reported in Cella et al.[11], the margin of error of .38 SD is equivalent to a difference of 5.7 points (SD = ~15 points) in TOI and 2 points (SD = 5 points) in LCS. Therefore, an observed improvement of 5.7 points or higher in TOI (or 2 points or higher in LCS) in one of the naloxegol arms when compared to the placebo arm suggests a benefit in favor of naloxegol. This sample size allows estimation with sufficient precision to detect a moderate effect size that falls within the published CMC range.

13.2.2 Accrual Rate and Accrual Duration

We anticipate accruing approximately 9 – 10 patients per month, based on our previous experience in clinical practice. This would mean completing the primary accrual within 20 – 22 months from study initiation.

13.2.3 Primary Endpoint Completion Date for ClinicalTrials.gov Reporting

For purpose of ClinicalTrial.gov reporting, the Primary Endpoint Completion Date (PECD) for this study is the time the last patient registered has been followed for at least one day.

13.3 Statistical Design and Analysis for the Primary Endpoint

13.3.1 Primary Endpoint

The primary endpoint of this study is feasibility and safety which will be evaluated by the following criteria:

(a) The rate of accrual remaining ≥ 80% of the expected (thus ≥ 147 patients by 2 years),

(b) ≥ 80% of patients who remain alive at 6 months continuing on the study medication, and completing the HRQoL and other forms, for at least 6 months, and

(c) The study continuing without meeting toxicity stopping criteria as specified in Section 13.5.1.

13.3.2 Statistical Design

This is a three-arm parallel group design with neither cross-over nor interim analysis.

13.3.3 Analysis Plan for the Primary Endpoint

The criteria for safety and feasibility will be evaluated as described below:

(a) The observed accrual rate will be calculated as the total number of patients accrued to the study over two years divided by 184, the total expected accrual of patients evaluable for the primary endpoint,

(b) The proportion of patients alive at 6 months who continue study drug and complete the HRQoL and other forms for at least 6 months will be calculated by arm, and

(c) The frequency of adverse events will be summarized by arm and compared between each treatment arm vs the placebo arm using Fisher's exact test.

13.4 Supplementary Analysis Plans

13.4.1 Secondary and Correlative Endpoints

1) The change from baseline to 6 months in trial outcome index (TOI), function subscales, and lung cancer subscale (LCS) of the Functional Assessment of Cancer Therapy-Lung (FACT-L)
2) Patient-reported outcome assessed by PRO-CTCAEs and a urinary hesitancy question
3) The Bowel Function-Diary (BF-Diary)
4) The level of pain and analgesic use
5) Unexpected clinical outcomes with systemic therapy
6) Progression-free survival
7) Overall survival
8) Prognostic effect of MOR expression/interaction on HRQoL

13.4.2 Secondary and Correlative Endpoint Analysis

1) Descriptive statistics and statistical plots will form the foundation of statistical analysis for this endpoint. HRQoL scores at each timepoint and changes in scores between 6 months and baseline will be summarized by mean (SD), median (inter-quartile range). Scores will be plotted to explore the pattern over time and to examine differences between treatment arms. Differences in HRQoL between the treatment arms and the placebo arm will be conducted through linear mixed models and growth curve models to account for repeated assessments. The model will adjust for baseline LCS and TOI, ECOG performance status,

and primary symptoms of advanced NSCLC (≤ 1 vs > 1 symptom) at enrollment. Because of exploratory nature, we will not adjust for multiple comparisons. The frequency and pattern of missing data will be summarized descriptively and sensitivity analyses will only be performed if the overall missing rate is more than 10% and most missing data are deemed not at random. Sensitivity analyses are composed of simple imputation, multiple imputations, and pattern mixture models and selection models.

HRQoL data beyond 6 months (until the end of the 2 year study period) will allow us to explore the effect of treatment on long-term HRQoL. HRQoL data collected beyond 6 months will be summarized and compared, using similar methods described for change in HRQoL at 6 months. This exploratory analysis may inform the design of future randomized long-term studies.

2) PRO-CTCAE and Urinary hesitancy items will be summarized by arm. PRO-CTCAE response will be compared between the treatment arms vs. placebo arm using a chi-square test or Fisher's exact test as appropriate. PRO-CTCAE and CTCAE data will be presented descriptively over time. Urinary hesitancy scores will be compared between treatment arms vs. placebo arm using Wilcoxon test.

3) OIC rating scale will be summarized by arm. Scores will be compared between treatment arms vs. placebo arm using Wilcoxon test.

4) Pain scores and analgesic use will be summarized by arm. Pain scores will be compared between treatment arms vs. placebo using Wilcoxon test. Frequencies of analgesic used will be compared using chi-square test or Fisher's exact test, as appropriate.

5) Frequency of discontinuation of systemic therapy will be summarized by arm and compared between each treatment arm vs the placebo arm using Fisher's exact test.

6) The event for PFS is disease progression/relapse or death. PFS time is defined as the time from randomization to disease progression/relapse, death, or loss to follow-up whichever occurs first. Progression will be assessed using the standard RECIST 1.1 criteria. Patient who are alive and disease-free at the end of study will be censored at that time point. PFS probabilities will be estimated by arm using the Kaplan-Meier estimator. In an exploratory manner, a Cox proportional hazards model will be used to determine the effect of naloxegol on PFS. Adjustment for known prognostic factors (age, sex, stage [IIIB vs IV], smoking status [non-smoker or light smoker vs heavy smoker]) will be included in the model if feasible. The model will be stratified by ECOG PS and planned use of bevacizumab.

7) The event for OS is death from any cause. OS time is defined as the time from randomization to death or loss to follow-up whichever occurs first. Patient who are alive at the end of the study will be censored at that time point. OS will be analyzed in the same manner as PFS.

8) MOR expression and activation will be included as a covariate in the linear mixed model from the analysis described in 13.4.2 1. An interaction between MOR expression/activation and treatment will be evaluated.

13.5 Study Monitoring

13.5.1 Adverse Event Stopping Rule

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of

the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy the following:

- If 5 or more patients in the first 20 treated patients (or 25% of all patients after 20 are accrued) experience a grade 4 or higher non-hematologic adverse event and there is a higher rate in the highest dose active treatment arm as opposed to the placebo arm.
- We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

13.5.2 Accrual Monitoring Stopping Rule

Slow Accrual: Patient accrual will be closely monitored by the study team on a monthly basis. If the accrual rate falls below 50% of the expected accrual rate, investigators will carefully review feedback from sites and consider taking measures to encourage patient enrollment.

13.6 Study Reporting

13.6.1 This study will be monitored by the Alliance Data Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every 6 months as per NCI guidelines.

13.6.2 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrials.gov" web site. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov.

13.7 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

There is no information currently available regarding differential effects of these regimens in subsets defined by race, gender, or ethnicity; and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for such subset analyses.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native					
Asian					
Native Hawaiian or Other Pacific Islander					
Black or African American	11	16			29
White	69	98	4	6	177
More Than One Race					
Total	80	114	4	6	204

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14.0 CORRELATIVE AND COMPANION STUDIES

There will be 1 substudy and all patients are encouraged to participate.

14.1 Biological mechanism of action, and biomarkers that would predict response/risk to the study drug

14.1.1 Background

Biological end-points based on our hypothesis will be evaluated in tumor biopsies and plasma, pre-treatment and plasma post-treatment. For practical reasons, obtaining post-treatment biopsies may not be feasible in this multi-center study. The hypothesis to be addressed is that high mu opioid receptors (MOR) in the tumors co-activates receptor tyrosine kinases for vascular endothelial growth factor receptor (VEGFR)-2 (on endothelium) and epidermal growth factor receptor (EGFR) on the tumor cells and downstream signaling pathways of mitogen activated protein kinase (MAPK/ERK) and protein kinase B (PKB/Akt) that promote cell proliferation and survival, respectively, and cyclo-oxygenase (COX)-2 signaling, leading to tumor progression and impairment of HRQoL. We anticipate that tumors with higher mu opioid receptor expression will show more responsiveness to naloxegol treatment and/or tumors with lower mu opioid receptor expression may show slower growth on their own. Thus, tumors with higher mu opioid receptors will show a correlative increase in the phosphorylation of endothelial VEGFR2, EGFR on endothelial/tumor cells, MAPK/ERK and Akt, Stat3 and increased COX-2/prostaglandin (PG)-E2 in association with higher cell proliferation (by proliferating cell nuclear antigen: PCNA) and cell survival (TUNEL staining) indices. Pain can influence pro-inflammatory and vasoactive neuropeptide substance P (SP), which can promote tumor growth-specific effects such as vascular permeability and angiogenesis, which may be higher in patients with more pain in association with beta-endorphin, the endogenous ligand for MOR. The levels of beta-endorphin and substance SP in the plasma will therefore correlate with increased MOR in the tumor and with pain. In addition, since opioid receptors can also modulate angiogenesis and lymphangiogenesis, these would correlate with MOR and opioid use and beta-endorphin levels.

14.1.2 Objectives

The main objective of the correlative science studies is to examine if MOR expression or activation is a prognostic marker in advanced NSCLC, and whether its expression/activation can be used to guide pain management. To examine this, the correlative studies will examine if any potential beneficial effect of selective peripheral MOR inhibition by naloxegol on HRQoL is limited to, or greater in, patients:

- Whose tumors demonstrate a higher level of MOR expression/activation
- With higher circulating levels of endogenous opioids, or
- Those requiring higher doses (≥5 mg/day average oral morphine equivalents [OME]) of pharmacological opioids

We will assess the mechanism of the study drug's impact by analyzing whether the HRQoL differences between the arms are greatest: 1) in patients with higher than the median MOR expression on their tumors; 2) in those with higher than the median circulating endogenous opioids; and 3) in those taking ≥ 5 mg/day average oral morphine at the start of the trial.

If our hypothesis proves to be true, this line of investigation can be further advanced in future studies to use fresh biopsies for isolating tumor cells and endothelial cells for mechanism based studies and can also be used in organ culture to determine the therapeutic potential of naloxegol on a case by case basis.

14.1.3 Methods

Expression of opioid receptors and correlative growth and survival-promoting signaling pathways in the tumor biopsies:

We provide the staining strategy with an example of one set of staining. Four to six micron thick sections will be co-stained with the following primary antibodies: goat anti-human CD31 (Santa Cruz Biotechnology, Santa Cruz, CA) at 1:50 dilution to label blood vessels, mouse anti-human total or phospho EGFR (Abcam, Cambridge, MA) at 1:100, and rabbit anti-human MOR (Chemicon International, Temecula, CA) at 1:100, followed by staining with species-specific secondary antibodies labeled with Cy2 (CD31), Cy3 (EGFR), and Cy5 (MOR) (Jackson Immunoresearch, Westgrove, PA). z-stacks of 0.5 micron thick images will be acquired using LSCM (Olympus FluoView 1000 BX2, Olympus Corporation, Center Valley, PA) for all 3 markers in the same field of view (FOV). MOR will be pseudo-colored green, EGFR red, and CD31 blue using Adobe Photoshop, and images from the same FOV will be merged to analyze for co-expression of molecular markers as described by us previously.[2]

Quantitative analysis of immunoreactive (ir) pixels for each marker: Each acquired image will be binarized and analyzed for immunoreactive pixels using Adobe Photoshop as described by us previously[5] and expressed as ir pixels divided by total stained area. To reduce non-specific background all acquisitions will be thresholded similarly for a specific antibody. Data will be expressed as ir-pixels per FOV at a fixed magnification.

Sets of markers examined will be as follows:

CD31, MOR, phospho-VEGFR2, Total VEGFR2

CD31, MOR, phospho-EGFR, Total EGFR

CD31, MOR, phospho-MAPK/ERK, Total MAPK/ERK

CD31, MOR, phospho-Stat3, Total Stat3 (this set will be tested if adequate number of slides are available)

Quantitative analysis of SP and beta-endorphin in the plasma:

SP will be analyzed in heparinized plasma using competitive ELISA (R&D Systems, Minneapolis, MN), using negative and positive controls with each set of analysis, as described by us.[80] Levels of beta-endorphin will be determined in EDTA-plasma, using competitive high sensitivity ELISA (Peninsula Laboratories International, Inc, San Carlos, CA). We have standardized this assay and recognize that it has to be run at least in duplicate on each sample for reproducibility.

These methods have been standardized in the investigator's laboratory using human and mouse plasma. Quality control assessments have been performed on human plasma, which will also be used while analyzing the plasma samples from this current study. Longitudinal studies on beta-endorphin and SP have been performed on the plasma of transgenic mice during cancer progression. These longitudinal studies have shown a significant correlation between tumor burden and the concentration of beta-endorphin in the plasma.

Anticipated Problems and Alternative Strategies

Limited number of slides or no biopsy slides (FNA): In general, throughout the study we will stain for 3 markers/section. We will ask for 4-6 unstained slides per patient. Each slide will be stained for 4 markers if fewer slides are available using our established immunofluorescent labeling techniques.[2,33,81] To maximize the analytical output and minimize the effect of regional heterogeneity, 3-5 different fields of view (FOV) will be imaged per section for each marker. All 4 markers per section will be analyzed in each FOV

and 2 sections will be stained per set of 4 markers. Therefore, with 4-6 slides we will be able to analyze 8-12 markers. However, based on our past experience with similar studies,[2-5] we realize the challenges involved in obtaining slides from limited tissue biopsies and/or FNA. In our previous study, biopsies from about 30 tumors analyzed for MOR immunoreactivity yielded significance in an analysis similar to that proposed in the current study.[5] In similar studies reported by other investigators, biopsies could not be available for analysis from all the patients, but significance could be achieved for the clinical correlations examined for intratumoral markers of hypoxia and angiogenesis with respect to % freedom from biochemical failure against time in years.[82] We anticipate analyzing 10-12 markers, but in the event of limited availability we will limit our analysis to 6-8 most important markers, namely MOR; phospho and total-EGFR, phospho and total-VEGFR2, and anti-CD31; and total and phospho- MAPK/ERK and -Stat3, which can be performed on 2 unstained slides. In cases where FNA is performed, we will request slides from the paraffin cell block, if available. Therefore, we are cautiously optimistic of obtaining the targeted sample size for correlative analytical studies.

Hemolysis: Another observation that we have made is occasionally blood samples are hemolyzed. The analysis using ELISA may be compromised on hemolyzed samples and they will need to be excluded from the study. To overcome this issue, we will examine the samples immediately upon arrival in the lab. If we find a hemolyzed sample, we will immediately contact the collecting center to consider the possibility of re-draw and replacing the sample.

Exploratory outcomes:

Measuring the circulating levels of beta-endorphin and SP is exploratory, but their translational potential is high for identifying novel markers of pain associated with tumor progression independently and also after opioid use. This is therefore a high risk, high reward analysis. It is based on our strong pre-clinical studies in cancer-bearing mice and in transgenic mice with sickle cell disease expressing human sickle hemoglobin, both of which experience constitutive chronic pain.[33, 81,83] Studies by other groups on sickle patients have clearly shown an increase in blood levels of SP in sickle patients at steady state as compared to ethnicity- and age-matched controls; as well as a further increase in sickle patient's blood during vaso-occlusive crises (VOC), a condition associated with acute severe pain.[84] In our mouse studies, sickle mice showed significantly increased blood levels of SP at steady state compared to control mice expressing normal human hemoglobin A. Upon treatment with imatinib, cromolyn sodium, cannabinoids and an investigational drug (AT200), SP levels decreased significantly, and correlated with decreased pain following these treatments.[80,85] Complementary to these observations, transgenic breast cancer bearing mice showed increased SP expression in the tumors of mice receiving chronic morphine treatment as compared to those receiving PBS.[33] These data provide convincing evidence of increased SP in the tumors and in the blood in response to pain as well as after treatment with morphine. Importantly, treatments influencing the pathobiology of the disease leading to decreased pain also led to a decrease in circulating SP. Together, these data in two conditions with chronic pain show that SP is modulated in response to disease pathobiology, pain and pain treatment. SP may therefore serve as a potential marker of pain and its response to therapy. In addition, since SP appears to mediate neurogenic inflammation and cancer progression in pre-clinical studies, its receptor NK1 provides an additional target to block the adverse effect of SP. Some NK1 receptor antagonists are FDA approved and can be utilized to reduce pain and/or reduce disease progression. Therefore, levels of SP will be critical to analyze and are likely to generate a novel hypothesis to be examined in future studies.

Timing of SP and beta-endorphin measurement:

We realize that due to the complex and heterogeneous tumor microenvironment which is further influenced by stress and different treatments for cancer and/or pain, the circulating levels of ligands can vary considerably. In transgenic sickle mice with severe systemic inflammation and pain, and in transgenic cancer-bearing (C3TAg) mice which have an inflammatory milieu and pain, we found that inflammatory cytokines and SP were both significantly modulated as early as 5 days and as late as 7 weeks of treatment, the last period of observation.[33,80,85,86] Therefore, we chose three time points for the current clinical study (i.e., at the start of the study to provide a baseline to compare subsequent effect of progression/treatments, and two relatively early time points [at 3 and 6 weeks]) with the expectation that we will detect a significant effect. Relatively early analysis of these biomarkers is important because it will provide a window of opportunity to offer additional treatment choices based on these biomarkers, such as NK1 antagonists if SP is increased or PAMORAs if beta-endorphin is increased. As described above, this would be supportive of our novel hypothesis of the role of pain associated mechanisms involving MOR/SP leading to the identification of actionable targets. We are cautiously optimistic of observing significant changes in the plasma levels of these markers within 6-8 weeks as compared to baseline and/or in response to therapy.

Correlation of tumor progression, inflammatory response and pain:

It is well known that inflammation is associated with both advanced cancer and pain independently as well as with cancer associated pain. In our pre-clinical studies, we observed a parallel increase in inflammatory cytokines and SP in the tumors of C3TAg mice treated with morphine.[33] Similarly, in transgenic sickle mice we found a significant increase in inflammatory cytokines and SP in the plasma and their release from skin biopsies as compared to that of control mice.[85] While SP levels were uniformly increased, individual cytokines released from the skin were variable and were further modulated in a heterogeneous manner with modulation of pain by different targeted therapies. Therefore, SP provides a more uniform measure of neuro-inflammation, which is relatively more specific to pain associated conditions. However, it could be an indicator of systemic inflammation as well. Therefore, its correlation with MOR may be critical for its association with pain leading to impairment of HRQoL.

Correlation between SP and MOR expression:

In pre-clinical studies, we found that treatment with morphine increased the expression of several inflammatory cytokines and SP in the tumors, correlating with increased tumor burden in transgenic C3TAg mice.[33] Importantly, while MOR expression was undetectable in early/small tumors, there was high expression of MOR in large tumors. Consistent with this observation, morphine administration stimulated the growth of relatively large, but not small tumors (at the time of tumor initiation).

Thus, increased MOR expression complements increased SP expression. This could occur in response to morphine treatment as observed by us in sickle mice, but also in response to increased beta-endorphin, a ligand for MOR. In our clinical study on patients with prostate cancer, we found that MOR expression in the tumor biopsies was independently associated with shorter time to progression, progression-free survival and overall survival, irrespective of opioid requirement for pain.[5] Therefore, in the absence of exogenously administered opioids, activation of MOR (whose expression is increased in advanced tumors) is likely due to endogenous ligands such as endorphins, which may be increased due to stress and/or in response to pain. Our rationale to analyze beta-endorphin is further complemented by a recent study on cancer patients showing significantly increased plasma beta-endorphin levels in patients treated with the COX inhibitor drug flurbiprofen axetil in combination

with morphine as compared to morphine treatment alone, for 7 days.[87] Satisfactory analgesia in this study was associated with increased plasma beta-endorphin levels as demonstrated by negative correlation between beta-endorphin in the plasma and pain scores (R^2, 0.929 and $P<0.01$). Therefore, beta-endorphin can be a prognostic marker for analgesia, in addition to its activation of mitogenic signaling via MOR in the tumors, plausibly contributing to cancer progression. Seminal observations from our group showed that like morphine, beta-endorphin activated MAPK/ERK signaling in endothelial cells.[1] Since both beta-endorphin and SP are released in conditions associated with pain and in response to morphine/pain treatment, their circulating levels may have a diagnostic as well as prognostic potential, with a bearing on improving HRQoL and clinical outcomes.

Tumor specimens will be evaluated for expression of the following markers by analysis of images acquired using laser scanning confocal microscopy (LSCM):

Mu opioid receptor[2-5]

Kappa opioid receptor[88]

COX-2 (partly mediates the pro-angiogenic activity of MOR)[31]

Total and phosphorylated VEGFR2 and EGFR (cross-activated by MOR)2

Total and phosphorylated Stat3, Akt and MAPK (phosphorylated by MOR activation)[1,2,38,42]

Substance P (SP: marker of neurogenic inflammation and pain)[85]

CD31 (marker of blood vessels, for assessment of microvessel density)[2]

LYVE1 (marker of lymphatic vessels)[33]

Circulating levels of beta-endorphin and SP will be determined in plasma samples obtained at registration and at 3 weeks (+/- 7 days) and 6 weeks (+/- 7 days) after initiation of the study medication.

All analysis will be performed in a double blind manner. The assays and analyses proposed herein are routinely performed in Dr. Kalpna Gupta's laboratory using antibodies for each marker that have been validated and published. Paraffin embedded tumor sections will be stained with three different primary antibodies and species-specific secondary antibodies tagged with different fluorophors. A montage of Z-stack images acquired using a LSCM will be analyzed to quantitate immunoreactive (ir) pixels for each marker using Adobe Photoshop and Image Processing tool-kit Plug-in functions (Reindeer Games, Ashville, NC) as described by us.[5]

The tumor microenvironment is composed of several different cellular entities critical to cancer progression which express opioid receptors, including tumor-, endothelial and lymphatic cells, of direct relevance to this proposal. Therefore, opioid-receptor associated activity will be analyzed in a cell-specific manner. Since associations with MOR will be defined, co-staining will be performed for each marker with MOR using three color immunostaining of tumor sections.

Expected results:

High MOR expression will be associated with endothelial, lymphatic and tumor cells. VEGFR2 phosphorylation associated with MOR will only be observed in the vasculature, whereas EGFR, Stat3 and MAPK/ERK will be observed in endothelial as well as non-endothelial cells. It is likely that higher MOR-ir will be accompanied by decreased kappa opioid receptor-ir, suggestive of increased MOR activity as compared to kappa opioid receptor in the tumors when opioids are used to treat pain. Correlative analysis with survival will reveal the significance of the mechanisms involved and additional targets to develop

strategies to ameliorate MOR-associated disease progression. Due to increased stress and pain, circulating levels of beta-endorphin and SP will be higher in subjects with higher disease burden, progression and pain. These will be even higher in subjects on higher doses of opioids, but may be attenuated in those receiving naloxegol that blocks peripheral opioid receptors. In this pilot study, statistical analysis of these correlative studies will be exploratory and hypothesis-generating.

Potential for future clinical translation:

Importantly, these correlative studies performed in a clinical setting will identify the receptors and signaling pathways activated in association with MOR. This would lead to future investigations to determine mechanisms underlying MOR-induced co-activation of these specific signaling pathways in human endothelial and/or cancer cells. In turn, these observations will provide targets to block MOR-induced tumor progression without compromising analgesia. Additionally, if we observe an inhibitory effect of naloxegol on mitogenic signaling pathways in the tumor, it could be further examined for its effect in combination with standard systemic anti-cancer therapies to improve clinical outcomes including HRQoL.

15.0 GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING

None

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17.0 MODEL CONSENT FORM

Study Title for Study Participants: Testing the addition of naloxegol (Movantik®) or placebo to anti-cancer therapy in advanced lung cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:

A Randomized, Double-Blind, Placebo-Controlled Pilot Study Of An Oral, Selective Peripheral Opioid Receptor Antagonist In Advanced Non-Small Cell Lung Cancer

What is the usual approach to my *lung cancer*?

You are being asked to take part in this study because you have been diagnosed with a common type of advanced lung cancer (non-small cell lung cancer: NSCLC). You have also used pain medicines (such as morphine or similar drugs, called opioids) in the past 4 weeks to control pain caused by your cancer. People who are not in a study are usually treated with a variety of FDA-approved medications. Many patients with advanced lung cancer also require opioid pain medications to control pain at some time during the course of their disease.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

Why is this study being done?

You have advanced lung cancer and will be receiving opioids to relieve some of the cancer-related pain that you are experiencing. Opioids relieve pain through their action inside the brain. However, by their action outside of the brain, opioid medications can cause unwanted side effects such as constipation, nausea, vomiting, dry mouth, and problems passing urine.

The purpose of this study is to test the safety and effects of naloxegol. Naloxegol is a medicine that blocks the actions of opioids outside the brain, without interfering with the pain-relieving effect of opioids inside the brain. The researchers want to see if naloxegol will relieve some of the side effects of the opioid pain medications you are taking. They also want to see if naloxegol fights off future growth in the cancer that you have, whether or not you are taking pain medications.

The effect of two different doses of naloxegol will be compared to placebo. A placebo is a pill that looks like the study drug but contains no medication.

There will be about 204 people taking part in this study.

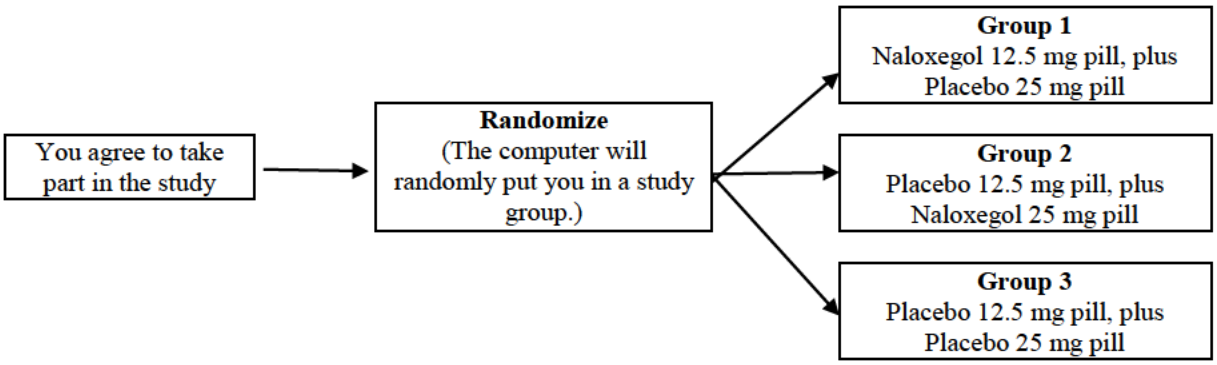
What are the study groups?

This study has three study groups.

All three groups will receive the usual anti-cancer therapy plus:

- Group 1 will receive a 12.5 mg naloxegol pill plus a placebo pill once a day.
- Group 2 will receive a 25 mg naloxegol pill plus a placebo pill once a day.
- Group 3 will receive two placebo pills once a day.

A computer will by chance assign you to one of the three treatment groups being evaluated in the study. This is called randomization. This is done by chance because no one knows if one study group will do better or worse than the others. Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



After you are randomized, you will start taking naloxegol/placebo. You will receive 2 bottles: one bottle of 12.5 mg of naloxegol/placebo tablets and one bottle of 25 mg naloxegol/placebo tablets. You will be asked to take one tablet from each bottle once a day.

The placebo is given in all three groups so that patients in all groups receive similar-looking pills. This way neither you nor your doctor can tell which group you are in, and that makes the study more objective. There is no plan to tell you whether you are receiving naloxegol or placebo while you are on study except in case of an emergency.

You will take one tablet at the same time once every day from each bottle on an empty stomach, at least 1 hour before eating or 2 hours after a meal. Both tablets should be taken at the same

time. Please swallow tablets whole, do not crush or chew. The tablets in the two bottles will look different from each other. One or both of the tablets could be a placebo.

You should not have grapefruit or grapefruit juice while on this study. You should also check with your doctor or pharmacist before using any new medicines, including over-the-counter drugs because of possible drug interactions.

You will be asked to record the day, number of pills taken, and time of each dose of naloxegol/placebo on a medication diary. You will be asked to bring the calendar and the pill bottles with you to your clinic visits. You will also be asked to record how much pain you are feeling and any pain medications you may have taken on another form.

How long will I be in this study?

You will receive *naloxegol/placebo* for up to 2 years or until you experience any severe side effects. If you receive naloxegol/placebo for 2 years, you may choose to find out at that time whether you were receiving naloxegol or placebo. If you were receiving naloxegol, you and your doctor will decide whether you should continue taking naloxegol. The study will not provide naloxegol after 2 years.

Whether or not you remain on study treatment, the study doctor will continue to follow your progress.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests (such as blood tests), and procedures (such as CT or other scans) you will have are part of the usual treatment and monitoring of your cancer. However, there are some extra tests that you will need to have if you take part in this study.

Before you begin the study medication:
You will complete some questionnaires before you start taking your study drug.

During the study:
You will be asked to come to the clinic for follow-up about 3 and 6 weeks after starting the study medication to see how you are doing physically and check your blood tests.

You will also be asked to complete questionnaires 3 weeks and 6 weeks after you start naloxegol/placebo, and then every 3 weeks for one year and then every 3 months. These surveys will be about your pain medications, your urinary functions, your bowel movements and your quality of life. This should take about 15 minutes to complete.

A patient study calendar that shows how often these *tests, and questionnaires* **will be done is attached at the end of this document.**

If you do not come to the clinic at these times, you may either mail the questionnaires to your study doctor, or the clinic staff may obtain the information needed from you over the phone.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- *The addition of naloxegol to usual anti-cancer therapy may not be better, and could possibly be worse, than the usual anti-cancer therapy given by itself for your cancer.*

The *Naloxegol* used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from naloxegol.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust naloxegol/placebo to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects of Naloxegol

COMMON, SOME MAY BE SERIOUS In 100 people receiving Naloxegol, more than 20 and up to 100 may have:
• Pain in the abdomen (stomach)

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Naloxegol, from 4 to 20 may have:
• Diarrhea • Nausea • Flatulence (bloating, gas) • Vomiting • Headache

RARE, SOME MAY BE SERIOUS In 100 people receiving Naloxegol, 3 or fewer may have:
• Perforation (tear) in the wall of the stomach, intestines or bowel • Symptoms due to blocking the effect of opioids ("opioid withdrawal"), such as excessive sweating, chills, diarrhea, pain in the abdomen (stomach), anxiety, irritability, and yawning.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

The topics discussed **in questionnaires** may cause you to feel embarrassed or uncomfortable. If this happens to you, please let your study doctor, nurse or other study staff know about your discomfort.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The *study medication naloxegol/placebo* used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if addition of naloxegol/placebo to standard anti-cancer therapy is better than the usual approach (anti-cancer therapy) so this study may or may not help you. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number).*

What are the costs of taking part in this study?

Naloxegol/placebo will be supplied at no charge for up to 2 years while you take part in this study. The cost of getting the *naloxegol/placebo* ready and giving it to you *is also provided at no charge.* It is possible that the *naloxegol/placebo* may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of *treating* your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors *will not* offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor and any drug company supporting the study.
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

The Alliance has received a Certificate of Confidentiality from the federal government, which will help us to protect your privacy. The Certificate protects against the involuntary release of information about you collected during the course of the study. The researchers involved in this project may not be forced to identify you in any legal proceedings (criminal, civil, administrative, or legislative) at the federal, state or local level. However, some information may be required by the Federal Food, Drug, and Cosmetic Act, the U.S. Department of Health and Human Services, or for purposes of program review or audit. Also, you may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests the release of information about you in writing (through, for example, a written request to release medical records to an insurance company), the Certificate does not protect against that voluntary disclosure.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

ADDITIONAL STUDIES SECTION:

This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records and you or your study doctor *will not* know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say "no" to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

Optional Sample Collections for Laboratory Studies and/or Biobanking for Possible Future Studies

Researchers are trying to learn more about pain, cancer, and other health problems. Much of this research is done using samples from your blood or tissue. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part in this study, the study doctor for the main study would like to collect *blood* for research on *substances in the body that cause pain and others that relieve pain. Researchers* would also like to study samples from your lung cancer tissue that were obtained from you for diagnosis. The tissue will be analyzed for factors that are involved in causing pain and others that are involved in promoting tumor growth. We are asking for your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by the Alliance Biorepository at Mayo Clinic and supported by the National Cancer Institute.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) About two extra teaspoons of blood will be collected from a vein in your arm once before starting the study medication and twice more (at about 3 and 6 weeks) after you start the study medication). All these blood samples will be collected at the time you are giving blood samples for routine (usual) tests related to your anti-cancer therapy. You will NOT have to undergo extra needle sticks to provide blood samples for these laboratory studies.
2) In addition, a sample from the tissue that was collected previously at the time of your biopsy or surgery will be sent to the Biobank. You will NOT be asked to undergo another biopsy to provide tissue for these laboratory studies.
3) Your sample and some related health information will be sent to a researcher for use in the study described above. Remaining samples may be stored in the Biobank, along with samples from other people who take part. The samples will be kept until they are used up.
4) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
5) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
6) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
2) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your samples are sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and *Alliance for Clinical Trials in Oncology* staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom *Alliance for Clinical Trials in Oncology* send your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part in these laboratory studies. The results may help other patients in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option:

SAMPLES FOR THE LABORATORY STUDIES:

I agree to have my specimen collected and I agree that my specimen sample(s) and related information may be used for the laboratory study(ies) described above.

YES NO

SAMPLES FOR FUTURE RESEARCH STUDIES:

My samples and related information may be kept in a Biobank for use in future health research.

YES NO

I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study *and any additional studies where I circled 'yes'.*

Participant's signature_____

Date of signature_____

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____

The following table summarizes your visit schedule for this study:

	Prior to the study	3 and 6 weeks after start of treatment	Every 6 weeks* until 1 year after start of treatment	Every 3 months
Tests & Assessments				
History and physical	X			
Blood Tests	X	X		
Monitoring	X	X	X**	X
Questionnaire booklets	X	X	X***	X
Patient Medication Diary		X	X	X

* You may be asked to visit the clinic more often than every 6 weeks.

** Monitoring will take place every 3 weeks. If you do not see your study doctor every 3 weeks, this monitoring will be done by telephone.

*** Some questionnaire booklets will be required every 3 weeks.

APPENDIX I: PAIN AND PAIN MEDICATION DIARY

[This version is to be used in the baseline Booklet A.]

INSTRUCTIONS TO THE PATIENT:

1. Complete one row for each 7-day-period of treatment.
2. Record the name, strength, and number of doses of pain medication you took per day during the past 7 days and how much pain you had on average during the 7-day period.

Did you take any pain medication(s) during this 7-day period?	If yes, name(s) of the medication(s)	Strength(s)	Average number of doses per day taken during this 7-day period	Average level of pain during this 7-day period (0-10, with 10 being worst pain imaginable)

[This version is to be used in the every-three-week Booklet C.]

INSTRUCTIONS TO THE PATIENT:

1. Complete <u>one</u> row for each 7-day-period of treatment.
2. Record the date, the name, strength, and number of doses of pain medication you took per day during each 7-day period, and how much pain you had on average during each 7-day period.
3. Use the last rows only if you need them.

Week	Date (first day of each 7-day period	Did you take any pain medication(s) during this 7-day period?	If yes, name(s) of the medication(s)	Strength(s)	Average number of doses per day taken during this 7-day period	Average level of pain during this 7-day period (0-10, with 10 being worst pain imaginable)
1.						
2						
3						

Physician's Office will complete this section:

1. Date patient started protocol treatment
   _____
2. Date patient was removed from study _____
3. Physician/Nurse/Data Manager's Signature

   _____

[This version is to be used in the every-three-month Booklet D.]

INSTRUCTIONS TO THE PATIENT:

1. Complete <u>one</u> row for each 7-day-period of treatment.
2. Record the date, the name, strength, and number of doses of pain medication you took per day during each 7-day period, and how much pain you had on average during each 7-day period.
3. Use the last rows only if you need them.

Week	Date (first day of each 7-day period	Did you take any pain medication(s) during this 7-day period?	If yes, name(s) of the medication(s)	Strength(s)	Average number of doses per day taken during this 7-day period	Average level of pain during this 7-day period (0-10, with 10 being worst pain imaginable)
1.						
2						
3						
4						
5						
6						
7						
8						

9						
10						
11						
12						
13						

Physician's Office will complete this section:

1. Date patient started protocol treatment
   _____
2. Date patient was removed from study _____
3. Physician/Nurse/Data Manager's Signature

   _____

APPENDIX II: PATIENT MEDICATION DIARY – NALOXEGOL/PLACEBO

Today's date _____

Patient Name_____ (initials acceptable) **Patient Study ID** _____

	INSTRUCTIONS TO THE PATIENT: 1. Complete this form while you take **naloxegol/placebo**. This form is a 30 day diary. You may need to complete more than one form between clinic visits. 2. You will take your dose of **naloxegol/placebo** daily. 3 Take the **naloxegol/placebo** pills at least one hour before a meal or at least two hours afterwards. 4. Record the date, the number of tablets you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time. 5. If a dose is missed, do not make up that dose; resume dosing with the next scheduled dose. 6. Swallow tablets whole, do not crush or chew. 7. You should not have grapefruit or grapefruit juice while on this study. In rare cases this medication can cause the following side effects: a) If you develop unusually severe, persistent or worsening pain in your abdomen. b) If you are unable to pass stools and gas, and your abdomen feels uncomfortably bloated. If these occur, stop taking the naloxegol/placebo pills and call your doctor/health care provider. 8. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am 9. Please return this form to your physician at your next appointment. You may need to return more than one form per clinic visit. You will also be asked to return your pill bottles at each visit.

Day	Date	Time of daily dose	Bottle #1 # of tablets taken	Bottle #2 # of tablets taken	Comments
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					
29					
30					
Patient's Signature					Date

APPENDIX III: CALCULATION OF EQUI-ANALGESIC DOSES OF OPIOID MEDICATIONS

Conversion of other opioid medications to Oral Morphine Equivalents (OME)

To calculate the total oral morphine equivalents (OME) that a patient is using:

1) Calculate the total dose of each opioid used per day. The doses of long-acting opioids or liquid preparations are calculated exactly as for short-acting or immediate release opioids.
2) Multiply that total amount by the number for that opioid from the table below (e.g. 1.5 for oral oxycodone), to get the OME.
3) Add up all the OMEs to get the total OME, as illustrated in the examples below.

Opioid	Parenteral (IV/IM/SC, in mg)	Oral (mg)
	Multiplication factor	**Multiplication factor**
Buprenorphine	75	-
Butorphanol	15	-
Codeine	0.25	0.15
Fentanyl	300	2* (transdermal: see below)
Hydrocodone	-	1
Hydromorphone	20	4
Levorphanol	15	7.5
Meperidine	0.4	0.1
Methadone**	13.5	4.7
Morphine	3	1
Nalbuphine	3	-
Oxycodone	-	1.5
Oxymorphone	30	3
Tapentadol	-	0.4

*Multiply the fentanyl patch strength by 2 to get the OME directly. Thus, a 25 microgram/hour fentanyl patch = 50 OME.[89]

Example 1:

The patient is using MS Contin 30 mg PO BID + oxycodone/acetaminophen (Percocet; 5 mg/325 mg strength) 2 tabs every 6 hours (for breakthrough pain):

MS Contin 30 mg x 2 times/day = 60 mg/day
Multiply 60 by 1 (the number for oral morphine) = 60 x 1 = 60 OME

+

Oxycodone 5 mg x 2 tabs x 4 times/day = 40 mg/day
Multiply 40 by 1.5 (the number for oral oxycodone) = 40 x 1.5 = 60 OME

Total OME = 60 + 60 = **120 OME**

Example 2:

The patient is using a fentanyl patch 50 micrograms/hour strength + morphine elixir (10 mg/5 ml strength) 5 ml every 4 hours (for breakthrough pain):

Fentanyl 50 micrograms/hour	
Multiply 50 by 2 (*see above) = 50 x 2 =	100 OME
	+
Morphine elixir 10 mg x 6 times/day = 60 mg/day	
Multiply 60 by 1 (the number for oral morphine) = 60 x 1 =	60 OME
Total OME = 100 + 60 =	**160 OME**

**For conversion of methadone to OMEs, we will use the conversion factors recommended by Walker et al.[90] This is a carefully conducted analysis of patients who switched from IV or oral methadone to morphine or other opioids. The authors recommend using a ratio of 1:4.7 for conversion of oral methadone to oral morphine, and a ratio of 1:13.5 for conversion of IV methadone to oral morphine. Of note, the conversion ratio remained constant (did not change) with increasing dose of methadone, unlike the change in ratio recommended when the conversion is in the opposite direction, i.e. when morphine is converted to methadone.[91]

APPENDIX IV: BOWEL FUNCTION-DIARY (BF-DIARY)

Module 1: Characteristics of last bowel movement	
Please record the time when this bowel movement occurred.	_____ Hour/min.
How much did you have to strain during this bowel movement?	☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely
During this bowel movement, how much did you feel that you were able to fully empty your bowels?	☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Completely
How much pain did you have around your rectum during this bowel movement?	☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe
During this bowel movement, how would you describe the shape and consistency of your stool?	☐ Separate hard lumps, like nuts (hard to pass) ☐ Sausage-shaped but lumpy ☐ Like sausage but with cracks on its surface ☐ Like a sausage or snake, smooth and soft ☐ Soft blobs with clear-cut edges (passed easily) ☐ Fluffy pieces with ragged edges, a mushy stool ☐ Watery, no solid pieces (entirely liquid)

Module 2: Past 24-hour Assessment	
In the past 24 hours, how often were you unable to have a bowel movement even though you felt like you had to?	☐ All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time
In the past 24 hours, how much bloating did you feel because of constipation?	☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe
In the past 24 hours, how much pain did you feel in your abdomen because of constipation?	☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe
In the past 24 hours, how much were you bothered by gas?	☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely
In the past 24 hours, how much were you bothered by a lack of appetite because of constipation?	☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely

From: Camilleri M, Rothman M, Ho KF, Etropolski M. Validation of a bowel function diary for assessing opioid-induced constipation. *Am J Gastroenterol*. 2011;106(3):497-506.[78]

APPENDIX V: PRO-CTCAE* AND URINARY HESITANCY QUESTION

Directions: Please check or mark the answer or number that best reflects your symptoms **during the past 7 days, including today**.

1.	In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

2.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost Constantly

3.	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

4.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

5.	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

6.	In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost Constantly

7.	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	○None	○ Mild	○ Moderate	○ Severe	○ Very severe

8.	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	○Not at all	○ A little bit	○ Somewhat	○ Quite a Bit	○ Very much

9.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost Constantly

10.	In the last 7 days, did you have any INCREASED PASSING OF GAS (FLATULENCE)?	
	○ Yes	○ No

11.	In the last 7 days, how OFTEN did you have a HEADACHE?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost Constantly

12.	In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

13.	In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
	○Not at all	○ A little bit	○ Somewhat	○ Quite a Bit	○ Very much

14.	In the last 7 days, how OFTEN did you have UNEXPECTED OR EXCESSIVE SWEATING DURING THE DAY OR NIGHTTIME (NOT RELATED TO HOT FLASHES)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

15.	In the last 7 days, what was the SEVERITY of your UNEXPECTED OR EXCESSIVE SWEATING DURING THE DAY OR NIGHTTIME (NOT RELATED TO HOT FLASHES)? at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

* The PRO-CTCAE™ items and information herein were developed by the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO-CTCAE™ is subject to NCI's Terms of Use.

6. Any trouble with your ability to urinate easily?

0 1 2 3 4 5 6 7 8 9 10

None	As bad as I can imagine

APPENDIX VI: FACT-L (VERSION 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

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Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
L1	My thinking is clear	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
L3	I feel tightness in my chest	0	1	2	3	4
L4	Breathing is easy for me	0	1	2	3	4
Q3	Have you ever smoked? No ___ Yes ___ If yes:					
L5	I regret my smoking	0	1	2	3	4

 16 November 2007

APPENDIX VII: PATIENT INFORMATION SHEETS

PATIENT INFORMATION SHEET
Patient Completed Booklet A
(Baseline)

You have been given a booklet to complete for this study. This booklet contains some questions about your 'quality-of-life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You are being asked to complete a questionnaire booklet for this study. This booklet must be completed on the day you enroll in the study. It contains the following questionnaires:

    - FACT-L Questionnaire
    - PRO-CTCAE and Urinary Hesitancy Question
    - Bowel Function Diary
    - Pain and Pain Medication Diary

2. Directions on how to complete each set of questions are written on the top of each set.

3. It is very important that you return the booklets to us, whether you finish the study or not.

4. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

5. After completing this booklet, please return it to your nurse or physician.

Thank you for taking the time to help us.

PATIENT INFORMATION SHEET
Patient Completed Booklet B
(3 and 6 weeks after the start of treatment, then every 6 weeks for the first year of treatment)

You have been given a booklet to complete for this study. This booklet contains some questions about your 'quality-of-life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You are being asked to complete this questionnaire booklet at the following time points:
    - 3 weeks after the start of treatment
    - 6 weeks after the start of treatment
    - Every 6 weeks for first year of treatment (i.e. week 12, week 18, week 24, etc.)

2. This booklet contains the following questionnaires:
    - FACT-L Questionnaire

3. Directions on how to complete each set of questions are written on the top of each set.

4. It is very important that you return the booklets to us, whether you finish the study or not.

5. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

6. After completing this booklet, please return it to your nurse or physician or mail it back in the provided envelope.

Thank you for taking the time to help us.

PATIENT INFORMATION SHEET
Patient Completed Booklet C
(Every 3 weeks for the first year of treatment)

You have been given a booklet to complete for this study. This booklet contains some questions about your 'quality-of-life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You are being asked to complete this questionnaire booklet every 3 weeks during the first year of your study treatment. It contains the following questionnaires:

    - PRO-CTCAE and Urinary Hesitancy Question
    - Bowel Function Diary
    - Pain and Pain Medication Diary

2. Directions on how to complete each set of questions are written on the top of each set.

3. It is very important that you return the booklets to us, whether you finish the study or not.

4. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

5. After completing this booklet, please return it to your nurse or physician or mail it back in the provided envelope.

Thank you for taking the time to help us.

PATIENT INFORMATION SHEET
Patient Completed Booklet D
(Every 3 months after the first year of treatment)

You have been given a booklet to complete for this study. This booklet contains some questions about your 'quality-of-life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. After the first year of your study treatment, you are being asked to complete this questionnaire booklet every 3 months (month 15, month 18, month 21, etc.). It contains the following questionnaires:

    - FACT-L Questionnaire
    - PRO-CTCAE and Urinary Hesitancy Question
    - Bowel Function Diary

2. Directions on how to complete each set of questions are written on the top of each set.

3. It is very important that you return the booklets to us, whether you finish the study or not.

4. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

5. After completing this booklet, please return it to your nurse or physician.

Thank you for taking the time to help us.

PATIENT INFORMATION SHEET
Patient Completed Booklet E
(Every 3 months after the first year of treatment)

You have been given a booklet to complete for this study. This booklet contains some questions about your 'quality-of-life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. After the first year of your study treatment, you are being asked to take this booklet home and complete it every week. You should return the booklet when you return to the clinic every 3 months (month 15, month 18, month 21, etc.) after the first year of study treatment. It contains the following questionnaire:

    - Pain and Pain Medication Diary

2. Directions on how to complete each set of questions are written on the top of each set.

3. It is very important that you return the booklets to us, whether you finish the study or not.

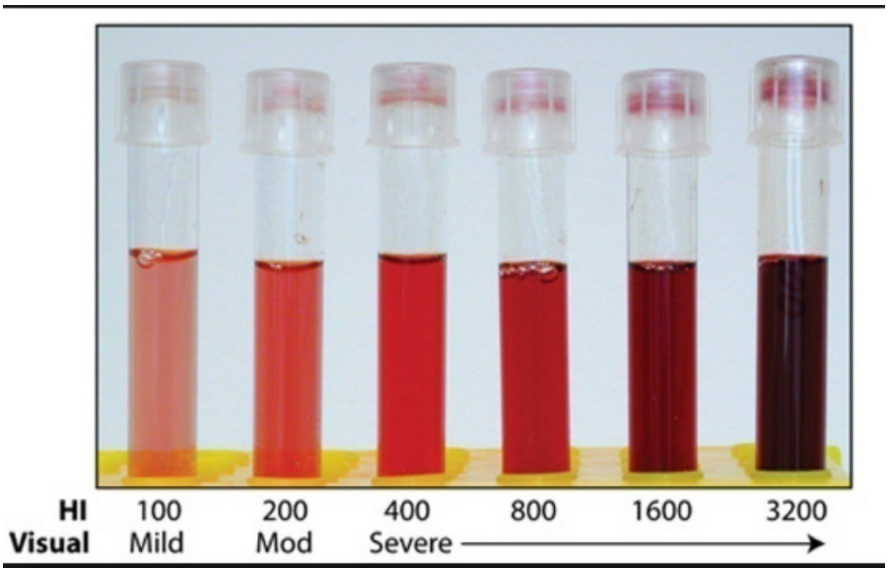
4. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

5. After completing this booklet, please return it to your nurse or physician or mail it back in the provided envelope.

Thank you for taking the time to help us.

APPENDIX VIII: HEMOLYZED PLASMA SAMPLES

Please note that hemolyzed plasma samples are NOT acceptable. Please re-draw if the samples are hemolyzed. Below is a picture demonstrating different levels of hemolysis in plasma. Please be aware that even mild hemolysis is not acceptable for this study plasma submission.



APPENDIX IX: NALOXEGOL WALLET CARD

[Note to investigators: This convenient wallet-sized information card is to be completed and then provided for the patient to clip out and retain at all times.]

INFORMATION ON POSSIBLE DRUG INTERACTIONS	
You are enrolled on a clinical trial of naloxegol (Movantik®). This clinical trial is sponsored by the National Cancer institute (NCI). Certain drugs may change the levels of liver enzymes such as CYP3A4 which process or break down naloxegol in the body. In addition, naloxegol may change levels of CYP3A4 and this may change how other medications are broken down. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	➢ Tell all of your prescribers (doctors, physician assistants, nurse practitioners or pharmacists) that you are taking part in a clinical trial. ➢ Before you enroll onto this clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are strong inducers or moderate/strong inhibitors of CYP3A4 ➢ Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/table.aspx for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is and can be contacted at