



**Memorial Sloan-Kettering Cancer Center  
IRB Protocol**

**IRB#: 05-025A(7)**

**Translational studies in analgesic pharmacology: analgesic synergy in clinical pain. A phase 2 study comparing a single dose of a 1:1 combination of methadone and morphine with morphine alone in patients with post-operative pain.**

THERAPEUTIC/DIAGNOSTIC PROTOCOL

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## 1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Translational studies in analgesic pharmacology: analgesic synergy in clinical pain. A phase 2 study comparing a single dose of a 1:1 combination of methadone and morphine with morphine alone in patients with post-operative pain.

The objective of this proposal is to compare the analgesic effects of a combination of morphine and methadone with morphine alone to determine synergistic activity of mu opioid analgesics in humans.

This is a randomized, double blind, parallel arm study (See Appendix 1).

We will administer a single dose of 1 mg of IV methadone plus 1 mg of morphine or 2 mg of IV morphine to patients one day after retroperitoneal lymph node dissection. We are planning for 70 patients to complete the study, 35 in each group.

All patients will receive Patient Controlled Analgesia (PCA) with IV morphine. The total amount of opioid available to patients will be equivalent to the standard amounts used after retroperitoneal lymph node dissection. Informed consent will be obtained from all patients pre-operatively. The PCA settings will start after the surgery at 1 mg/hour continuous infusion and 1mg every 10 minutes as needed. Clinician activated boluses (CAB) of morphine 5 mg IV will be available to the patient. The day after the surgery, the PCA will be stopped for the period of the study and we will ask the patient to request pain medication as soon as he feels at least moderate pain. During the period of the trial the physician will have no other clinical or other responsibilities. A physician will be available to monitor the time to the patient's request for pain medications, assess pain intensity and administer the drugs to replace the PCA promptly upon the patient's request. No more than 2 patients per the doctor per floor will be enrolled on the same day. When the patient requests pain medication, baseline pain intensity will be assessed and open label 2 mg of morphine administered. After administration of morphine the patient's pain relief, pain intensity, and side effects reported by the patient will be assessed every 10 minutes, and/or at the time the patient requests analgesia medication. In addition, respiratory rate will be recorded during these intervals. Immediately upon the second request for analgesia, the study drug in a double blind fashion (1 mg of IV methadone plus 1 mg of morphine or 2 mg of IV morphine), will be administered by the doctor. After administration of the study drug, pain relief, pain intensity, side effects reported by the patient and respiratory rate will be assessed every 10 minutes, and/or at the time the patient requests analgesia medication. Upon the third request for analgesia medication the study is completed, and the PCA will be restarted at the pre-study dose. We will also collect information about the total dose of morphine received while on IV PCA, the dose of morphine received during the last hour before stopping the PCA, and the time from stopping PCA to first request for analgesic medication.



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Morphine 2 mg intravenously will be administered upon the first request for an analgesic medication. Upon the second request, depending on the randomization, the patient will receive morphine 2 mg intravenously or a combination of morphine 1 mg and methadone 1 mg intravenously. There will be no dose escalation.

	<b>Upon the 1<sup>st</sup> Request for Analgesic Medication</b>	<b>Upon the 2<sup>nd</sup> Request for Analgesic Medication</b>
<b>Randomized to Group 1</b>	morphine 2 mg	morphine 2 mg
<b>Randomized to Group 2</b>	morphine 2 mg	morphine 1 mg and methadone 1 mg

**2.0 OBJECTIVES AND SCIENTIFIC AIMS**

- The objective of this study is to compare the analgesic effects of a combination of morphine and methadone with morphine alone to determine synergistic activity of mu opioid analgesics in humans.

**3.0 BACKGROUND AND RATIONALE**

Much is known about basic mechanisms of nociception and analgesia in animal models of experimental pain (1). Very few of these basic mechanisms, however, have been confirmed in humans suffering clinical pain (2). A better mechanistic classification of clinical pain syndromes offers the possibility of improved analgesic therapies and more rational drug development strategies (3,4).

Biochemical and functional characterizations of mu receptor subtypes have been accomplished in the laboratory, but the specific pharmacological profiles of mu opioid receptor subtypes have not been confirmed in clinical pain studies. For example, animal models reveal incomplete cross-tolerance among many mu opioids (5-9). In the treatment of cancer pain, clinicians commonly switch a patient who is highly tolerant to one mu selective opioid to another mu selective opioid in a process termed “opioid rotation” (10-11). Switching the patient to a different opioid often restores analgesia at a lower dose. This incomplete cross-tolerance suggests that drugs previously classed as “mu selective” may actually be acting via different mu receptor subtypes. At our institution, pain specialists sometimes add methadone to the regimen of patients on high doses of other opioids in an attempt to forego the need for a new increase in opioid dose. These clinical attempts to take advantage of the incomplete cross tolerance and possible synergy among different opioids have not been studied, and their efficacy is therefore unknown.



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We have obtained experimental data that demonstrate a profound analgesic synergy between morphine and methadone when co-administered systemically in mice [see *data*] (12).

If this type of synergy can be demonstrated in clinical pain, it will be a relatively unique example of translating concepts of fundamental aspects of opioid actions seen in the laboratory to the clinical area, and provide a basis for offering new and scientifically-based analgesic regimens. This may provide better pain relief with less opioid related side effects in clinical practice.

While studying the potency of methadone in single dose studies, its analgesic potency was found to be equivalent to the potency of morphine when the drugs were administered parenterally (13).

A double-blinded investigation was performed to assess pain scores and opioid requirements in the first 24 hours post-operatively after the same doses of morphine and methadone (0.3 mg/kg) was administered intra-operatively parenterally as a single dose. No difference in the amount of analgesic requirements post-operatively or the visual analogue scale pain score was observed between the group that received morphine and the group that received methadone (14).

In another double-blind study, morphine and methadone efficacy was examined in a post-operative pain control model. Patients in each group received a 20-mg dose of the opioid (morphine or methadone) intra-operatively. Rescue doses of the same opioid were available. There was no significant difference in the amount of supplementary opioid requirements between the two groups in the immediate post-operative period (about 8 hours) (15).

The third double-blind randomized trial compared post-operative analgesia after peri-operative loading doses of methadone and morphine. Methadone or morphine, 0.25 mg/kg, was given intravenously at induction of anesthesia and rescues were administered in the recovery room. The mean analgesic doses of morphine and methadone were similar (0.43 mg/kg and 0.45 mg/kg, respectively), with no significant difference in pain control or opioid requirements between the two groups in the post-operative period (about 12 hours). After 12 hours, the group receiving repeated administration of methadone had lower pain scores and less supplementary opioid requirement (16).

These studies support the equianalgesic effect of morphine and methadone when administered as single doses parenterally in the post-operative pain model in humans. We conclude that to evaluate synergy, we need to conduct a single dose study to avoid the confounding effects of methadone accumulation.



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**Pre-clinical data:**

The proposed clinical study is based on the following experimental studies.

*Methods:*

In these studies, analgesia was measured in mice 30 min post-injection (unless otherwise stated) using the radiant heat tail-flick assay (12). Baseline latencies ranged between 2.0 and 3.2 sec. A maximal cutoff latency of 10 sec was set to minimize tissue damage. Analgesia was assessed quantitatively as a doubling or greater of the baseline latency for each mouse. Drugs were administered systemically via subcutaneous injections. Groups of mice were compared using the Fisher Exact Test. ED50 values and 95% confidence limits were calculated by the Litchfield-Wilcoxon method.

Synergy was evaluated using isobolographic analysis. Significance was defined as the lack of overlap of 95% CL for the predicted and observed analgesia.

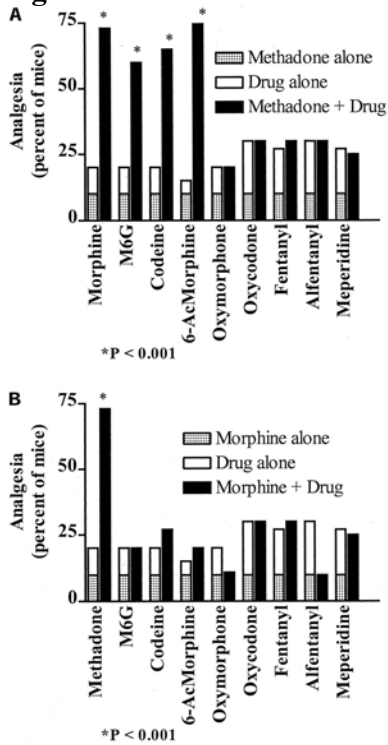
To examine the gastrointestinal transit immediately after subcutaneous (s.c.) injection, mice received a per os (p.o.) charcoal meal (10% charcoal with 2.5% gum tragacanth, w/v). Thirty minutes after the charcoal meal, the animals were sacrificed by cervical dislocation and the distance the meal traveled was measured.

*Results:*

The analgesia provided by the combination of morphine and L-methadone (73%) is significantly greater than the sum of their independent actions (20%),  $P < .001$ . The interaction of the morphine metabolite M6G with L-methadone (60%) is three times greater than the additive effect of the two drugs (20%;  $P < .001$ ) (Fig. 1A and 1B).



Figures 1A and 1B.

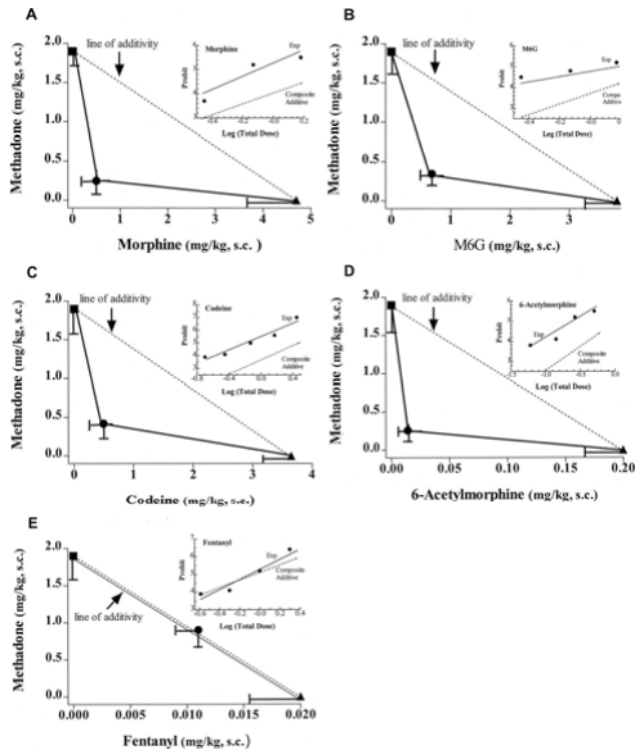


The interactions of oxymorphone, oxycodone, fentanyl, alfentanil, meperidine and [Dmt1]-DALDA with L-methadone were shown to be additive and not synergistic (Fig. 1A). The same compounds were also co-administered with morphine, but no statistically significant synergistic interactions were found (Fig. 1B).

The ED<sub>50</sub> values of morphine and L-methadone administered individually were 3.8 mg/kg (2.6, 5.4) and 1.9 mg/kg (1.4, 2.4), respectively. However, when co-administered, the ED<sub>50</sub> of the morphine/L-methadone combination is 0.52/0.26 mg/kg (0.35, 0.8; 0.17, 0.4), 3.5 times less than their ED<sub>50</sub> values when administered individually. Isobolographic analysis of this interaction indicates synergistic interactions between morphine and L-methadone; the ED<sub>50</sub> of the combination of drugs falls below the line of additivity of the two individual ED<sub>50</sub> values (Fig. 2A).



Figure 2.

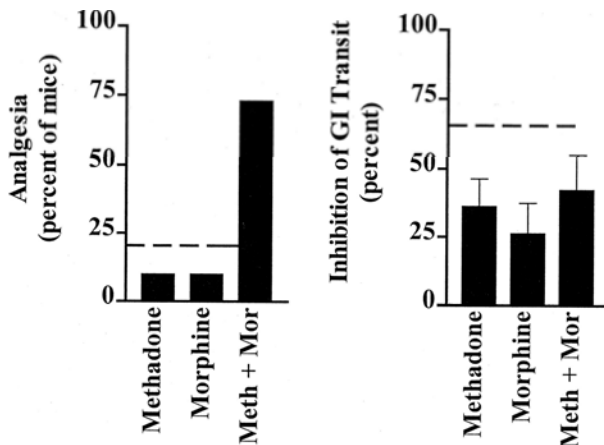


As an example of isobolographic analysis of a drug combination where synergy is not present, fentanyl and L-methadone are shown (Fig. 2E). Administered individually, fentanyl has an ED<sub>50</sub> value of 0.25 mg/kg (0.013, 0.03). When administered with L-methadone, the ED<sub>50</sub> value is 0.011/0.9 mg/kg (0.0058, 0.015; 0.015, 1.2) When plotted on the isobole, this ED<sub>50</sub> value falls along the line of additivity and is therefore not considered synergistic. Fentanyl and alfentanil were given twenty minutes post L-methadone injection (ten minutes prior to testing) in order for the peak effects to coincide.

Synergy seen between L-methadone and morphine was restricted to analgesia and did not extend to other mu opioid receptor actions, such as gastrointestinal transit.



Figures 3A and 3B.



Morphine decreased gastrointestinal transit relative to saline treated animals ( $28.1 \pm 1.5$  cm) by 26% ( $20.7 \pm 1.9$  cm) at the 0.5 mg/kg dose. Gastrointestinal transit was reduced by 36% ( $18 \pm 1.9$  cm) in the 0.25 mg/kg L-methadone treated animals. When we administered the combination of morphine and L-methadone (0.5 and 0.25 mg/kg, respectively), transit was inhibited by 42% ( $16.2 \pm 1.9$  cm). The expected additive effect of the combination of morphine and L-methadone would be an inhibition of 62.5%. Morphine and L-methadone, when co-administered in the gastrointestinal transit assay did not therefore exhibit a synergistic side effect (Fig. 3B). This is in contrast, therefore, to the effect seen with the same doses of morphine and L-methadone when co-administered in the tail-flick assay, where a profound analgesic synergy is observed (Fig. 3A). Both analgesia and gastrointestinal transit are mu receptor actions and are readily reversed by naloxone.

#### Conclusion:

These animal experiments demonstrate synergistic analgesic effects between some mu opioid agonists such as morphine and methadone, but not others such as methadone and fentanyl. The finding of enhanced analgesia without enhanced bowel dysmotility also demonstrates an interesting dissociation of mu opioid actions. Furthermore, the lack of synergy in inhibition of gastrointestinal transit suggests that co-administration of morphine and methadone to patients will result in increased analgesia without worsening constipation and, therefore, may constitute a useful strategy in the treatment of pain.

## 4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

### 4.1 Design

This is a randomized, double blind, parallel arm study. We will administer a single dose of 1 mg of IV methadone plus 1 mg of morphine or 2 mg of IV morphine to patients one day after surgery (See Appendix 1).



## 4.2 Intervention

All patients will receive Patient Controlled Analgesia (PCA) with IV morphine as per routine post-operative analgesic care. The total amount of morphine available to patients will be equivalent to the standard amounts used after surgery. Informed consent will be obtained from all patients pre-operatively. The PCA settings will start in the recovery room at 1 mg/hour continuous infusion and 1mg every 10 minutes as needed, clinician activated boluses will be available, and the PCA will be titrated to pain control as needed.

The day after the surgery, the PCA will be stopped temporarily, and we will ask the patient to request pain medication as soon as he feels at least moderate pain (See Appendix 1). If two hours pass before a first request for pain medication is made, the patient will be removed from the protocol. During the period of the trial the doctor will have no other clinical or other responsibilities. A doctor will be available to monitor the time to the patients' request for pain medications, assess pain intensity and administer the drugs to replace the PCA promptly upon the patient's request. No more than 2 patients per doctor per floor will be enrolled on the same day.

Upon the first request for analgesia, immediately before administration of morphine 2 mg and every 10 minutes after administration of morphine 2 mg, we will record the patient's pain relief, pain intensity, respiratory rate, and side effects as reported by the patient. If four hours pass before a second request for pain medication is made, the patient will be removed from the protocol.

Upon the second request for analgesia, immediately before administration of the blinded study drug (1 mg of IV methadone plus 1 mg of morphine or 2 mg of IV morphine), every 10 minutes thereafter, and at the time of the third request for analgesia, we will record the patient's pain relief, pain intensity, respiratory rate, and side effects as reported by the patient.

Upon a third request for analgesia, the study is completed and the PCA will be restarted at the pre-study dose. If four hours pass before a third request for pain medication is made, the patient will be removed from the protocol.

## 5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Morphine, a phenanthrene derivative, is the prototype opioid agonist. All other opiates are compared to morphine in determining their relative analgesic potency. Because of its widespread availability, it is the drug of choice for the treatment of post-operative pain and severe pain associated with cancer (17). There is no ceiling to its analgesic effect, although side effects, particularly sedation, respiratory depression and confusion may intervene before optimal analgesia is achieved (18, 19). It is metabolized in the liver, where it undergoes glucuronidation at the 3 and 6 positions. In single dose studies it is equipotent to methadone (20). The duration of analgesia is 3-4 hours. Because of the low dose used, we do not expect



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significant side effects in patients who have been already receiving morphine for over 12 hours.

Methadone, the 50/50 racemic combination of d-methadone and l-methadone, has been in widespread use for decades and has been studied extensively. There is no evidence of organ toxicity from chronic opioid use, including chronic methadone use (21). The main concern when using methadone for the treatment of pain is its long and unpredictable half-life which, with chronic administration, is associated with the risk of delayed opioid toxicity with side effects such as sedation, confusion and respiratory depression. For this reason methadone is generally viewed as a second line opioid, generally used after other opioids with a more predictable dose-response have been tried. This is a single dose study and therefore drug accumulation will not occur. Because of the low dose used, we do not expect toxic effects or significant side effects in patients who would be receiving morphine for over 12 hours by the time the study begins.

Preservative-free methadone and morphine combination (1 mg morphine+1 mg methadone) and parenteral morphine (2 mg of morphine IV) will be prepared, vialled and blinded by the MSKCC pharmacy. The methadone injection will be provided in single use vials containing 1 mg/ml, 0.5 ml, or 1 mg/ml, 2 ml. The morphine injection will be provided in vials containing 5 mg/ml, 1ml. Morphine and methadone are compatible for 7 days. Drugs will be dispensed by the pharmacy to the clinical investigator in a blinded fashion on the day of the study.

## **6.0 CRITERIA FOR SUBJECT ELIGIBILITY**

Planned retroperitoneal lymph node dissection usually requiring post-operative analgesia with PCA at 1 mg continuous infusion and 1 mg every 10 minutes as needed (See Appendix 2).

### **6.1 Subject Inclusion Criteria**

- Retroperitoneal lymph node dissection
- Planned post-operative analgesia with PCA at 1 mg continuous infusion and 1 mg every 10 minutes
- 18 years of age or older
- English-speaking
- Give informed consent to participate in this study



## 6.2 Subject Exclusion Criteria

- Known hypersensitivity to methadone or morphine
- Patients with past or present history of substance abuse
- Patients with a history of methadone treatment
- Patients with a history of chronic pain requiring daily analgesic use for more than 3 months
- Patients treated with opioids within one month from the scheduled surgery
- Creatinine clearance less than 50 mg/kg (using Cockcroft-Gault Equation).
- Neurologic or psychiatric disease sufficient, in the doctor's opinion, to compromise data collection

## 7.0 RECRUITMENT PLAN

Patients will be recruited in the pre-operative period.

## 8.0 PRETREATMENT EVALUATION

Demographic (age, ethnicity) and clinical data, including weight, height, past medical and surgical history, past treatment with opioids, concurrent drug therapies, drug-related side effects, and serum creatinine clearance within one month of surgery will be collected (See Appendix 3). We will also collect the data on the total dose of morphine received while on IV PCA, dose of morphine received during the last hour before stopping the PCA, and the time from stopping the PCA to first request for analgesic medication (See Appendix 4).

## 9.0 TREATMENT/INTERVENTION PLAN

We will administer a single dose of 1 mg of methadone with 1 mg IV of morphine or 2 mg of IV morphine alone to patients the day following surgery.

Following surgery, all patients will receive Patient Controlled Analgesia (PCA) with IV morphine. As per post-operative standard care, the PCA settings will start at 1 mg/hour



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continuous infusion and 1mg every 10 minutes as needed and titrated up as needed. CABs as needed will be available (See Appendix 1).

The day after the surgery the PCA will be stopped for the period of the study. We will ask the patient to request pain medication as soon as he feels moderate pain. The doctor will be present to monitor the time of the patient's request, assess pain intensity and administer drugs to replace the PCA promptly upon the patient's request. If two hours pass before a first request for pain medication is made, the patient will be removed from the protocol. Not more than two patients per doctor per floor will be enrolled on the same day. During the period of the trial, the doctor will have no clinical or other responsibilities.

1. When the patient requests pain medication, baseline pain intensity will be assessed and open label 2 mg of morphine IV administered. After administration of morphine, the patient's pain relief, pain intensity, respiratory rate, and side effects reported by the patient will be assessed every 10 minutes, and at the time of the second request for analgesia medication. If four hours pass before a second request for pain medication is made, the patient will be removed from the protocol.

2. Immediately upon a second request for analgesia, the study drug in a double blind fashion (1 mg of methadone IV plus 1 mg of morphine IV or 2 mg of morphine IV), will be administered by the doctor. After administration of the study drug, the patient's pain relief, pain intensity, respiratory rate, and side effects reported by the patient will be assessed every 10 minutes, and at the time of the third request for analgesia medication.

3. Upon a third request for analgesia medication or after four hours if no medication is requested, the study is completed and the PCA will be restarted at the pre-study dose. If four hours pass before a third request for pain medication is made, the patient will be removed from the protocol.

The total amount of opioid available to patients will be equivalent to the standard amounts used after retroperitoneal lymph node dissection.

## **10.0 EVALUATION DURING TREATMENT/INTERVENTION**

Immediately after the first request for the analgesia, before administration of the open label morphine 2 mg IV, every 10 minutes thereafter and at the time of the second request for the analgesia, we will record (See Appendix 4):



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- Pain relief scores on a 0-100% scale
- Pain intensity scores on a 0-10, 11 point, verbal scale
- Respiratory rate
- Side effects from the pain medication and their severity rated by the patient on a 0-3 scale (none, mild, moderate, severe)
- Time to the second request for the pain medication
- Global assessment. The patients will be asked: "How effective was the medication in relieving your pain?" The patient will choose among: 1) not effective 2) slightly effective 3) moderately effective 4) very effective 5) extremely effective.

Immediately before administration of the study drug, i.e. morphine 2 mg IV or morphine 1 mg with methadone 1 mg IV, every 10 minutes and at the time of the third request for analgesia, we will record (See Appendix 5):

- Pain relief scores on a 0-100% scale
- Pain intensity scores on a 0-10, 11 point, verbal scale
- Respiratory rate
- Side effects from the pain medication and their severity rated by the patient on a 0-3 scale (none, mild, moderate, severe)
- Global assessment. The patients will be asked: "How effective was the medication in relieving your pain?" The patient will choose among: 1) not effective 2) slightly effective 3) moderately effective 4) very effective 5) extremely effective.
- Time to the third request for the pain medication (upon which the study is completed)

## **11.0 TOXICITIES/SIDE EFFECTS**

Methadone has been in widespread use for decades and has been studied extensively. The most frequently observed side effects include sedation, nausea, vomiting, constipation, confusion and hallucinations, which are more pronounced in ambulatory patients and less common at lower doses. Methadone accumulation is not a concern in the current study because of the single dose design. Methadone-related side effects are easily reversed by naloxone.



Morphine is the standard opioid used for post-operative care. Subjects will receive a dose of 2 mg morphine intravenously, immediately when they request the analgesia medication. This dose may be slightly lower or higher than the dose of morphine received via continuous infusion previously. This may result in temporary improvement or worsening of pain control. The most serious side effect is respiratory depression, particularly with rapid administration. Low doses of intravenous morphine have little effect on cardio-vascular stability. High dose morphine may cause sympathetic over activity, dysphoria and convulsions. Nausea, vomiting, constipation, headache, anxiety, pruritus and urinary retention may be seen at lower doses and easily reversed by naloxone.

Given the relatively small amount of opioid used in the study drug (morphine 1 mg plus methadone 1 mg), we do not expect any side effects. However, due to the potential for synergism and, therefore, potentiation of the effect, we will closely monitor the patient for the presence of side effects (see Section 10, Evaluation During Treatment). NCI Common Toxicity Criteria 3.0 will be used to categorize and grade toxicity. Toxicities of grade 2 or less will be treated symptomatically. For patients with grade 3 or 4 toxicities, morphine and methadone will be stopped and an appropriate alternative analgesic regimen will be started.

## 12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Primary endpoint will be the difference between the pain relief offered by a combination of 1 mg morphine with 1 mg methadone intravenously (IV) and 2 mg of IV morphine alone. The outcome measure will be pain relief evaluated as the area under the curve (AUC) (Houde). AUC is the area under the drug level-time curve made by plotting pain relief (0-100%) to the time to the next request for pain medication (see Appendix 6).

Time (t) for each AUC will include:

For area A:

- t<sub>0</sub>, time of the first request for the analgesia and open administration of 2 mg morphine;
- t<sub>2, 3, ..., n</sub>, time of assessments 10 minutes apart;
- t<sub>n</sub>, time of the second request for the analgesia and study drug administration.

For area B:

- t<sub>0</sub>, time of the second request for the analgesia and study drug administration;
- t<sub>2, 3, ..., n</sub>, time of assessments 10 minutes apart;
- t<sub>n</sub>, time of the third request for the analgesia and completion of the study.

Effectiveness of the study drug will be estimated by comparing it to the open label 2 mg morphine IV. Ratio of pain relief offered by a combination of 1 mg morphine and 1 mg methadone IV to the analgesia provided by open label 2 mg morphine IV will be compared to the ratio of pain relief offered by 2mg morphine given in the blind fashion to the open label 2 mg morphine IV (see Appendix 6).

Hypothesis: AUC B2/A ratio is higher than the AUC B1/A ratio.





### 13.0 CRITERIA FOR REMOVAL FROM STUDY

- Patients that develop complications after surgery resulting in: inability to use the PCA, inability to evaluate the patient or new pain beyond the post-surgical pain.
- Patients who require immediate post-operative opioid analgesia other than PCA morphine.
- Patients who require no analgesic medication 2 hours following the PCA being stopped.
- Patients who require no analgesic medication 4 hours following open label morphine 2 mg IV administration.
- Patients who require no analgesic medication 4 hours following the study drug (1 mg of methadone IV plus 1 mg of morphine IV or 2 mg of morphine IV).
- Patients that require new analgesic medications or analgesic adjuvants (including steroids) for the treatment of pain.

### 14.0 BIostatISTICS

The primary comparison will be the difference in pain relief recorded as the "area under the curve" (AUC) between the initial 2 mg morphine dose and the study drug. AUC will be estimated by plotting % of pain relief over the time (see Appendix 6).

Time (t) for each AUC will include:

For area A:

- t<sub>0</sub>, time of the first request for the analgesia and opened administration of 2 mg morphine;
- t<sub>2, 3, ...</sub>, time of assessments 10 minutes apart
- t<sub>n</sub>, time of the second request for analgesic medication and study drug administration.

For area B:

- t<sub>0</sub> time of the second request for analgesic medication and study drug administration;
- t<sub>2, 3, ...</sub>, time of assessments 10 minutes apart;
- t<sub>n</sub>, time of the third request for analgesic medication and completion of the study.

Pain relief at the time of the request for pain medication will be considered baseline and each patient will serve as his own control. Should the pain relief score at the time of the second pain medication administration be reported higher than the baseline, projected AUC will be used, extending it to the baseline.

AUC for 2 mg morphine (area B1) and AUC for a combination of 1 mg morphine and 1 mg methadone (area B2) will be compared to the AUC for open label 2 mg morphine (area A).



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If the true difference between mean ratio B/A for morphine plus methadone vs morphine alone is .68 times the within-group standard deviation, then with 35 patients completing the study per arm there would be an 80% chance of a significant comparison with a two-sided t-test at  $p < 0.05$ .

The main analysis will be the analysis of covariance, using baseline pain as a covariate, and analyze time-to-first-rescue (the time from stopping PCA to first request for analgesic medication), and changes in pain intensity as secondary outcomes. We will also collect the information about the total dose of morphine received while on IV PCA and the dose of morphine received during the last hour before stopping the PCA and the time from stopping PCA to first request for analgesic medication to stratify subjects during analysis.

We are planning to review the data after 10 cases and may need to adjust the dose of morphine as well as morphine and methadone accordingly, by doubling the dosage. With the change of the dose, a new patient accrual will be started. The data for the initial opioid dose will be analyzed separately.

## **15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES**

### **15.1 Research Participant Registration**

The following person(s) can obtain informed consent:

Andrew Faskowitz, DO  
Dana Tarcatu, MD  
Cristina Tamasdan, MD  
Roma Tickoo, MD  
Damian Martino, MD  
Natalie Moryl, MD  
Eugenie Obbens, MD  
Kirk Stevens, MD  
Khan Abdulquader, MD

Confirm in the electronic medical record that the patient has received the Notice of Privacy Practice. This must be obtained before the eligibility confirmation and obtaining of the research informed consent.

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain written informed consent, by following procedures defined in section entitled Informed Consent Procedures.



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All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am - 5:30pm at (646) 735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the informed consent form, the completed signature page of the Research Authorization and a completed Eligibility Checklist must be faxed to PPR.

During the registration process registering individuals will be required to answer specific eligibility questions and provide the following information:

Registering Individual	[Last, First Name]
Notice of Privacy Status	[Yes, No, N/A]
Research Authorization	[Date]
MSKCC IRB Protocol#	
Attending of Record (if applicable)	[Last, First Name]
Consenting Professional	[Last, First Name]
Informed Consent Date	
Participant's Full Name	[Last, First Name]
Participant MRN	

### **15.2 Randomization**

After meeting eligibility criteria, the patient will be assigned to the morphine/methadone combination arm or morphine alone arm randomly, using simple randomization. Randomization Codes will be generated by the Clinical Research Database (CRDB) in conjunction with the Department of Epidemiology and Biostatistics after signing the consent. Medications will be dispensed by the hospital pharmacy in a double-blind manner on the days of the study.

### **16.0 DATA MANAGEMENT ISSUES**

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.



## 16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and the extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period, and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

## 16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: <http://cancertrials.nci.nih.gov/researchers/dsm/index.html>. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: <http://mskweb2.mskcc.org/irb/index.htm>

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center’s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

## 17.0 PROTECTION OF HUMAN SUBJECTS

Given the relatively small amount of opioid used in the study drug (morphine 1 mg plus methadone 1 mg), we do not expect any side effects. However, due to the potential for synergism and, therefore, potentiation of the effect, we will closely monitor the patient for the



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presence of side effects (see Section 10, Evaluation During Treatment). NCI Common Toxicity Criteria will be used to categorize and grade toxicity. Toxicities of grade 2 or less will be treated symptomatically. For patients with grade 3 or 4 toxicities, morphine and methadone will be stopped and an appropriate alternative analgesic regimen will be started.

### **17.1 Privacy**

It is the responsibility of the Research Staff to ensure that protocol patients have received the Center's Notice of Privacy Practices. The doctors will obtain acknowledgment before the patient participates in this study.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Doctor and approved by the IRB and Privacy Board.

### **17.2 Serious Adverse Event (SAE) Reporting**

Serious adverse events (requiring immediate reporting as described in this section) include, but are not limited to the following:

- Any death which occurs while the patient is enrolled in the study including the follow-up period, or within 30 days of completing the study.
- Life threatening event
- Prolongation of an existing hospitalization
- Medically important event \*\*
- Disability/Incapacity (persistent or significant)

\*\*Medically important events that may not result in death, be life-threatening or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the experience may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

### **17.2 Serious Adverse Event (SAE) Reporting**

Any SAE must be reported to the IRB as soon as possible but no later than 5 calendar days. The IRB requires a Clinical Research Database (CRDB) AE report to be delivered



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to the Institutional SAE Manager (307 East 63<sup>rd</sup> Street, 1<sup>st</sup> Floor) containing the following information:

Fields populated from the CRDB:

- Subject's name
- Medical record number
- Disease/histology (if applicable)
- Protocol number

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

## **18.0 INFORMED CONSENT PROCEDURES**

All patients must provide written informed consent prior to registration and treatment. Those physicians authorized to obtain informed consent are listed on the title page.

### **18.1 Research Authorization**

Procedures for obtaining Research Authorization: Before any protocol-specific procedures are carried out, doctors and/or designated staff will fully explain the details of the protocol, study procedures, and the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must sign the Research Authorization component of the informed consent form. The Research Authorization requires a separate set of signatures from the patient. The original signed documents will become part of the patient's medical record, and each patient will receive a copy of the signed documents.



## 19.0 REFERENCE(S)

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## **20.0 APPENDICES**

- Appendix 1, Proposed Study Design Schema
- Appendix 2, Inclusion and Exclusion Criteria
- Appendix 3, Pretreatment Evaluation





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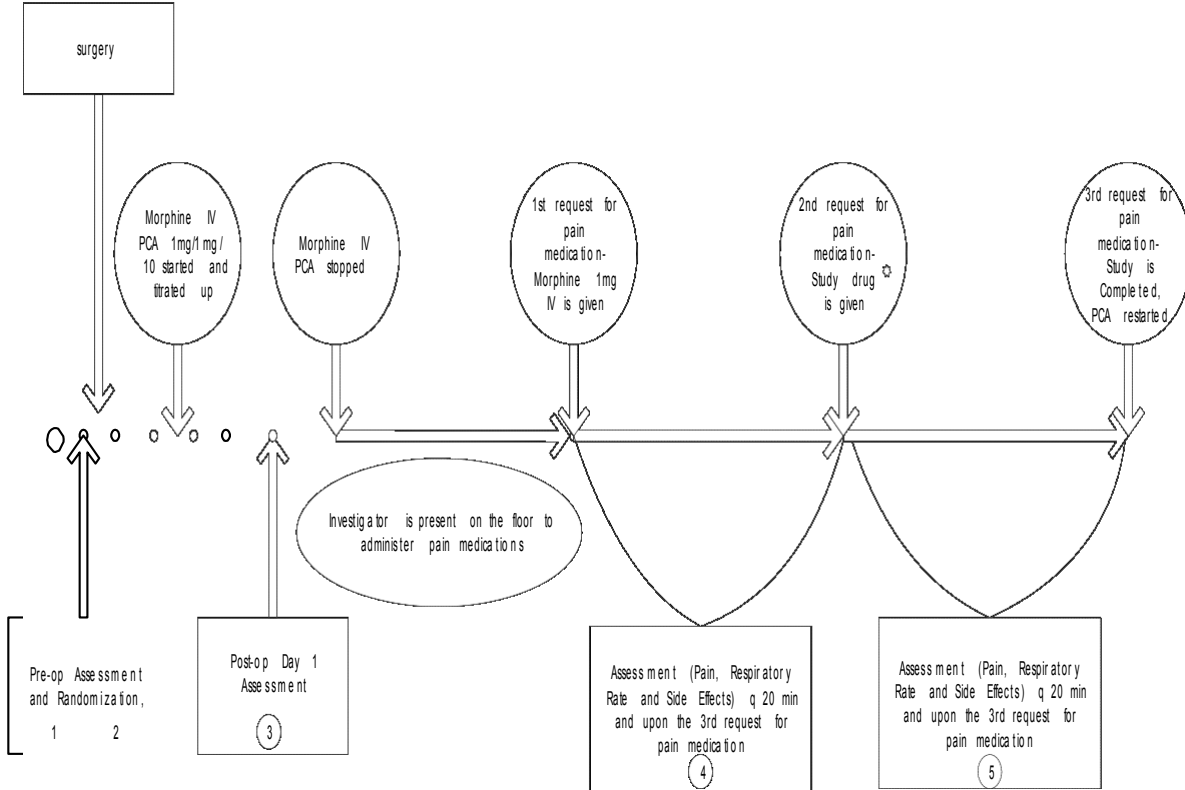
**IRB#: 05-025A(7)**

Appendix 4, Assessment Form 1 (After Morphine Administration)  
Appendix 5, Assessment Form 2 (After Study Drug Administration)



**SYNERGY: Appendix 1: Proposed Study Design Schema**

Proposed Study Design for Morphine-Methadone Synergy Study



\* Study drug: randomized to morphine 1 mg IV or morphine 0.5 mg and 0.5 mg IV (double blind)



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**SYNERGY: Appendix 2: Inclusion and Exclusion Criteria**

PRE-OP ASSESSMENT FOR RANDOMIZATION

Date: \_\_\_/\_\_\_/\_\_\_\_\_

<b>Inclusion criteria</b>	
Scheduled for retroperitoneal lymph node dissection	
18-y-o or older	
English-speaking	
Informed consent signed	
<b>Exclusion criteria</b>	
Anesthesiologist disapproves morphine continuous	
H/o hypersensitivity to morphine or methadone	
H/o substance abuse	
H/o methadone treatment	
H/o opioid treatment for chronic pain	
H/o opioids within 1 month	
Creatinine clearance less than 50%	
Neurological or psychiatric disorder interfering with data collection (doctors discretion)- with comments (use additional sheet if necessary)	
Comments	



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**SYNERGY: Appendix 3: Pre-treatment Evaluation**

Patient name:  
MRN:

<b>Age</b>	
<b>Ethnicity</b>	
<b>Weight</b>	
<b>Height</b>	
<b>Past Medical History</b>	
<b>Past Surgical History</b>	
<b>H/o Opioid Use</b>	
<b>Current Medications</b>	
<b>Drug-related side effects using NCI scale (sleepiness, confusion, hallucinations, nausea/vomiting, others), 0-3, 4-point scale</b>	



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**SYNERGY: Appendix 4: Assessment Form 1**

**1st Treatment (Morphine)**

Date: \_\_\_/\_\_\_/\_\_\_

Randomization #:

Patient name:  
MRN:

**BEFORE DISCONTINUATION OF PCA:**

- On a scale of 0-10, where 0 is no pain and 10 is the worst pain you can imagine, how would you rate the intensity of your pain right now?
- On a scale of 0-10, where 0 is no pain and 10 is the worst pain you can imagine, how would you rate the intensity of your pain when you try to move?

Baseline PCA Basal: \_\_\_ Rescue: \_\_\_ Lockout Interval: \_\_\_ PCA Stopped at: \_\_\_  
 Morphine PCA Started (Time):  
 Total Dose Received:  
 Dose Received in the Last 1 Hour: \_\_\_\_\_

**1<sup>ST</sup> TREATMENT (MORPHINE ALONE)**

Time of the First Request for Analgesic Medication: \_\_\_\_\_

Time from Discontinuation of IV PCA to the First Request for Analgesic Medication: \_\_\_\_\_



**At the time of the first request for analgesic medication**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
3. Respirations per minute: \_\_\_\_\_
4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 10 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
3. Respirations per minute: \_\_\_\_\_
4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 20 minutes after treatment started**

6. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
3. Respirations per minute: \_\_\_\_\_
4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 30 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
3. Respirations per minute: \_\_\_\_\_
4. Side effects reported by the patient: \_\_\_\_\_



**Follow-up 40 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 50 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 60 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 5. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 70 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 80 minutes after treatment started**



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- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 90 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 100 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 110 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 120 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_





**Follow-up 130 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 140 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 150 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 160 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 170 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?



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3. Respirations per minute: \_\_\_\_\_

4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 180 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?

2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?

3. Respirations per minute: \_\_\_\_\_

4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 190 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?

2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?

3. Respirations per minute: \_\_\_\_\_

4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 200 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?

2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?

3. Respirations per minute: \_\_\_\_\_

4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 210 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?

2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?

3. Respirations per minute: \_\_\_\_\_

4. Side effects reported by the patient: \_\_\_\_\_



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**Follow-up 220 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
3. Respirations per minute: \_\_\_\_\_
4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 230 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
3. Respirations per minute: \_\_\_\_\_
4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 240 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
3. Respirations per minute: \_\_\_\_\_
4. Side effects reported by the patient: \_\_\_\_\_

TIME OF THE SECOND REQUEST FOR ANALGESIC MEDICATION: \_\_\_\_\_

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**SYNERGY: Appendix 5: Assessment Form 2**

**2nd Treatment (Study Drug)**

Date: \_\_\_/\_\_\_/\_\_\_

Randomization #:

Patient name:  
MRN:

**2nd TREATMENT (STUDY DRUG)**

Time of the Second Request for Analgesic Medication: \_\_\_\_\_

Time from the First Request for Analgesic Medication: \_\_\_\_\_

**At the time of the second request for analgesic medication**

- On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- Respirations per minute: \_\_\_\_\_
- Side effects reported by the patient: \_\_\_\_\_

**Follow-up 10 minutes after treatment started**

- On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- Respirations per minute: \_\_\_\_\_
- Side effects reported by the patient: \_\_\_\_\_

**Follow-up 20 minutes after treatment started**

- On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?



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- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 30 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 40 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 50 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 60 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?



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3. Respirations per minute: \_\_\_\_\_

6. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 70 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?

2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?

3. Respirations per minute: \_\_\_\_\_

4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 80 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?

2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?

3. Respirations per minute: \_\_\_\_\_

4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 90 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?

2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?

3. Respirations per minute: \_\_\_\_\_

4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 100 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?

2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?

3. Respirations per minute: \_\_\_\_\_

4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 110 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete



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pain relief, how would you rate your pain relief right now?

2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?

3. Respirations per minute: \_\_\_\_\_

4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 120 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?

2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?

3. Respirations per minute: \_\_\_\_\_

4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 130 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?

2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?

3. Respirations per minute: \_\_\_\_\_

4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 140 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?

2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?

3. Respirations per minute: \_\_\_\_\_

4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 150 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?

2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?

3. Respirations per minute: \_\_\_\_\_

4. Side effects reported by the patient: \_\_\_\_\_



**Follow-up 160 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 170 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 5. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 180 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 190 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_





**Follow-up 200 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 210 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 220 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_

**Follow-up 230 minutes after treatment started**

- 1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
- 2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
- 3. Respirations per minute: \_\_\_\_\_
- 4. Side effects reported by the patient: \_\_\_\_\_



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**Follow-up 240 minutes after treatment started**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
  2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
  3. Respirations per minute: \_\_\_\_\_
  4. Side effects reported by the patient: \_\_\_\_\_
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**TIME OF THE THIRD REQUEST FOR ANALGESIC MEDICATION:** \_\_\_\_\_

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**At time of third request for analgesic medication**

1. On a scale of 0-100%, where 0 is no pain relief and 100% is complete pain relief, how would you rate your pain relief right now?
2. On a scale of 0-10, where 0 is no pain and 10 is the worse pain you can imagine, how would you rate the intensity of your pain right now?
3. Respirations per minute: \_\_\_\_\_
4. Side effects reported by the patient: \_\_\_\_\_



**SYNERGY: Appendix 6: Schema, Pain Relief as Measured as the Area Under the Curve**

**Pain Relief, 0-100%, Measured as the Area Under the Curve**

