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Randomized, single-blind, placebo-controlled study on the effect of postoperative administration of single dose ketamine after mastectomy on pain

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Amended:	[date]

This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for current Good Clinical Practice, and applicable regulatory requirements.

_____
Signature

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Date

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

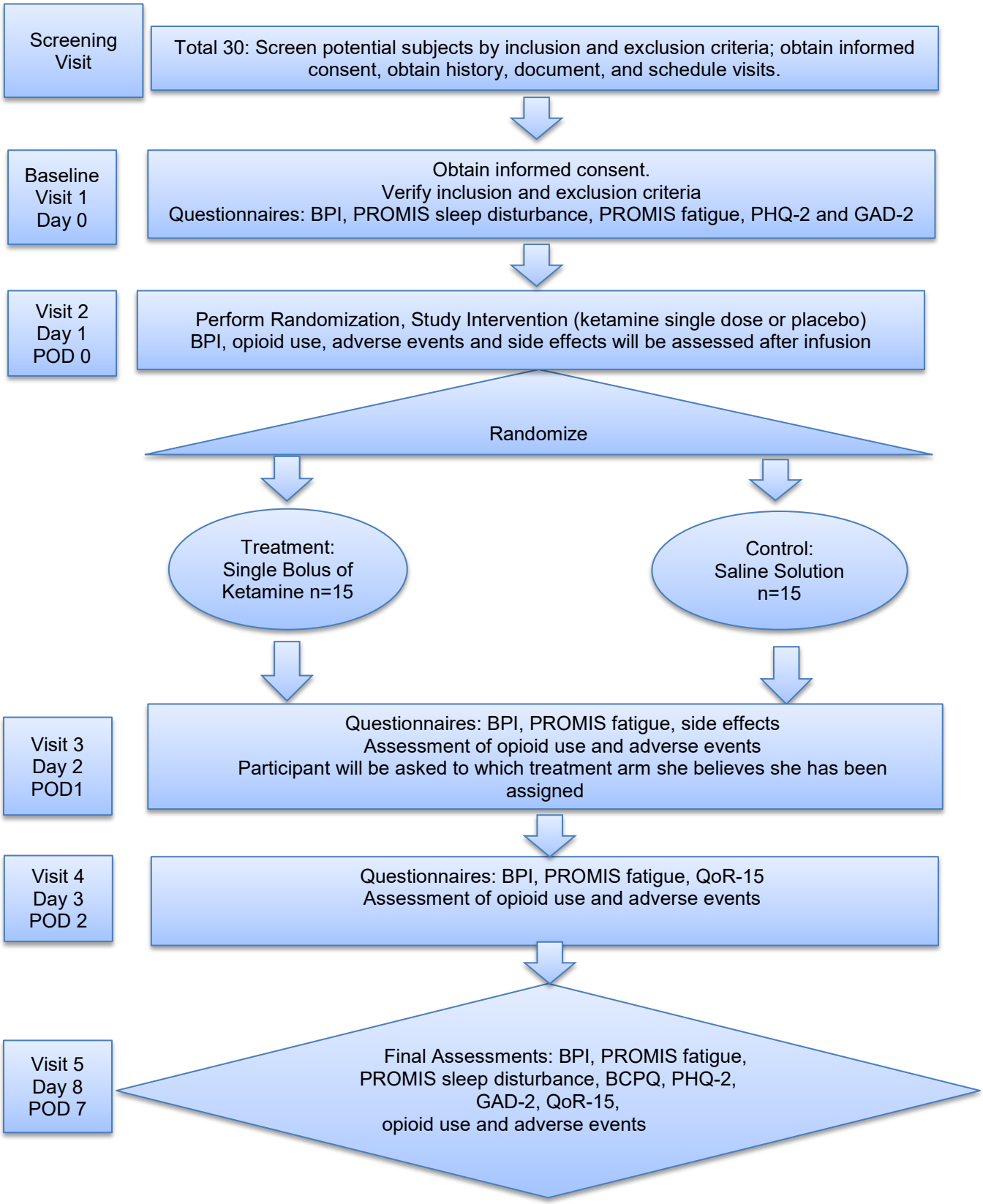
AE	Adverse Event/Adverse Experience
ASA	American Society of Anesthesiologists
BCPQ	Breast Cancer Pain Questionnaire
BMI	Body Mass Index
BPI	Brief Pain Inventory
CFR	Code of Federal Regulations
CIMU	Conflict of Interest Management Unit
CTO	Clinical Trials Office
CRF	Case Report Forms
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMC	Data and Safety Monitoring Committee
eCRF	Electronic Case Report Form
ED	Emergency Department
FDA	Food and Drug Administration
GAD-2	Generalized Anxiety Disorder-2
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
HSR	Human Subject Research
ICF	Informed Consent Form
IEC	Independent Ethics Committee
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IV	Intravenously
MOP	Manual of Procedures
MRN	Medical Record Number
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
NYU	New York University
NYULH	New York University Langone Health

OR	Operating Room
PACU	Post Anesthesia Care Unit
PCC	Perlmutter Cancer Center
PHI	Protected Health Information
PHQ-2	Patient Health Questionnaire-2
PI	Principal Investigator
POD	Postoperative Day
PROMIS	Patient-Reported Outcomes Measurement Information System
QC	Quality Control
QoR-15	Quality of Recovery
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical and Analytical Plan
SOP	Standard Operating Procedure
Sub-I	Sub-Investigator
TP	Treating Physician
UP	Unanticipated Problems
US	United States

Protocol Summary

Title	Randomized, single-blind, placebo-controlled study on the effect of postoperative administration of single dose ketamine after mastectomy on pain
Short Title	Effect of postoperative single dose of ketamine on pain after mastectomy
Brief Summary	This is a randomized, single blinded, placebo-controlled trial to study the effectiveness of a subanesthetic dose (0.6mg/kg) of ketamine versus placebo (saline) on postoperative pain on adult women undergoing mastectomy.
Objectives	To examine the effect of a subanesthetic dose (0.6mg/kg) of ketamine vs. saline control on postoperative pain in subjects who have undergone mastectomy.
Methodology	Randomized, single blinded, placebo-controlled trial
Study Duration	Approximately 6 months
Participant Duration	7 days for 5 visits
Enrollment Period	Up to six weeks before surgery
Duration of Study Product Administration	At least 30 minutes at one time point
Population	Adults women, aged 18 to 80 years, who will undergo mastectomy
Number of participants	30 total participants (15 in treatment group, 15 in control group)
Description of Study Product (Ketamine) Administration	Ketamine[(+/-)-2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone] is a white, crystalline powder or clear liquid. Ketamine at a dose of 0.6 mg/kg will be administered intravenously (IV) while the participant is recovering in the PACU. The study drug will be administered over at least 30 minutes at one time point and will be administered after subject has been deemed to be stable (hemodynamically stable, awake) by the study team on POD 0.
Reference Therapy	Saline. Saline is a prescription medicine used for fluid and electrolyte replenishment for intravenous administration. This is placebo drug in this study.
Key Procedures	IV administration of ketamine or saline Self-reported questionnaires Medical records review (opioid use and dosage assessments)
Statistical Analysis	Descriptive statistics will be used to summarize continuous variables. The normality of the distributions for continuous variables will be tested using Q-Q plots and Shapiro–Wilk tests. Differences between arms will be compared with two-sample t-test if outcome is normally distributed or with Wilcoxon's rank-sum test otherwise.

Schematic of Study Design



1 Introduction, Background Information and Scientific Rationale

Ketamine is an effective analgesic that can be administered pre-operatively, intra-operatively or postoperatively.[1–10] Although pre-operative administration of a single bolus dose of ketamine prior to incision has shown mixed results,[11–17] its use as a continuous infusion intra-operatively or postoperatively can reduce opioid consumption after surgery.[3–10,18–21]

An alternative to ketamine infusion is single dose ketamine. Recently, ketamine has emerged as a powerful antidepressant and anxiolytic with enduring effects that can last a week.[22–25] A single ketamine bolus (0.3-0.6mg/kg) can effectively activate the cortical top-down system for mood regulation[26-39]. Single bolus ketamine has also been used in the emergency department (ED) to provide long-lasting post-discharge pain relief and minimize opioid prescriptions[40-42]. In a recent pilot randomized controlled trial (RCT) of single-dose ketamine in the postoperative care unit (PACU), we found that ketamine reduced the affective component of pain for 7 days after bariatric surgery.[43] This study utilized a ketamine dose of 0.4 mg/kg based on ideal body weight. In addition, patients had relatively low levels of baseline anxiety and depression. To ensure robust treatment effects in our current study, we have increased the effective dose to 0.6 mg/kg, which is in the range of the therapeutic dose for mood disorders and pain in the ED [65-67]. We hypothesize that single bolus dose ketamine may potentially be more helpful in certain surgical populations with high baseline depression or anxiety.

Patients undergoing mastectomy for breast cancer have higher levels of depression and anxiety[62-64]. Postmastectomy pain is associated with more postoperative pain than laparoscopic bariatric surgeries[43]. We hypothesize that a single-dose (0.6 mg kg^{-1}) administration of ketamine after surgery may be able to relieve postoperative pain), improve mood and postoperative recovery, and decrease opioid requirements in patients undergoing mastectomy.

Thirty subjects undergoing mastectomy will be randomized to receive a single-bolus ketamine (0.6mg/kg) administered after surgery in the post-anesthesia care unit (PACU) or placebo (saline) control. All subjects will receive standard of care routine postoperative multimodal analgesia throughout hospital stay and after discharge. The Brief Pain Inventory (BPI) pain severity score at 24h and 48h post-surgery will serve as the primary endpoint. Secondary endpoints include responses on BPI (pain severity and interference subscales), opioid use, Quality of Recovery (QoR-15), National Institute of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) scales for fatigue and sleep, Patient Health Questionnaire-2 (PHQ-2), Generalized Anxiety Disorder-2 (GAD-2), and Breast Cancer Pain Questionnaire. Side effects will also be assessed.

1.1 Name and Description of the Study Drug and Placebo

Ketamine [(+/-)-2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone] is a white, crystalline powder or clear liquid. It is a schedule III substance and is classified as a dissociative anesthetic. Ketamine is available as a racemic mixture with the S-(+)- isomer being more potent than the R-(-)- isomer. It is commercially supplied as the hydrochloride salt in 0.5 mg/mL and 5 mg/mL ketamine base equivalents. Clinically, it is commonly used as an anesthetic induction agent for diagnostic and surgical procedures prior to the administration of general anesthetics. It is also used as a low dose infusion for analgesia.

Ketamine is a FDA-approved general anesthetic and analgesic agent that has been safely used clinically over the last 50 years. For general anesthesia, the induction dose ranges from 1mg/kg to 4.5 mg/kg. At sub anesthetic doses (< 1mg/kg), ketamine is a potent analgesic with a clinically effective half-life of 45 min. It is also a powerful antidepressant and anxiolytic, as a single dose (0.3-0.6mg/kg) which can produce up to 14 days of mood stabilization.

Saline is a prescription medicine used for fluid and electrolyte replenishment for intravenous administration.

1.1.1 *Clinical Data to Date*

1.2 Rationale

Ketamine is known to have analgesic effects as well as mood elevating effects. Ketamine is often administered as a continuous infusion. However, single doses have also been used and are simpler to implement. In previous studies for depression and pain, a dose range of 0.3-0.6 mg/kg was used. In our prior study of ketamine for bariatric surgery, we used 0.4 mg/kg for ideal body weight[43]. To further evaluate a single dose of ketamine for postoperative pain, we will use 0.6 mg/kg, which is in the range of the therapeutic dose for mood disorders and pain[65-67]. We hypothesize that postoperative use of ketamine can lead to improvement in pain indices including BPI, a decrease in opioid requirement, and mood improvements as measured by psychometric indices in subjects undergoing mastectomy surgery, a population with typically high baseline depression or anxiety.

1.3 Known Potential Risks

The risks for ketamine are well studied. In general, ketamine is a well-tolerated medication[1,4]. There may also be risks that are currently unforeseeable.

Psychological Effects: Decreased awareness of general environment, sedation, dream-like state, vivid dreams, feelings of invulnerability, increased distractibility, disorientation, and subjects may be generally uncommunicative. Additionally, hallucinations, impaired thought processes, delirium, out-of-body experiences, and changes in perception about body, surroundings, time and sounds can occur. Emergence reactions have occurred in approximately 12 percent of subjects[70].

Physiological: Anesthesia, cataplexy, immobility, tachycardia, increased blood pressure, nystagmus, hypersalivation, increased urinary output, profound insensitivity to pain, amnesia, slurred speech, and lack of coordination.

Cardiovascular*:* Cardiovascular side effects have included elevated blood pressure and heart rate following administration of ketamine alone. However, hypotension and bradycardia have been observed. Other arrhythmias such as ventricular tachycardia are rare.

Respiratory: Respiratory side effects have included stimulated respiration, although severe depression of respiration or apnea may occur following rapid intravenous administration of ketamine. Laryngospasms and other forms of airway obstruction have occurred during ketamine anesthesia. Additionally, hypersalivation or the increased production of salivary and tracheobronchial secretions may occur, which may be clinically significant during extubation or post-op airway protection.

Ocular: Ocular side effects have included diplopia, nystagmus, and a slight elevation in intraocular pressure.

Oral: Hypersalivation or increased salivary secretions can occur during ketamine administration.

Gastrointestinal: Gastrointestinal side effects have included anorexia, nausea, and vomiting. It is possible that severe nausea and vomiting may occur during the post-op period due to the dual effects of the recent general anesthetic and ketamine administration.

Musculoskeletal: Musculoskeletal side effects have included enhanced skeletal muscle tone manifested by tonic and conic movements sometimes resembling seizures.

Local: Local side effects have included pain and exanthema at the injection site.

Dermatologic: Dermatologic side effects have included transient erythema and/or morbilliform rash.

Psychiatric: Psychiatric side effects have included anxiety, euphoria, dysphoria, illusions, hallucinations, flashbacks, blunted affect, catatonia and psychotic episodes.

Neurologic: Impaired attention/memory/judgment, disorientation, delirium, diplopia, and blurred vision.

Urinary: Increased urinary output; rarely cystitis.

Duration of Effects: Onset of analgesic effect of ketamine is within 1-5 minutes if injected. The effects of ketamine generally last 30-45 minutes if injected as a single bolus. However, some residual symptoms such as nausea and vomiting may persist longer than general effects.

Drug Interactions: Benzodiazepines may decrease ketamine-associated emotional distress but does not decrease cognitive or behavioral effects of ketamine. Acute administration of diazepam increases the half-life of ketamine. Lamotrigine significantly decreases ketamine-induced perceptual abnormalities but increases the mood elevating effects. Haloperidol may decrease impairment by ketamine in executive control functions, but does not affect psychosis, perceptual changes, negative schizophrenic-like symptoms, or euphoria. Alfentanil is additive to ketamine in decreasing pain and increasing cognitive impairment. Physostigmine and 4-aminopyridine can antagonize some pharmacodynamic effects of ketamine.

Contraindications include increased intracranial pressure (ICP), glaucoma, or acute globe injury. Caution is suggested in patients with cardiovascular illness, porphyria, or thyroid disorder.

Side effects typically end 30 minutes after the termination of infusion. These risks will be mitigated using the strategies described in the protection against risks and dose adjustments sections. There are no expected side effects associated with the administration of saline.

There are no known side effects associated with completing the questionnaires. There may be some mild level of fatigue associated with answering the questions.

Confidentiality risks: The risk is privacy violation via the unexpected release of protected health information through health records or research data or the release of randomization information. As a result, this study involves the possibility of psychological and social risks related to breach of confidentiality.

1.3.1 Protection against Risks

Given that ketamine will be given in the recovery room, all participants will be monitored by the study care team and PACU physicians, if any of these effects mentioned above were to occur. For the risks of physiological effects and cardiovascular side effects, the single bolus ketamine dose will be given over at least a 30-minute period to minimize these effects from happening. For the risks of psychomimetic side effects, such side effects may be treated with reassurance.

The investigators have many layers of protection to minimize the risk of inadvertent release of protected health information. The methods for de-identification of data will mitigate this risk. We will take all necessary precautions to maintain complete confidentiality of data and prevent unauthorized access to the data. Data will only be collected from subjects who consent and whose physicians deem safe to proceed with data collection. Participants will be allowed to exit the study at any time. Participants who withdraw consent will be counseled that their withdrawal only affects uses and sharing of information after their written request to withdraw authorization has been received, and that their authorization may not be withdrawn for uses or disclosures that have previously made or need to be made to complete analyses or report data from the research. For the confidentiality of randomization, only the physician administering the study drug will know which group the subject(s) is/are in for the both experimental and control group.

All data and records generated during this study will be kept confidential in accordance with institutional policies and HIPAA on subject privacy. The study investigators will not use such data and records for any other purpose other than conducting the study. Privacy protection procedures are in place and good clinical practice guidelines will be followed throughout the study to minimize the risks associated with breach of confidentiality. This risk will be minimized by strict compliance with HIPAA procedures for securing PHI.

Information that could be used to identify the subject will only be shared with researchers who have approval of the IRB.

1.*4 Known Potential Benefits*

Perioperative ketamine improves pain and reduces opioid use in the acute postoperative period. Additionally, other benefits may include a reduction in depression and anxiety symptoms and improvements on long-term pain management and function. There is a potential benefit gained to study subjects for better postoperative analgesia and mood elevation as well as faster recovery from surgery. There is also a potential for longer term benefit on the affective component of pain from the mood elevating effects of ketamine. In addition, there is benefit in society for better understanding of the postoperative analgesic and mood elevating strategies, physical function, sleep quality, and opioid use requirements. It is possible some present subjects will not benefit but future patients may benefit from this study. The information obtained from this research may help others in the future.

2 Objectives and Purpose

Ketamine in the perioperative period is most frequently administered as an infusion. In our previous study of ketamine in bariatric surgery, we administered a single dose of 0.4 mg/kg in the recovery room and noted improvements in the affective component of pain.[43] In this study, we will examine a single dose of ketamine at 0.6 mg/kg in the recovery room in patients undergoing mastectomy to obtain a preliminary assessment of efficacy for pain. Mood, sleep quality, function and opioid requirements will also be measured.

2.1 Primary Objective

The primary objective is to examine the effect of a sub anesthetic dose of (0.6mg/kg) of ketamine vs. saline control on postoperative pain in subjects who have undergone mastectomy.

2.2 Secondary Objectives

The secondary objective is to examine the effects of a sub anesthetic dose of (0.6mg/kg) of ketamine vs. saline control on pain interference, mood, recovery (sleep quality and physical function), and opioid use in patients who have undergone mastectomy. Incidence of side effects will also be evaluated through the psycho-behavioral questionnaire.

3 Study Design and Endpoints

3.1 Description of Study Design

This is a randomized, single-blind, placebo-controlled, two-arm parallel, single-center study.

Thirty subjects (15 in each arm) will be accrued. Randomization lists will be sent only to the study physician administering study drug. Participant and assessor of outcome measures will be blinded. The surgeon, anesthesiologist, and the research team members conducting the follow up visits will not know which group the subjects are assigned to. The physician administrating the study will be aware of whether ketamine or placebo is administered. On the day of the mastectomy surgery, the subject will be randomly assigned to the control or the experimental group.

Adult women who will be undergoing mastectomy will be screened for eligibility to participate in the study. Prospective subjects will be recruited, screened and consented prior to surgery. Eligible subjects will be randomized to one of the two groups in a 1:1 ratio to receive either intravenously (IV) ketamine (0.6mg/kg) or matching equal dose of placebo. Only women will be recruited in this study, as mastectomies are primarily done in women. As men represent less than 1% of breast cancer cases and mastectomy may have a different psychosocial impact on them, we will only enroll women for this study[68]. There is no limitation as to racial and ethnic origin.

Participation in the study will not alter the subject's surgical or anesthetic care, post-anesthetic care, or standard of care on the floor. In the PACU, subjects, if deemed medically stable by the study physician, will receive equal dosage of 0.6mg/kg IV ketamine or saline placebo. All subjects will also receive standard post-anesthetic monitoring and care, as well as routine care after transfer out of the PACU. There is no restriction on the use of other analgesics throughout this study. Subjects are followed, and endpoints (see

below) are collected from subject reports as well as from medical charts (opioid use). During the study, subjects will fill out self-reported questionnaires assessing pain, mood (fatigue) and function (physical), side effects, and quality of postsurgical recovery including sleep quality.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

Brief Pain Inventory-short form (BPI) pain severity subscale will be used as the primary endpoint at 24h and 48h postoperatively.

3.2.2 Secondary Study Endpoints

For the secondary endpoint postoperative pain, function (physical), sleep quality, opioid use, quality of recovery, side effects and mood (fatigue) will be assessed.

1) *BPI* (both pain severity and interference) scores at baseline, 1+1, 2+2, and 7+2 days after surgery to assess pain. The BPI severity subscale will be administered post-infusion as well.
2) *Opioid use* will be assessed in the PACU and on postoperative day (POD) 0, 1+1, 2+2, and 7+2. The opioid use and dosage assessment will be assessed through medical records and subject reports.
3) *Patient-Reported Outcomes Measurement Information System (PROMIS) fatigue scale* was developed by the National Institute of Health (NIH) to measure fatigue, an important symptom in postoperative recovery. This scale will be assessed at baseline at POD 1+1, 2+2, and 7+2 days after surgery.
4) *Patient-Reported Outcomes Measurement Information System (PROMIS) sleep disturbance* assesses sleep in postoperative recovery and will be measured at baseline and 7+2 days post-surgery.
5) Patient Health Questionnaire-2 (PHQ-2) and Generalized Anxiety Disorder-2 (GAD-2) assess for symptoms of depression and anxiety and will be measured at baseline and POD 7+2.
6) *Breast Cancer Pain Questionnaire (BCPQ)* assesses pain location, frequency and severity as well as sensory disturbance after breast surgery. BCPQ will be completed at 7+2 days post-surgery.
7) Quality of Recovery (QoR-15) This scale will be assed at POD 2+2, and 7+2.
8) Side effects of study drug administration will be assessed after infusion on POD 0 and on POD 1+1 with a psycho-behavioral questionnaire.

4 Study Enrollment and Withdrawal

4.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Adult women, aged 18 to 80 years old, who will undergo mastectomy.
2. Willing to comply with all study procedures and be available for the duration of the study.
3. Will be scheduled for elective breast surgery for oncologic indication as follows: mastectomy +/- lymph node dissection, prophylactic mastectomy, unilateral or bilateral, with immediate reconstruction
4. No distant metastases.
5. Subject is American Society of Anesthesiologists (ASA) physical status 1, 2, or 3.
6. Subject is medically stable.

4.1.1 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this trial.

4.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Cognitive impairment (by history) or clinical signs of altered mental status such as confusion, amnesia, disorientation, fluctuating levels of alertness, etc. that may interference with adherence to study procedures and/or participant safety.
2. Past ketamine or phencyclidine misuse or abuse.
3. Schizophrenia or history of psychosis.
4. Known sensitivity or allergy to ketamine.
5. Liver or renal insufficiency.

6. History of uncontrolled hypertension, chest pain, cardiac arrythmia, stroke, head trauma, intracranial mass or hemorrhage or pressure, glaucoma, acute globe injury, uncontrolled thyroid disease, porphyria, or any other contraindication to ketamine. Use of lamotrigine, alfentanil, physostigmine, and 4-aminopyridine are contraindicated
7. Pregnancy or nursing women
8. BMI>35.
9. Currently participating in another pain interventional trial.
10. Unwillingness to give informed consent.
11. Non-English speaking patients as QoR-15 and BCPQ have not been validated in all other languages

4.2.1 Vulnerable Subjects

Vulnerable subject populations will not be included in the study.

4.3 Strategies for Recruitment and Consent

This study will utilize EPIC to identify prospective subjects.

The privacy of prospective subjects will be protected during the identification process. The research team consists of study surgeons, investigators, treating physicians and research coordinators—they will all have access to EPIC. Study staff members are experienced at consenting patients or prospective subjects for anesthesiology studies, and they include physicians as well as qualified designated team members. Prospective subjects who are eligible for the study will be recruited prior to their surgery date. Eligible patients or prospective subjects will be assessed for capacity to give informed consent by a study team member. Medical status/stability will be addressed by members of the research team. Eligible patients or prospective subjects will be invited to participate in the study. Data will be discarded at least 3 years after close out or 5 years after final reporting, whichever is longer, by deleting from the network.

Any recruitment information sent by email will utilize Send Safe email.

To first screen for eligible subjects, participating study surgeons, investigators, treating physician will review their operating and other schedules on EPIC to identify eligible patients or prospective subjects for study recruitment. Only patients who have agreed to be contacted for future research will be contacted. Research team members will also screen for eligible prospective subjects on all participating physicians' schedules on EPIC and will contact these prospective subjects on their behalf with permission of study surgeons, investigators, treating physician. The subjects' data will be screened to see if they match the study's eligibility criteria. The research team members will search EPIC as many times as needed until all 30 eligible subjects are recruited. Once eligible subjects are identified, recruitment can either be in-person or over the phone.

1) Recruited in-person
   A research team member will speak to the eligible subject in-person at NYU Langone Health Perlmutter Cancer Centers, outpatient facilities, and hospitals. The study surgeon may also talk to subjects about the study during their appointment and can refer subjects who are eligible. Surgeons may give potential participants the research subject letter and key information document to introduce the study. Once a subject has been referred, a study team member will call the subject through the "recruitment over the phone" strategies listed below. Should the potential subjects agree, the study team member will provide the subjects with information regarding the next steps for participation. The subject will be given the copy of the informed consent document and given sufficient time to read over the form, and ask all questions. Once all of her questions have been answered, the informed consent will be signed.

2) Recruitment over the phone
   a. The telephone script will be used to communicate the reason they are being contacted and subjects will be asked if they are interested in participating in this specific study. Research

team members will call prospective subjects or arrange a video conference session (WebEx only). The following methods will be implemented to obtain informed consent.

i. The prospective subject will be emailed a copy of the informed consent via SendSafe and will send back a signed copy of the informed consent form (the prospective subject may print, sign, and scan a physical copy or a signature can be captured electronically on the informed consent form) to a research team member via SendSafe after on-site discussion taking place between study personnel and prospective subject or an initial telephone call or video conference takes place between study personnel and the remote prospective subject.
ii. The prospective subject will be emailed a copy of the informed consent form via SendSafe after on-site discussion taking place between study personnel and prospective subject or an initial telephone call or video conference takes place between study personnel and the remote prospective subject and the research team member will obtain prospective subject signature in-person on the day of surgery. The prospective subject can print and sign a physical copy and return later in person.
iii. The subject will remotely receive a link to the informed consent form (after on-site discussion taking place between study personnel and prospective subject or an initial telephone call or video conference takes place between study personnel and the remote prospective subject), sign and return informed consent document through a REDCap link that will be sent via SendSafe e-mail. The REDCap link to the final and approved informed consent document and questionnaires will be IRB approved via a modification before being used.
iv. In cases of remote consent, before the patient or prospective subject signs the consent, a videoconference or call will be scheduled with the patient or prospective subject to review the informed consent. The study team member will then explain the consent to the prospective subject and ask if the prospective subject has any questions before the prospective subject electronically signs.

Once informed consent is given, the study team member will provide the prospective subjects with information regarding the next steps for participation. Consent may occur up to two months before surgery. Subjects will also be consented no sooner than 2 days before their surgery.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact research-contact-optout@nyumc.org or 1-855-777-7858.

The inclusion and exclusion criteria in this study should not have a negative effect on the enrollment of the desired populations. Treatment will take place at the NYU Langone Health Tisch/Kimmel Hospital or NYU Langone Brooklyn under the supervision of the PI. Prospective subjects will receive detailed information regarding this study; its investigational nature, required study procedures, alternative treatments, risks and potential benefits of the study. They will also receive the informed consent document to read. All questions are answered by the PI and qualified research personnel.

Recruitment and consenting will take place in a private area such as exam room (if in person) or remotely (phone call and video conference call) to protect the patient or prospective subject's privacy.

4.4 Registration Procedures

4.4.1 General Guidelines

Each patient or prospective subject must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient's standard of care. Enrollment in the study requires that all inclusion and exclusion criteria have been met.

4.5 Duration of Study Participation

For the participation in the study, the study will continue for 7 days or 1 week after surgery. There are 5 visits in total, each visit lasting less than 1 hour.

4.6 Total Number of Participants and Sites

Recruitment will take place at NYU Langone Health Perlmutter Cancer Centers, outpatient facilities, and hospitals. Recruitment will end when approximately 30 participants are accrued. It is expected that approximately 50 participants will be enrolled in order to produce 30 evaluable participants.

Target accrual for this study is 30 subjects over 6 months. The sites include NYU Langone Health Tisch/Kimmel Hospital or NYU Langone Hospital Brooklyn.

4.7 Participant Withdrawal or Termination

4.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request for any reason, and without repercussion. The investigator and sponsor have the right to discontinue a subject from study treatment or withdraw a subject from the study at any time. If a subject is discontinued from the study at the discretion of a PI or other delegated individual, the reason for discontinuation procedures will be noted in the subject's research record.
. An investigator may terminate participation in the study if, but are not limited to:

- Subject withdrawal of consent at any time.
- Disease progression.
- Intolerable toxicity.
- Any medical condition that the investigator or sponsor determines may jeopardize the subject's safety if the subject continues treatment with the study drug.
- The investigator or sponsor determines it is in the best interest of the subject.
- Failure of the subject to adhere to protocol procedure requirements.
- Study termination by sponsor.
- Any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) prior to surgery.

Criteria for discontinuing study intervention includes but not limited to:

- Allergic reaction thought to be related to study drug.
- Uncontrolled hypertension, hypotension, or arrhythmia thought to be related to study drug.
- Severe psychomimetic side effects.
- Medical events/logistical reasons not related to study therapy.

Study physician will be responsible for determining whether study interventions will be discontinued, based on his or her clinical judgement. In the case of cardiovascular side effects, if such side effects persist despite treatment based on PACU clinician's decisions, study drug may be discontinued. The reason for the dose discontinuation should be documented.

Psychomimetic side effects will be monitored by study and PACU physicians. Such side effects may be treated with reassurance. If participants continue to complain of anxiety or dysphoria or are agitated, pharmacologic agents (such as benzodiazepines) may be administered based on clinical judgement of PACU clinicians. If psychomimetic side effects are felt to be severe, with severe hallucinations, delusions, or agitation, study drug will be discontinued.
Additionally, in the event of any discontinuation of study intervention, with consent, participants will continue with the completion of remaining study visits.

4.7.2 Handling of Participant Withdrawals or Termination

Subjects, who choose to withdraw consent, can do so by notifying the treating physician, the Principal Investigator or research staff in writing or verbally. Any data remaining after formal withdrawal, will be destroyed/discarded per Institutional guidelines. Subject will be informed whether the data will be retained and analyzed up to the point of withdrawal. The study team will document the reason for discontinuation in the subjects' research record. Every effort will be made to undertake protocol-specified safety follow-up procedures to capture AEs, serious adverse events (SAEs), and unanticipated problems (UPs). If subjects withdraw or discontinue early replacement participants will be allowed.

4.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Demonstration of efficacy that would warrant stopping.
- Insufficient compliance to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

5 Study Agent/Procedural Intervention

5.1 Study Agent(s) and Control Description

Ketamine is an FDA-approved general anesthetic and analgesic agent that has been safely used clinically over the last 50 years. For general anesthesia, the intravenous induction doses range from 1 mg/kg to 4.5mg/kg. At subanesthetic doses (<1mg/km), ketamine is a potent analgesic with a clinically effective half-life of 45 min.[53-55] Off label it is also used as a powerful antidepressant and anxiolytic as a single dose (0.3-0.6mg/kg) which can produce up to 14 days of mood stabilization.[56-60]

This study is IND exempt as 21 CFR 312.2(b)(1) and 21 CFR 312.2(b)(5) as the study meets the all of the following criteria:

1. The drug product is lawfully marketed in the US.
2. The investigation is not intended to be reported to FDA as a well-controlled study in support of new indication and there is no intent to use it to support any significant change in the labeling of the drug.
3. In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
4. The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increase the risk (or decreases the acceptability of the risk) associated with the use of the drug product.
    a. The risks for ketamine are well studied. In general, ketamine is a well-tolerated medication[1,4]. In previous studies for depression and pain, a dose range of 0.3-0.6 mg/kg was used. In our prior study of ketamine for bariatric surgery, we used 0.4 mg/kg for ideal body weight[43]. To further evaluate a single dose of ketamine for postoperative pain, we will use 0.6 mg/kg, which is in the range of the therapeutic dose for mood disorders and pain[65-67].
5. The investigation is conducted in compliance with the requirements for review by an IRB and with the requirements for informed consent.
6. The investigation is conducted in compliance with 21 CFR 312.7 (no intention to promote or commercialize the drug product).

5.1.1 Acquisition

Study drug will be ordered and obtained from NYULH inpatient pharmacy.

5.1.2 Formulation, Appearance, Packaging, and Labeling

Ketamine is a nonbarbiturate general anesthetic chemically designated dl 2-(0-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride. It is formulated as a slightly acid (pH 3.5-5.5) sterile solution for intravenous or intramuscular injection. Ketamine is available from NYULH inpatient pharmacy in concentrations of 50 mg/ml.

5.1.3 Product Storage and Stability

The study drug should be stored between 20° to 25°C (68° to 77°F).

The control solution, 0.9% normal saline will be stored at temperatures between 20° 25°C (68° to 77°F).

5.1.4 Preparation

Study drug is obtained from NYULH inpatient pharmacy (212-263-5048). Study physician is not blinded. Ketamine will be diluted to 2-10 mg/ml in normal saline by study physician. 0.9% normal saline will be used as the control.

5.1.5 Dosing and Administration

Single bolus ketamine: For the single bolus dose arm, ketamine at a dose of 0.6 mg/kg will be administered while the participant is recovering in the PACU on the day of surgery. The study drug will be administered over at least 30 minutes at one time point and will be administered after subject has been deemed to be stable (hemodynamically stable, awake) by the study team on POD 0.

Control/Placebo: Participants randomized into this group will receive matching volume of saline infusion in the PACU over at least 30 minutes at one time point (no ketamine).

5.1.5.1 Route of Administration: The planned route of administration is intravenously for the ketamine study drug and placebo drug.

5.1.5.2 Tracking of Dose:

Drug protocol adherence will be recorded and verified through patient's electronic medical record.

5.1.5.3 Administration of Intervention

The intervention will be delivered in person at NYULH. The study physician will administer the study intervention via a pump to deliver 0.6 mg/kg ketamine or equal volume saline over at least 30 minutes.

5.1.5.4 Procedures for Training Interventionists and Monitoring Intervention Fidelity

Study drug will be administered by study physicians who are anesthesiologists or pain medicine specialists. Protocol and study procedures will be reviewed with study team members and study physicians.

5.1.5.5 Assessment of Subject Compliance with Study Intervention

Subject compliance with receiving the study drug will be recorded in subjects' records.

5.1.6 Study Agent Accountability Procedures

Study drug will be ordered by study physician when participant arrives to PACU. Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. Controlled substance disposal procedures will be followed per pharmacy procedure.

6 Study Procedures and Schedule

6.1 Study Schedule

6.1.1 Screening

Screening/Introductory Visit (Day -28 to -1)

- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Obtain informed consent of potential participant verified by signature on written informed consent or electronic informed consent.
- Obtain medical/medications history and demographic information.
- Schedule baseline visit for participants who are have been screened for eligibility and interested in participating and/or learning more about the study.
- Provide participants with instructions needed to prepare for the first study visit.

Enrollment/Baseline Visit (Visit 1, Day 0)

- Obtain informed consent of potential participant verified by signature on written informed consent or electronic consent.
- Verify inclusion/exclusion criteria.
- Subjects will complete the questionnaire packet for baseline assessments which will include BPI, PROMIS sleep disturbance, PROMIS fatigue, PHQ-2, and GAD-2. This will be done either in-person, over the phone or electronically via REDCap link sent to subject.

6.1.2 Intermediate Visits

Study Visit 2 (Visit 2, Day 1, POD 0)

- Perform randomization.
- Administer the study intervention, ketamine single dose or placebo. Administration of normal saline placebo is standard of care.
- BPI pain severity subscale, opioid use, and side effects (psycho-behavioral questionnaire) will be assessed in person after infusion.
- Record adverse events as reported by participant or observed by investigator and study team.

Study Visit 3 (Visit 3, Day 2, POD 1+1)

- Subjects will complete a questionnaire packet containing, BPI, PROMIS fatigue. Side effects (psycho-behavioral questionnaire) will be assessed.
- Assessment of opioid use.
- Participant will be asked to which treatment arm she believes she is assigned.
- If participant is still in the hospital, study staff may administer questionnaires in person or electronically via REDCap.
- If the participant has already been released from the hospital, a research team member will either send the subject an electronic REDCap link to the questionnaires or call the subject to answer the questionnaires on the phone.
- Record adverse events as reported by participant or observed by investigator and study team.

Study visit 4 (Visit 4, Day 3, POD2+2)

- BPI, PROMIS fatigue, QoR-15 will be assessed
- Assessment of opioid use.
- Record adverse events as reported by participant or observed by investigator and study team.
- If participant is still in the hospital, study staff may administer questionnaires in person or electronically via REDCap.
- If the participant has already been released from the hospital, a research team member will either send the subject an electronic REDCap link to the questionnaires or call the subject to answer the questionnaires on the phone.

6.1.3 Final Study Visit

Study Visit 5 (Visit 5, Day 8, POD 7+2)

- Subjects will complete a questionnaire packet containing BPI, PROMIS fatigue, QoR-15, BCPQ, PHQ-2, GAD-2, and PROMIS sleep disturbance.

- Assessment of opioid use.
- Record adverse events as reported by participant or observed by investigator and study team.
- If participant is still in the hospital, study staff may administer questionnaires in person or electronically via REDCap.
- If the participant has already been released from the hospital, a research team member will either send the subject an electronic REDCap link to the questionnaires or call the subject to answer the questionnaires on the phone.

6.1.4 Withdrawal/Early Termination Visit/Lost to Follow-up

Participants are free to withdraw from participation in the study at any time upon request. However, participants should be counseled that they may request stopping the interventional drug but continue to be in the study. They also will be told that follow-up for adverse events is recommended for safety.

Lost to follow-up is defined by the inability to reach a participant after a minimum of two phone calls. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

6.1.5 Unscheduled Visit

Unscheduled visits will be documented in the subjects' record.

6.2 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

6.3 Rescue Medications, Treatments, and Procedures

Cardiovascular side effects may be treated based on PACU clinician's decisions. If such side effects persist despite treatment, study drug may be halted.

Psychomimetic side effects will be monitored by study and PACU physicians. Such side effects may be treated with reassurance. If participants continue to complain of anxiety or dysphoria or are agitated, pharmacologic agents (such as benzodiazepines) may be administered based on clinical judgement of PACU clinicians. Benzodiazepine administration will be at discretion of PACU clinician; midazolam in titrated doses of 0.5-1 mg could be considered. If psychomimetic side effects are felt to be severe, with severe hallucinations, delusions, or agitation, study drug will be discontinued.

7 Assessment of Safety

7.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal

- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

7.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

7.4 Classification of an Adverse Event

7.4.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

7.4.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- ***Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should*

be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- ***Probably Related*** *– There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.*
- ***Possibly Related*** *– There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.*
- ***Unlikely to be related*** *– A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).*
- ***Not Related*** *– The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.*

7.4.3 Expectedness

The principal investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

7.5 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator

should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

7.6 Reporting Procedures

7.6.1 Adverse Event Reporting

Adverse Event Reporting Period

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation.

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs and symptoms should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be definitely and probably related to the study treatment or study participation should be recorded and reported immediately.

7.6.2 Serious Adverse Event Reporting

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported within 5 or 10 days of PI notification are those that are:

- related to study participation,
- unexpected, and
- Harmful or have the potential to cause harm

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, related and unrelated, will be recorded on the SAE Form and submitted within 24 hours of site awareness.
- Other SAEs will be submitted within 72 hours of site awareness.

This information should be reported to the PI and to the DSMC. All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly.

Adverse events that do not fit the above immediately reportable criteria must still be reported to the IRB at each annual review, either in a summary or tabular format.

7.6.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the Data Coordinating Center (DCC)/study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB 5 or 10 days of the investigator or the study team becoming aware of the event. Unexpected death of unknown causality and any event requiring immediate intervention to prevent subject harm requires 5 calendar days.
- Any other UP will be reported to the IRB within 5 or 10 days of the investigator or the study team becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 5 or 10 days of the IRB's receipt of the report of the problem from the investigator and the study team.

7.6.4 Reportable Events

The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation). Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file. The Principal Investigator is responsible for reporting all unexpected problems involving risk to participants or others to NYULH Perlmutter Cancer Center CTO.

7.6.5 Reporting Procedures – Notifying the Study Sponsor and Perlmutter Cancer Center

The following describes events that must be reported to the study sponsor and Perlmutter Cancer Center in an expedited fashion. Any member of the study team who becomes aware of an event informs the rest of the study team staff and the PI/Sub-I. The PI/Sub-I determines if the event is unexpected and related to the trial and if the event is harmful to the subject.

The study team member will complete a NYULH CTO Medical Events Form within the following timelines in an expedited fashion:

Initial Report: within 24 hours:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the NYULH CTO Medical Events Form and submitted to the DCC/study sponsor within 24 hours of site awareness.
- All report forms must be signed and dated by the Principal Investigator. If the Principal Investigator is not available at the time of the initial report, then the form can be submitted by a Sub-Investigator. This form should be reviewed by the Principal Investigator, whom sign/date initial report upon return.

Report to: NYUPCCsafetyreports@nyulangone.org

AND

Principal Investigator
Lisa Doan, MD
Associate Professor at NYU Grossman School of Medicine Department of Anesthesiology, Perioperative Care and Pain Medicine
240 E 38th St, 14th floor, New York, NY 10016
Lisa.Doan@nyulangone.org

AND

PCC Medical Monitor

Follow-up report: within 48 hours:
As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

Other Reportable events:

- **Deviations from the study protocol**
  Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but ***no later than 5 or 10 days*** of the protocol deviation.

- ***Withdrawal of IRB approval***
  An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but no later than ***10 days*** of the IRB notification of withdrawal of approval.

7.6.6 Reporting Procedures – Notifying the IRB

Federal regulations require timely reporting by investigators to the NYULH IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULH IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

This section also specifies the NYULH IRB requirements for investigator reporting of unanticipated problems posing risk to subjects or others, including adverse events. The IRB requirements reflect the current guidance documents released by the Office of Human Research Protections (OHRP), and the Food and Drug Administration (FDA) and are respectively entitled "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" and "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – improving Human Subject Protection".

The NYULH IRB address is:
NYULH School of Medicine IRB
1 Park Avenue, 6th Floor
New York, NY 10016

Report Promptly, but no later than 5 or 10 days:
Researchers are required to submit reports of the following problems promptly but no later than 5 or 10 days from the time the investigator becomes aware of the event:

Unanticipated problems including adverse events that are unexpected and related

- *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB- approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
- *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*

- *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:
The following events also require prompt reporting to the IRB, though ***no later than 5 or 10 days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations***(includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation). The contact information for submitting safety reports is noted below:

Email: NYUPCCsafetyreports@nyulangone.org

AND

Principal Investigator
Lisa Doan, MD
Associate Professor at NYU Grossman School of Medicine Department of Anesthesiology, Perioperative Care and Pain Medicine
240 E 38th St, 14th floor, New York, NY 10016
Lisa.Doan@nyulangone.org

AND

PCC Assigned Medical Monitor

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

7.7 Study Halting Rules
There are no predefined stopping rules.

8 Clinical Monitoring
Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). The completeness, accuracy and consistency of the data, and adherence to ICH Good Clinical Practice guidelines will be followed.

9 Data Safety Monitoring

The PI and the Perlmutter Cancer Center Data Safety Monitoring Committee (DSMC) will be responsible for conducting systematic and periodic reviews of aggregate data and adverse events in accordance with the data safety monitoring *plan.* The PI and DSMC are responsible for overall data safety monitoring of the study.

The trial will be monitored for all adverse events, such as adverse medical symptoms to the study drug, and serious adverse events, such as an adverse study drug-related events every 6 months by the DSMC. The PI will also review these adverse effects once a month.

The following adverse effects will be monitored:

- Allergic reaction thought to be related to study drug
- Uncontrolled hypertension, hypotension, or arrhythmia thought to be related to study drug
- Severe psychomimetic side effects
- Severe respiratory event in PACU (such as reintubation, laryngospasm, or bronchospasm)

At the NYULH Perlmutter Cancer Center, all investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, IRB review and DSMC review as well as internal auditing.

The review of unanticipated problems and trial conduct for this trial occurs at several levels:

(1) Principal Investigator: Unanticipated problems are evaluated regularly by the principal investigator in conjunction with the research nurses, data manager and research team. In addition, serious adverse events are monitored for this study on a monthly basis by the research team.

(2) DSMC, semi-annually.

(3) Institutional Review Board (IRB): An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all unanticipated problems, total enrollment with demographics, protocol violations, and current status of subjects as well as available research data.

(4) In addition, the quality assurance unit will monitor this trial every 3 months, to verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to ICH Good Clinical Practice guidelines. The quality assurance unit's specialist will send an email notification of upcoming monitoring visit at least 2 weeks prior to each visit. The regulatory binder may also be requested for review. Monitoring visit reports are issued after each visit (usually within 24 hours of last day of monitoring).

10 Statistical Considerations

The primary outcome will be assessed with the BPI pain subscale at 24h postoperatively. We hypothesize subjects who received ketamine will have lower scores than those who received placebo. Secondary outcomes include changes in BPI (pain and interference subscales), PROMIS fatigue, PROMIS sleep, QoR-15, and BCPQ.

Descriptive statistics will be used to summarize continuous variables with mean and standard deviation, or categorical variables with frequency and percentage. The normality of the distributions for continuous variables will be tested using Q-Q plots and Shapiro–Wilk tests. If they are skewed, they will also be summarized using median and the inter-quartile range. A two-sided p-value<0.05 will be considered statistically significant. All analyses will be conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

10.1 Statistical and Analytical Plans (SAP)

Descriptive statistics will be used to summarize the demographic and baseline characteristics, with mean and standard deviation for continuous variable, or frequency and percentage for categorical variables. If continuous variables are skewed, the median and inter-quartile range will be used as well. To test differences in the demographic and baseline characteristics between the two arms, clinical variables that are continuous will be compared using Wilcoxon's rank-sum test, and those categorical variables will be compared using the Fisher's exact test. The baseline balance will be determined by following both statistical and clinical significance criterion, with the latter as the primary.

The primary endpoints are the BPI pain subscale at 24 and 48 hours. The difference between ketamine and placebo will be compared using Wilcoxon's rank-sum test. A mixed-model repeated measures (MMRM) approach will be used to assess differences of repeated measures for the BPI pain subscales at 24h and 48h between two treatment regimes. The MMRM model will include the baseline pain subscale, factors for treatment, time, and treatment by time interaction. Unbalanced baseline variables will also be included. SAS PROC MIXED will be used to perform the analysis. Model-based least square means will be obtained for difference between two treatment arms at each time point.

Secondary endpoints include scales for postoperative pain, mood, fatigue/sleep, and recovery. The difference of secondary outcomes between ketamine and placebo will be compared using Wilcoxon's rank-sum test. In addition, for outcomes with single occasion (such as PHQ-2 and GAD-2 scales) linear regression models will be utilized to quantify the effects of the ketamine treatment against the control while controlling for their preoperative value and unbalanced baseline variables. Their model-adjusted pairwise differences will be quantified using point estimates associated with 95% confidence intervals. Outcome variables that are obtained on more than one occasion (such as BPI, opioid use and fatigue scales at 1+1, 2+2, and 7+2 days after surgery) will also be analyzed with an MMRM approach to assess differences between two treatment regimes. The MMRM model will include factors for treatment, time, treatment-by-time interaction, their preoperative values and unbalanced baseline variables.

9.1.1 Sample Size Determination

This is a pilot study with limited resources so that it is not powered to detect a hypothesized effect size for the BPI subscale at 24 hours and 48 hours. We expect to randomize 15 participants to each arm. With 15 subjects per arm, we have 80% power to test an effect size of 1.1 with a significance level (alpha) of 0.05 using a two-sided Wilcoxon's rank-sum test assuming data are generated from normal distributions.

9.2 Measures to Minimize Bias

9.2.1 Enrollment/Randomization/Masking Procedures

The subjects will be randomized in a 1:1 ratio. The treatment subjects will receive 0.6 mg/kg of the study drug, and the control subjects will receive an equal volume of saline. Participants will be randomized with random size permuted blocks, blinded with respect to treatment assignments. Dr. Binhuan Wang will generate the randomization list.

9.2.2 Evaluation of Success of Blinding

The subject will be asked if they know what group they were placed in at POD 1+1. If they are unsure that will be evaluated as successful blinding.

9.2.3 Breaking the Study Blind/Participant Code

In this single-blind study, the blind will not be broken.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as

being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

An electronic database capture system will be created to record the data for this trial. Research coordinators will input clinical trial data into the database. This database is password protected and only the PI, assigned study team members, and CTO staff will have access to the database. DataCore, a core resource of the institution, will provide the primary data collection instrument for the study. All data requested in the system must be reported. All missing data must be explained. The quality assurance specialists will monitor this trial every 3 months for data entry accuracy.

REDCap (Research Electronic Data Capture) is a secure web application capture system that will be created to record the data for this study. This database is password protected; the PI and designated study team personnel will have access to the database. REDCap is the primary data collection instrument for this study. All data requested in the system must be reported. All missing data must be explained. The quality assurance specialists will monitor this trial every 3 months for data entry accuracy.

Source documentation refers to original records of observations, clinical findings, and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into any electronic medical record or REDCap. Relevant source documentation to be reviewed by the DSMC throughout the study includes:

1. Baseline measures to assess pre-protocol status
2. Concurrent medications
3. Treatment records
4. Adverse events

Data Collection
Principal Investigator and IRB approved study personnel trained on this protocol will identify subjects. The following data elements will be captured from the subject’s medical record and entered into the research database by the assigned data/research coordinator:

- age/ date of birth
- race

- MRN
- gender
- ethnicity
- participant enrollment location
- zip code
- disease site

12 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

This study will be monitored according to the monitoring plan detailed below. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit. A risk-based, data-driven monitoring approach will be used to verify data for this trial which will also include a centralized review of data for quality, trends, consistency and general safety review. A quality assurance specialist will make regularly scheduled trips to the investigational site to review the progress of the trial, study data and site processes. At each visit, the monitor will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and study manual and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

During scheduled monitoring visits, the investigator and the investigational site staff must be available to meet with the quality assurance specialist in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor. In addition to on-site monitoring visits, the Sponsor and/or representatives will also be routinely reviewing data. Any queries identified through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct, which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database.

At any time during the course of the study, representatives of the FDA and/or local regulatory agencies may review the conduct or results of the study at the investigational site. The investigator must promptly inform NYULH PCC CTO and sponsor of any audit requests by health authorities, and will provide sponsor with the results of any such audits and with copies of any regulatory documents related to such audits.

In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families.

Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator or a research team member who has completed requisite training for human subject research and has been instructed by the Principal Investigator about the potential participant will explain the research study to the participant and answer any questions/concerns that may arise prior to obtaining written informed consent for participation and HIPPA authorization.

All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. The Investigator will explain to each potential participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, potential compensation and or costs incurred by the patient and any discomfort this trial may entail. This informed consent should be given by means of standard written statement, written in non-technical language. All patients will be required to sign a written informed consent prior to being registered on this study. No patient can enter the study before his/her informed consent has been obtained.

Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their families or think about it prior to agreeing to participate. Patients or prospective subjects will be given adequate time to read the consent form. They will be given time to ask questions about the study in private exam rooms, if in person, or remotely through phone calls and video conferences. Questions will be answered by a participating physician, or qualified research study team member all of whom have completed requisite training for human subject research. Every effort will be made to answer questions raised by patients and their families regarding the protocol and alternative therapies prior to asking a patient to sign the consent form.

The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care

will not be adversely affected if they decline to participate in this study. Investigators will stress that participation in the study is completely voluntary and will not affect the care patients receive or result in any loss of benefits to which patients are otherwise entitled.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process and the justification for such alteration will likewise be documented. The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB approval. The consenting process and documentation will follow Human Subject Research Standard Operating Procedures (HSR 301 Informed Consent Process and Documentation).

13.3.3 Documentation of Consent

The Principal Investigator or IRB approved sub-investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the subject's medical chart.

13.4 Posting of Clinical Trial Consent Form

The informed consent form will be posted on the Federal website after the clinical trial is closed to recruitment and no later than 60 days after the last study visit by any subject, as required by the protocol. Per institutional guidelines, SOP#: HSR-601, instructs the principal investigator on registration and results reporting on clinicaltrials.gov.

13.5 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Health Center. This will not include the participant's contact or

identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Health research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Health.

13.6 Research Use of Stored Data

Intended Use: Data collected under this protocol may be used to study the administration of ketamine after surgery may be able to relieve postoperative pain, improve mood (fatigue), sleep quality, physical function, and decrease the opioid requirements in subjects undergoing mastectomy. In addition, we want to determine if ketamine may potentially be more helpful in certain surgical populations with high baseline depression or anxiety. The objective is to examine the effect of a sub anesthetic dose of (0.6mg/kg) of ketamine vs. saline control on postoperative pain in subjects who have undergone mastectomy. No genetic testing will be performed.

13.7 Future Research Use of Stored Data

These data will only be used for the purposes of this study, not for future research.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap a 21 CFR Part 11-compliant data capture system provided by NYU Langone Health DataCore. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained. The investigator will retain study essential documents according to NYU Langone Health data retention policy. De-identified information will be retained indefinitely.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 5 or 10 days of identification of the protocol deviation, or within 5 or 10 working days of the scheduled protocol-required activity.

Protocol deviations must be reported to the IRB per guidelines. The PI/study staff is responsible for knowing and adhering to their IRB requirements.

14.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

15 Study Finances

15.1 Funding Source

This study is funded by the NYU Langone Health Department of Anesthesiology, Perioperative Care, and Pain Medicine and by the NYU Langone Interdisciplinary Research Pain Program.

14.2 Study Costs

There is no additional cost for participation in this study. Study sponsor will cover cost of ketamine. Subject and her health insurance will be responsible for costs associated with the surgical procedure.

15.3 Participant Reimbursements or Payments

Subjects will not receive payment for participation this this study.

16 Study Administration

16.1 Study Leadership

The PI and the investigators of the research team will oversee subjects screening, subject recruitment, study visits, and study procedures.

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the IRB has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Health Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULH investigators will follow the applicable conflict of interest policies.

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19 Schedule of Events

STUDY ASSESSMENTS & PROCEDURES	*Screening (Day -28 to -1)*	*Baseline/Enrollment (Visit 1, Day 0)*	*(Visit 2, Day 1, POD 0)*	*(Visit 3, Day 2, POD 1+1)*	*(Visit 4, Day 3, POD 2+2)*	*(Visit 5, Day 8, POD 7+2)*
Informed Consent	*X*	*X*				
Review and verify of Inclusion/Exclusion Criteria	*X*	*X*				
Demographics[1]	*X*					
Medical history and medication history	*X*					
Randomization and administer study intervention ketamine single-dose infusion or placebo			*X*			
Participants will be asked which treatment arm she believes she has been assigned				*X*		
Brief Pain Inventory (BPI)		*X*	*X*[2]	*X*	*X*	*X*
PROMIS sleep disturbance		*X*				*X*
PROMIS fatigue		*X*		*X*	*X*	*X*
Breast cancer pain questionnaire (BCPQ)						*X*
Opioid use and dosage assessment (medical records) and subject reports			*X*	*X*	*X*	*X*
Assessment of Adverse Events			*X*	*X*	*X*	*X*
Quality of Recovery (QoR-15)					*X*	*X*
Patient Health Questionnaire-2 (PHQ-2)		*X*				*X*
Generalized Anxiety Disorder-2 (GAD-2)		*X*				*X*
Side Effects (Psycho-Behavioral Questionnaire)			*X*	*X*		

[1]Demographics should be collected, includes: age/ date of birth, race, MRN, gender, ethnicity, participant enrollment location, zip code, and disease site.
[2]Only the pain severity subscale.