UCSF Helen Diller Family Comprehensive Cancer Center

Pilot study of ketamine-assisted talk therapy for demoralization in advanced GI cancer

Protocol Number: CC# 238011
Investigational Product(s): Ketamine

Version Number: 2.5
Version Date: **November 07**, 2024

IND Number: 166544

NCT Number: [redacted]06077487

Principal Investigator (Sponsor-Investigator)
Brian T. Anderson, MD, MSc
University of California, San Francisco
[redacted]

Co-Principal Investigator
Andrea Rosati, MD, PhD
University of California, San Francisco
[redacted]

Statistician
Joan F. Hilton, DSc, MPH

Revision History

Version 2.5	11-07-2024	Version 1.6	08-08-2023
Version 2.4	10-14-2024	Version 1.5	07-21-2023
Version 2.3	08-25-2024	Version 1.4	06-23-2023
Version 2.2	04-18-2024	Version 1.3	06-08-2023
Version 2.1	03-22-2024	Version 1.2	05-16-2023
Version 2.0	03-13-2024	Version 1.1	01-22-2023
Version 1.9	01-22-2024	Version 1.0	09-23-2022
Version 1.8	10-27-2023		
Version 1.7	08-22-2023		

Protocol Signature Page

1. I agree to follow this protocol version as approved by the UCSF Protocol Review and Monitoring Committee (PRMC), Institutional Review Board (IRB), and Data and Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.
3. I certify that I, and the study staff, have received the required training to conduct this research protocol.
4. I agree to maintain adequate and accurate records in accordance with IRB policies, federal, state and local laws and regulations.

Signature of UCSF Principal Investigator

Date

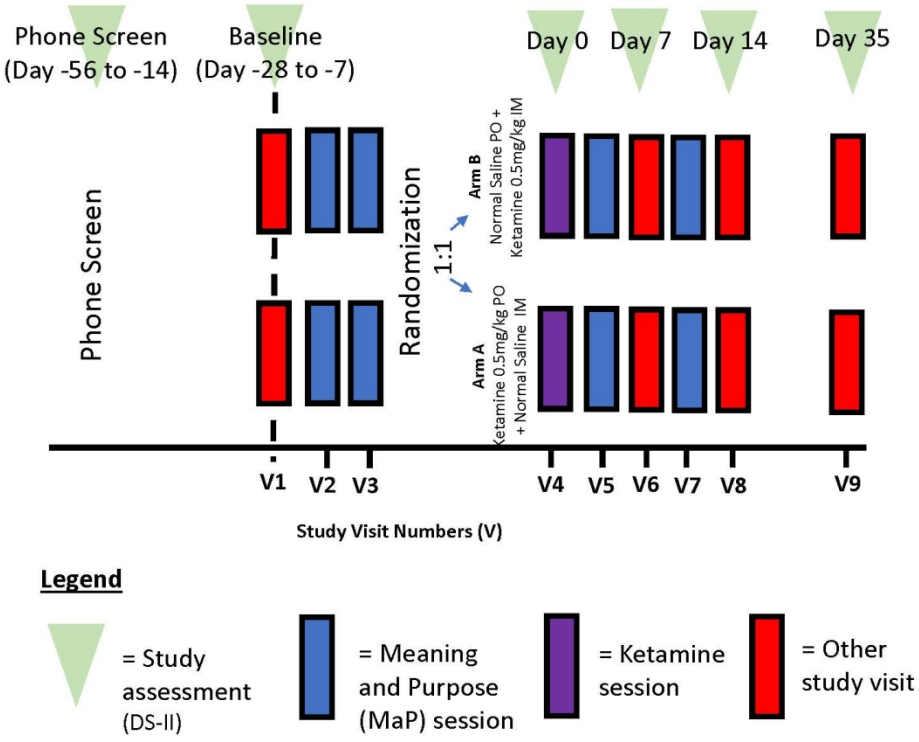
Name of UCSF Principal Investigator (Printed)

Abstract

Title	Pilot study of ketamine-assisted talk therapy for demoralization in advanced GI cancer
Study Description	This is a single-site, parallel-arm double-blind randomized controlled pilot trial (N=12) of 0.5mg/kg oral ketamine vs. 0.5mg/kg intramuscular ketamine, each administered as a single dose, in combination with 4 sessions of Meaning and Purpose therapy (MaP), for adults diagnosed with stage 3 or 4 gastrointestinal (GI) cancers (i.e., primary pancreatic, colorectal, hepatocellular, biliary, and gastro-esophageal cancers) who have moderate-to-severe demoralization. The combination of ketamine and Meaning and Purpose therapy will be referred to as K-MaP. MaP is a brief, existential behavioral intervention. It is a form of talk therapy designed to help patients cope with demoralization through a review of the patient's value and worth, their key relationships, and sources of fulfillment and meaning in life [1]. Participants will have 2 sessions of MaP before drug administration, and 2 sessions after drug administration. The expected study duration from enrollment to study completion is up to 63 days for each participant. Demoralization is a clinically significant and measurable form of existential distress characterized by poor coping and a sense of helplessness, hopelessness, and a loss of meaning and purpose in life [2, 3]. Demoralization will be measured by Demoralization Scale-II (DS-II), a validated measure [4]. The scale includes 16 items, the total score range is 0-32, and a score of 10 or higher indicates moderate-to-severe demoralization [4, 5]. DS-II will be assessed at baseline, after 2 sessions of MaP but before ketamine, and then 1, 2, and 5 weeks after ketamine. A change in the DS-II of at least 2 points has been considered clinically meaningful in palliative care patients and will be used as a minimum point reduction indicative of efficacy [4].
Phase of Study	Pilot
Investigational Products	Ketamine
Study population	Adult stage 3 and 4 GI cancer patients with moderate to severe demoralization.
Primary Objective	To assess the feasibility of Meaning and Purpose therapy combined with ketamine (K-MaP) in demoralized patients.

Secondary Objectives	1. To characterize the preliminary safety and tolerability of K-MaP in demoralized patients with stage 3 and 4 GI cancers. 2. To assess the magnitude and durability of improvement from randomization in psychosocial distress. 3. To assess the magnitude and durability of improvement from randomization in pain. 4. To assess the magnitude of change from randomization in opioid analgesic use. 5. To assess the magnitude and durability of change from randomization in interoceptive awareness.
Sample Size	12 patients, 6 patients per arm. Arm A: (0.5 mg/kg of ketamine, PO) Arm B: (0.5 mg/kg of ketamine, IM)
Duration of Study Treatment	Ketamine will be given once on Day 0/Visit 4. Patients will receive MaP therapy 4 times, twice before ketamine administration (Day 0), and twice afterward: 1. Day -13 to -4/Visit 2 2. Day -12 to -1/Visit 3 3. Day 3 (+/- 2 days)/Visit 5 4. Day 11 (+/-2 days)/Visit 7 The duration of treatment for K-MaP therapy (ketamine and MaP) is approximately up to 28 days.
Duration of Follow up	Patients will be followed up to 35 days (+/-2 days) after ketamine administration.

Study Schema



List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMP	Basic Metabolic Panel
BPI-SF	Brief Pain Inventory-Short Form
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CEQ	Challenging Experience Questionnaire
CMP	Comprehensive Metabolic Panel
CNS	central nervous system
CR	complete response
CRF	case report form
C-SSRS	Columbia Suicidality Severity Rating Scale
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DFS	disease-free survival
DLT	Dose-limiting toxicity
DS-II	Demoralization Scale II
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECG/EKG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FACIT-Pal-14	Functional Assessment of Chronic Illness Therapy Palliative Care 14 Item Version
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
GAD7	General Anxiety Disorder-7
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBcAb	hepatitis B core antibody
HC Ab	hepatitis C antibody

List of Abbreviations

HDFCCC	Helen Diller Family Comprehensive Cancer Center
HBD	Heartbeat Detection Task
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IA	Interoceptive accuracy
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDS	Investigational Drug Services (UCSF)
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
K-MaP	Ketamine and Meaning and Purpose
MaP	Meaning and Purpose
MEQ	Mystical Experience Questionnaire
MME	Morphine Milligram Equivalents
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	overall response rate
PD	disease progression
PDAC	pancreatic ductal adenocarcinoma
PHQ9	Patient Health Questionnaire-9
PK	pharmacokinetics
PO	*Per os* (by mouth, orally)
PR	partial response
PRMC	Protocol Review and Monitoring Committee (UCSF)
RR	Respiration rate
SC	Skin conductance
SD	stable disease
UP	Unanticipated problem

Table of Contents

Table of Contents

1 Introduction

1.1 Background on Indication

Patients with advanced-stage gastrointestinal (GI) cancers—including pancreatic, gastro-esophageal, colorectal, hepatocellular, and biliary cancers—often face significant psychological distress due to the aggressive nature of these malignancies, poor prognoses, and challenging treatment regimens [6-19]. Among the various forms of psychological distress, demoralization—a clinically significant and measurable [22, 23] form of existential distress characterized by poor coping and a sense of helplessness, hopelessness, and a loss of meaning and purpose in life [2, 24]—has been increasingly recognized as a significant concern in this population. Demoralization is associated with physical symptom burden and poor quality of life, and it is highly prevalent (13-73%) among patients with serious medical illness (e.g., advanced cancer) [25-30]. In patients with cancer, demoralization is often more strongly associated with suicidal ideation than is major depressive disorder (MDD) [31, 32]. Prevalence rates of clinically significant demoralization among end-of-life and palliative care (EOLPC) patients is typically reported as 20-30% when using the two most widely used measures for this condition—the Demoralization Scale (DS, a patient-reported outcome) and the Diagnostic Criteria in Psychosomatic Research (DCPR, a clinician-rated assessment) [33-36]**.** Previous studies involving patients with progressive disease (including GI malignancies) have demonstrated a strong positive correlation between demoralization and depression, respectively measured by the Demoralization Scale-II (DS-II) and Patient Health Questionnaire-9 (PHQ-9) surveys [33, 37]..

Given the high prevalence of demoralization among patients with GI cancers and the limitations of existing treatments, there is a critical need for novel therapeutic approaches. Currently, no medication has an FDA indication for the treatment of demoralization, and no FDA-approved medications have been reliably shown to improve demoralization. Several psychotherapies have been shown to produce small-to-moderate treatment effects on psychosocial distress in EOLPC patients [39, 40]. These interventions often involve weeks of individual or group psychotherapy, treatment effects are often measured only in comparison to waitlist controls or treatment-as-usual (TAU), and treatment allocation typically cannot be masked. For example, in one of the largest (n=321) and best-designed trials of an existential psychotherapy for EOLPC patients, Breitbart et al. showed that, for patients with advanced cancer, 7 sessions of Meaning-Centered Psychotherapy (MCP) produced statistically significant improvements (with small-to-medium effect sizes) in spiritual well-being, meaning-in-life and quality of life when compared to enhanced usual care; but there were no statistically significant effects when MCP was compared to supportive psychotherapy [41]. When Kissane et al. administered 6-sessions of the existential psychotherapy, Meaning and Purpose therapy (MaP), to 45 advanced cancer patients in an exploratory pilot study (with no inclusion criterion based on degree of distress at baseline) they found no meaningful pre-post improvement in demoralization by the DS-II (Cohen's d = 0.16, 95% CI -0.29, 0.86) [42]. In a relatively large RCT (n=305) of outpatient oncology patients, Rodin et al. compared usual care (UC) alone with UC plus Managing Cancer and Living Meaningfully (CALM)—an attachment- and existential-based psychotherapy [43]. Participants in the active treatment arm were supposed to receive 3-6 sessions of CALM therapy over 3-6 months, with at least 3 sessions by month 3. The effect size for the between-groups difference (Cohen's d) in improvement from baseline on the 24-item Demoralization Scale was negligible at 3- and 6-months. Only in a subgroup analysis of patients with moderate death anxiety at baseline did the authors find effect sizes for improvement in demoralization of d = 0.1 and d = 0.5 at 3- and 6-months, respectively.

1.2 Background on the Investigational Product(s) and Associated Known Toxicities

Ketamine is a centrally-acting NMDA glutamate receptor antagonist that is a DEA Schedule 3 medicine and FDA-approved as a dissociative anesthetic. Esketamine (the s-stereoisomer of

ketamine) was approved by the FDA in 2019 for treatment-resistant depression. Ketamine is used widely for procedural sedation and is frequently used off-label for chronic pain and psychiatric disorders, including depression and anxiety. The use of ketamine for treatment of depression is supported by specialty medical societies including the American Psychiatric Society and the American Society of Ketamine Physicians, Psychotherapists, and Practitioners. The UCSF Lexicomp label lists depression as an indication for ketamine. Ketamine therapy for psychiatric illness is offered widely in California, including by the SF Veterans Administration Medical Center, UCLA, and UCSD. The UCSF P&T committee approved use of ketamine for depression in June 2018.

This section of text is excerpted from the UCSF UpToDate Lexicomp on Ketamine:[44]

> Ketamine is a racemic mixture of two enantiomers, S-ketamine and R-ketamine. Ketamine is a standard anesthetic drug that is also administered for analgesia and sedation [2,3]. In addition, ketamine and esketamine can rapidly and transiently alleviate treatment-resistant unipolar major depression, including suicidal ideation [4,5]. For unipolar major depression, the efficacy of ketamine and esketamine appear to be comparable [1]. However, no head-to-head trials comparing the two drugs have been published.
>
> The optimal method of administering ketamine for treatment resistant depression has not been established [26]. Although most studies have given ketamine intravenously, it can also be administered with intramuscular, intranasal, oral, subcutaneous, and sublingual formulations [2,12,25,27-29].
>
> For treatment-resistant depression, repeated administration of oral ketamine can provide short-term improvement. A small, three-week randomized trial compared add-on oral ketamine 1 mg/kg with placebo in patients receiving usual care (n = 40) [25]. Most of the patients had melancholic features and comorbid psychopathology. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients who received active drug than placebo (32 versus 6 percent). The number needed to treat was approximately four, meaning that for every four patients treated with ketamine and every four treated with placebo, one additional response occurred with ketamine. Follow-up assessments one week after treatment found that the benefit of ketamine persisted. In addition, adverse effects were mild and transient.
>
> The dose of ketamine for treatment-resistant depression varies depending upon the route and frequency of administration [26,29]. For any particular route of administration, no one dose has been established among the different doses tested.
>
> It appears that ketamine can be used concurrently with most standard antidepressants without reducing efficacy or increasing side effects [37]. Across randomized trials, ketamine has been administered either as monotherapy or as add-on therapy to antidepressants and antipsychotics [4,16,25,34,36,38-40].
>
> Ketamine is metabolized primarily by hepatic cytochrome P450 2B6 and 3A4 [37]. Concomitant drugs that induce these enzymes may decrease exposure to ketamine and drugs that inhibit these enzymes may increase exposure; these effects may necessitate adjusting ketamine doses.
>
> **Adverse effects** — Adverse effects such as psychotomimetic effects may occur more often with ketamine than with esketamine [1]. However, no head-to-head trials comparing the two drugs have been published.

One review of adverse effects in patients treated for resistant depression with ketamine found that side effects occur more often with ketamine than placebo or active controls [12]. However, most side effects resolved spontaneously.

Short term — Short-term ketamine for treatment-resistant depression is generally safe and well tolerated [6,29,35,66]. In a pooled analysis of three randomized trials, which called for either a single infusion of intravenous ketamine 0.5 mg/kg over 40 minutes or multiple infusions over a 12-day period, 97 patients received a total of 205 infusions [35]. During the 205 infusions, early discontinuation due to adverse effects (hypertension, anxiety, or hypotension) occurred in 2 percent.

For patients with treatment-resistant depression who receive intravenous ketamine, side effects peak within two hours [3]. In short-term studies (e.g., ≤30 days), transient adverse effects included:

Dissociation and psychotomimetic effects – A review of 60 studies (randomized trials and observational studies with nearly 900 patients) found that dissociation and psychotomimetic effects were reported in more than 70 percent of the studies [12]. Studies of intravenous ketamine were two times more likely to report dissociation and psychotomimetic effects than non-intravenous studies.

Randomized trials, which typically administered a single intravenous dose of ketamine, indicate that ketamine causes significant, clinically large dissociative and psychotomimetic effects at 40 to 60 minutes after initiating infusion, which subsequently resolved within four hours [4,6,36,38,40,45]. In one trial that administered repeated infusions for up to four weeks, the intensity of dissociative symptoms appeared to diminish with repeated infusions [36]. Results from another trial suggest that dissociation occurs in a dose response manner. (See 'Intravenous' above.)

Multiple randomized trials studying ketamine for treatment-resistant depression have excluded patients with psychotic features [16,25,28,34-36,40,56].

Cardiovascular – A review of 60 studies (randomized trials and observational studies) found that nearly 40 percent of the studies described cardiovascular changes [12]. In randomized trials, which typically administered a single intravenous dose of ketamine, hemodynamic effects included time-limited increases in blood pressure and heart rate:

Systolic blood pressure – In four randomized trials, mean increases in systolic blood pressure ranged from 8 to 19 mmHg within 40 minutes of infusion, which normalized in four hours or less [4,16,40]. In a pooled analysis of three randomized trials that included 97 patients who received a total of 205 infusions, the transient average peak increase was 20 mmHg [35].

Diastolic blood pressure – In a pooled analysis of three randomized trials that included 97 patients who received a total of 205 infusions, the transient average peak increase in diastolic blood pressure was 13 mmHg [35]. Two subsequent randomized trials found that mean increases ranged from 8 to 13 mmHg within 40 minutes of infusion, which normalized in two hours or less [16,40].

In addition, a retrospective study included 66 patients with a mean age of 57 years who received an average of 10 ketamine infusions, 0.5 mg/kg over 40 minutes [69]. Essential hypertension controlled by pharmacotherapy was present in 36 percent. An increase in systolic pressure >30 mmHg or in diastolic pressure >15 mmHg during at least one infusion occurred in 50 percent of the patients. Nearly 80 percent of the blood pressure

elevations occurred 30 to 40 minutes after onset of the infusion, and all of the elevated readings resolved within 70 minutes of onset.
Pulse – In one randomized trial, the mean heart rate increased by 9 beats/minute within two hours of infusion, which subsequently normalized [16].

Results from randomized trials suggest that elevated blood pressure and pulse occur at higher doses in a dose response manner. (See 'Intravenous' above.)

Other cardiovascular changes that may occur include chest pain, palpitations, and/or pressure, which generally resolved within 90 minutes of receiving ketamine [12].

Other – Other common, transient adverse effects of ketamine in randomized trials included [36,40,53]:

- Anxiety
- Blurred vision
- Dizziness
- Headache
- Nausea or vomiting

End of text is excerpted from the UCSF UpToDate Lexicomp on Ketamine:[44]

1.3 Rationale for the Proposed Study

Ketamine has demonstrated efficacy for the treatment of depression, suicidality, and pain in non-cancer patients [45-48]. Multiple case series demonstrate that ketamine has promise for the treatment of psychosocial distress, suicidality, and pain in the hospice setting, but more research is needed among distressed patients with cancer [49-52]. Pre-clinical and clinical data suggest that ketamine modulates glutamate-mediated neural circuits implicated in mood disorders, such as depression and demoralization [53, 54].

This study is designed to assess the feasibility and preliminary safety and efficacy of oral vs. intramuscular ketamine, in conjunction with a manualized talk therapy, as a treatment for patients diagnosed with advanced GI cancers and moderate-to-severe demoralization. This double-blinded pilot study will assess the effects of two different doses and routes of ketamine administration (0.5mg/kg PO and 0.5mg/kg IM) in patients with advanced GI cancer, providing data that can be used to optimize ketamine treatment for this patient population.

Several prior clinical trials have demonstrated that ketamine treatment is safe and effective for treatment-resistant depression, and esketamine is now FDA-approved for this purpose. This study offers an opportunity to explore the utility of this therapy among demoralized GI cancer patients using a ketamine formulation which is FDA-approved for other indications using two different routes of administration (PO and IM) that may be more accessible and tolerable than the more extensively studied intravenous (IV) and intranasal (IN) routes of ketamine administration.

There are minor risks involved in this study. Generally, oral and IM ketamine are safe and well-tolerated. As noted above, transient increases in systolic blood pressure and heart rate occur in a minority of patients receiving this therapy. Patients may experience transient anxiety and/or dissociative effects. All of these effects are dose dependent. Study participants will be monitored continuously throughout the ketamine treatment session and followed closely in the weeks afterward in their subsequent talk therapy sessions.

Rationale for Dose Selection

We will test two different doses and routes of ketamine administration: 0.5mg/kg PO and 0.5mg/kg IM. These doses were selected on the basis of existing data. As a safety precaution, we will use a maximum limit of oral ketamine of 60 mg, given that higher doses have not been evaluated in clinical trial settings in the U.S.

Case series and one published clinical trial of oral ketamine as a treatment of depression in patients with advanced cancer have shown that a daily oral dose of 0.5mg/kg is well-tolerated and briefly improved depression symptoms [55-57]. An ongoing trial of weekly oral ketamine for anxiety in patients with pancreatic ductal adenocarcinoma (PDAC) is using a dose of 0.5mg/kg PO [58]. The bioavailability of oral ketamine is estimated to be 10-17% [59].

Clinical trials investigating the use of intramuscular ketamine for the treatment of depression in palliative populations and the general public have used starting doses ranging from 0.1mg/kg - 1.0mg/kg IM [60-62], all of which have been reported to be relatively well-tolerated. The bioavailability of intramuscular ketamine is 93% [63, 64].Similar or higher doses of ketamine are frequently used in various clinical settings. Many trials of IV ketamine for unipolar depression have used a dose of 0.5mg/kg administered as a slow infusion [65], while one survey of n=98 community clinics administering off-label ketamine for psychiatric conditions uses doses ranging from 0.5-3.0mg/kg IV [66]. A retrospective study of n=420 patients receiving IM ketamine for depression found starting doses ranging from 0.3 - 2.15mg/kg IM, with a median starting dose of 0.55mg/kg IM [67]. A second case series of n = 40 patients utilized a protocol involving a starting dose of ketamine 1.0mg/kg IM, divided into two 0.5m/kg IM doses spaced 15 minutes apart [68]. In a recent systematic review of ketamine in palliative care populations, patients were most commonly started at starting doses of ketamine 0.5mg/kg SC or IV [69]. Another survey of three ketamine clinics (two of which are in the San Francisco Bay Area) provided data on n=253 patients treated with off-label ketamine-assisted psychotherapy using sublingual administration (with a bioavailability of 15-25%) at doses of 25-400 mg, and often in the range of 200-250 mg [70]. Finally, in an FDA-related abuse liability study published in 2011, 100 mg of oral ketamine was used as a control drug for the serotonin 2C receptor agonist lorcaserin [71].

Additionally, a previous protocol by colleagues at UCSF (CC#20807, PI: Dr. Brieze Bell) obtained UCSF IRB approval, pending FDA approval, for a dosing regimen of ketamine 1.67mg/kg sublingual (SL) during an initial Ketamine session, with dose escalation up to 3.3mg/kg SL at subsequent Ketamine sessions. *Note: This trial was not initiated due to being on FDA clinical hold pending the production of Chemistry Manufacturing and Control data for the novel sublingual formulation.* Correcting for bioavailability, our study's oral and intramuscular ketamine doses are lower than those proposed in the Dr. Bell's protocol, but equal to or greater than those from the above-mentioned ongoing trial of oral ketamine to treat anxiety in PDAC patients [58].

Volume of distribution and terminal clearance of ketamine do not differ by age, disease state, route of administration (oral, intramuscular, subcutaneous, inhaled, intranasal, intravenous), administration form (S- or RS-ketamine), or analyte (S-, R- or RS-ketamine), suggesting that one set of ketamine PK parameters may be used to determine dosing in a variety of conditions by any route of administration [72]. Thus, the safety profile of oral ketamine is expected to be like that of any other route of administration. The FDA-approved drug label for intravenous/intramuscular ketamine (Ketalar) includes that the liquid formulation may be administered intravenously with an initial dose in the range of 1-4.5 mg/kg or intramuscularly at doses of 6.5-13 mg/kg. The bioavailability of ketamine is 93% for intramuscular injection and only 17% for oral administration [64]. Per the ketamine drug label, regarding intravenous administration, "the average amount required to produce 5 to 10 minutes of surgical anesthesia within 30 seconds following injection is 2 mg/kg." Therefore, extrapolating from this amount of ketamine, the average 70 kg person would be administered 140 mg intravenously, and sometimes repeatedly if further doses were needed. Thus, our proposed

doses of oral and intramuscular ketamine, each at 0.5 mg/kg, will result in significantly lower levels of drug exposure than what is already permitted by the ketamine drug label for surgical anesthesia.

2 Study Objectives

2.1 Hypothesis

We hypothesize that K-MaP therapy is safe and feasible for administration to patients with advanced GI cancers with moderate-to-severe demoralization. In addition, we hypothesize that stage 3 and 4 GI cancer patients will tolerate K-MaP therapy, and patient experiences during K-MaP therapy may result in improvements from randomization in measures of psychosocial distress, pain, opioid analgesic use, and interoceptive awareness.

2.2 Primary Objective and Endpoint(s)

Primary Objective	Endpoint(s)	Time Frame
To assess the feasibility of Meaning and Purpose therapy combined with ketamine (K-MaP) in demoralized patients with advanced GI cancers.	1. Rate of recruitment (i.e., proportion enrolled and fully eligible vs screened participants). 2. Proportion of enrolled participants completing (i) K-MaP intervention (receiving ketamine, all four Meaning and Purpose therapy sessions) and (ii) all DS-II assessments, by arm. 3. Qualitative review of clinician fidelity to manualized K-MaP intervention. 4. Qualitative feedback on acceptability to participants of the intervention and assessments (20-minute interview with participants upon study termination), by arm.	1. From time of screening to enrollment. 2. From Day -28 to Day 14 (about 28 days). 3. From Day -14 to Day 14 (about 28 days). 4. On Day 35.

2.3 Secondary Objectives and Endpoints

Secondary Objective	Endpoint(s)	Time Frame

1. To characterize the preliminary safety and tolerability of K-MaP in patients with stage 3 and 4 GI cancers.	1. Adverse events (AEs), Unexpected AEs, and Serious AEs, by CTCAE (v.5.0). 2. Vital signs (heart rate and blood pressure) 3. Patient-reported outcome: challenging experiences (CEQ)	1. Day -28 through Day 35. 2. Day 0 (multiple time points on day of ketamine administration). 3. Day 0, 3-4 hours after ketamine administration.
2. To assess the magnitude and durability of improvement from randomization in psychosocial distress.	1. Clinician-rated outcomes: Global clinical impression of severity(CGI-S), Demoralization (DI), Mood symptoms (GRID-HAMD-6). 2. Patient-reported outcomes: Demoralization (DS-II), Depression (PHQ9), Anxiety (GAD7), Quality of Life (FACIT-Pal-14).	From Day -28 to Day 35.
3. To assess the magnitude and durability of improvement from randomization in pain.	Patient-reported outcome: pain (BPI-SF)	From Day -28 to Day 35.
4. To assess the magnitude of change from randomization in opioid analgesic use.	Patient-reported outcome: Opioid use (<24hr morphine milligram equivalence [MME])	From Day -28 to Day 35.
5. To assess the magnitude of change from randomization in interoceptive awareness.	Patient-reported outcome: interoceptive awareness (MAIA-2)	From Day 0 to Day 7

2.4 Exploratory (Correlative) Objectives

Exploratory Objective	Endpoint(s)	Time Frame
1. To assess how the participants' subjective experiences with ketamine may be related to clinical outcomes.	Patient-reported outcome: Subjective reports of participants' ketamine experiences on Day 0 will be transcribed, inductively coded and analyzed to identify phenomenological content that may be related to clinical outcomes Patient-reported outcome: Challenging and mystical experience questionnaire (CEQ and MEQ) scores correlated with changes in reported measures of demoralization (DS-II), pain (BPI-SF), and opioid use (MME).	Day 0 From Day -28 to 35.
2. To assess how the participants' changes in measures of cardiac interoception following receipt of ketamine may be related to subjective experiences with ketamine and clinical outcomes.	Patient-reported outcome: Changes in scores on a heartbeat detection task (HBD) conducted before and after ketamine correlated with scores on the mystical experience questionnaire (MEQ) as well as changes in reported measures of interoceptive awareness (MAIA-2), demoralization (DS-II), pain (BPI-SF), and opioid use (MME).	From Day -28 to 35.

3 Study Design

3.1 Characteristics

This is a parallel-arm, double-blind, randomized controlled pilot trial (N=12) of two different dose levels of ketamine administered as a single dose, in combination with 4 sessions of Meaning and Purpose therapy (MaP) for stage 3 and 4 GI cancer patients (including those with primary pancreatic, gastroesophageal, hepatocellular, biliary, and colorectal malignancies) experiencing moderate-to-severe demoralization.

Demoralization is a clinically significant and measurable form of existential distress characterized by poor coping and a sense of helplessness, hopelessness, and a loss of meaning and purpose in life [2, 3]. Demoralization will be measured by Demoralization Scale-II (DS-II), a validated measure [4]. The scale includes 16 items, and a total score of 10 or higher indicates moderate-to-severe demoralization.

Participants will be administered 2 sessions of MaP before drug administration, and 2 sessions after drug administration. The combination of ketamine and Meaning and Purpose therapy will be referred to as K-MaP.

Adult GI oncology patients at HDFCCC and other Bay Area medical centers will be referred by their clinical teams. Referred patients must demonstrate clinically significant and stable demoralization as measured by DS-II ≥10/32 two times ≥7 days apart (both during screening) to be eligible for the study. The first measurement of the DS-II scale will occur over the phone. After a verbal waiver of consent,

the study team will read the questions to the potential participant, and the potential participant's answers will be recorded by the study team. If the score is ≥10/32, the study team will talk to the participant about joining the study. The data from the phone screen will only be used for screening and will not be used as research results. The second DS-II measurement will be given to the participant in person after they have signed the informed consent form on the day of enrollment (i.e. baseline, between Day -28 and -7). The DS-II questions will be administered to the patient either on paper or electronically with a tablet (using REDCap). Following best practices with patient-reported outcomes [73], participants will fill out the second DS-II without clinician or study staff involvement. In the event that a participant has a question about how to fill out the questionnaire, study staff will be trained only to read the instructions printed at the top of the measure or to assist the participant with reading a particular item, but staff will say nothing beyond reading the wording on the instrument itself. The DS-II will be scored by summing the responses to all 16 items to generate a total score. Participants must score a 10 or higher in order to be eligible for the study.

If the participant meets all of the eligibility criteria, they will be randomized 1:1 on Day 0 to one of two cohorts (0.5 mg/kg of ketamine PO or 0.5 mg/kg of ketamine IM). The study is double-blinded, meaning neither the study participants nor the study investigators will know which dose of ketamine each participant is receiving. Participants randomized to receive ketamine 0.5 mg/kg PO will receive an equivalent quantity of normal saline (placebo) via an intramuscular injection after ingesting oral ketamine, and those who are randomized to receive ketamine 0.5 mg/kg IM will receive their IM injection after ingesting an equivalent quantity of normal saline (placebo) orally. Orally administered ketamine and normal saline (placebo) will be mixed in cranberry juice immediately prior to being administered to the patient.

K-MaP will consist of 4 sessions of Meaning and Purpose (MaP) therapy and a single dose of ketamine on Day 0. Two MaP sessions will occur prior to ketamine therapy at least 2 days apart, the 1st session between Days -13 and -4, and the second session between Days -12 and -1. The two sessions of MaP after ketamine administration will occur on Days 3 (+/- 2 days) and 11 (+/- 2 days). All five intervention visits will be booked at the participant's baseline visit (see Study Schema).

3.2 Sample Size

We estimate an enrollment rate of 1-2 participants per month, for an enrollment period lasting 6 months. It is expected that approximately 50% of patients being referred to the study will meet eligibility criteria at the time of screening. The study team thus aims to screen 24 or more potential participants.

3.3 Eligibility Criteria

3.3.1 Inclusion Criteria

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

1. Must have a diagnosis of a stage 3 or 4 primary GI (i.e., pancreatic, colorectal, hepatocellular, biliary, and gastro-esophageal) cancer.
2. Must be willing to sign the informed consent form (ICF) and follow the study procedures as outlined in the ICF for the duration of the study.
3. Must be 18 years or older.
4. Must speak English and/or Spanish.
5. Must have a Palliative Performance Score (PPS v. 2.0) greater than or equal to 40%.
   Note: See Appendix 1.
6. Must be able to swallow liquid oral medication.

7. Must self-report moderate-to-severe demoralization (DS-II≥10 per Demoralization Scale-II) that is stable.
   Note: Stable is defined as DS-II ≥10/32 two times ≥7 days apart.
8. Must discontinue the following medications and refrain from taking them for the duration of study participation (participants who require these medications will be taken off study):
   a) Lamotrigine
   b) Clozapine
   c) PRN (as-needed) anxiolytics
      Note: Benzodiazepine use may be allowed if used in a regular, scheduled way. Consultation with the Principal Investigator is recommended.
   d) Dopamine agonists
   e) Lithium
9. Female-born participants of child-bearing potential with male-born partners must use highly effective contraception for at least 1 month prior to ketamine administration (on day 0) and agree to use such a method for an additional 2 months after ketamine administration.
10. Male-born participants with female-born partners of child-bearing potential must use highly effective contraception for at least 1 month prior to ketamine administration and agree to use such a method for an additional 2 months after ketamine administration.

    Note: Highly effective contraception include:
    - *Intrauterine device (IUD)*
    - *Intrauterine hormone-releasing system (IUS)*
    - *Non-oral hormonal methods, including injected, intravaginal, implanted, transdermal*
    - *Oral hormones plus a barrier contraception (condom, diaphragm, or spermicide)*
    - *Double barrier method (at least two of the following: condom, diaphragm, and spermicide)*
    - *Vasectomy*
    - *Abstinence from penile-vaginal intercourse**
      **The reliability of abstinence should be evaluated carefully with the participant in relation to their general lifestyle. An additional acceptable birth control method should be discussed with the participant in case they decide to engage in penile-vaginal intercourse during the course of the study.*

11. Must agree to the following lifestyle considerations:
    a) Continue receiving psychotherapy or other behavioral interventions for mental health as usual. Current interventions should not be stopped, and new interventions should not be started during the study period once participants are enrolled in the study.
    b) Consume no more than a modest quantity (e.g., 1 cup) of caffeine or xanthine-containing products (e.g., coffee or tea) the morning of receiving ketamine (on Day 0/Visit 4).
    c) Abstain from alcohol for 24 hours before receiving ketamine.
    d) Abstain from using any nicotine-containing products (including nicotine patches) for 3 hours before receiving ketamine.
    e) If cannabis products are used regularly, participants will be asked to continue using their regular amount but will be asked not to use cannabis within 24 hours prior to receiving ketamine.
    f) If prescribed a regular dose of benzodiazepines, will be asked not to take their medication the morning of the ketamine administration visit.
    g) If taking any psychostimulants (e.g., methylphenidate), will be asked not to take psychostimulant drugs (other than caffeine) the morning of the ketamine administration visit.
    h) Will be advised to maintain their usual opioid regimen.

Note: Input will be obtained from the participant's regular clinical providers on appropriate pain management for the participant during the study, particularly in the case of analgesics associated with adverse reactions of concern with ketamine (e.g., tramadol and any opioid may increase the risk of respiratory depression from ketamine).

3.3.2 Exclusion Criteria

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

1. Has a known allergic or severe reactions to the non-psychoactive components of liquid ketamine.
2. Has received treatment with another investigational drug or intervention within 1 month of signing Informed Consent Form (ICF).
3. If deemed by the clinical judgment of the study investigators to be unsafe for undergoing the intervention.
4. Has used ketamine within 5 years of signing ICF.
   Note: Ketamine used for anesthesia for medical procedures is permissible.
5. Has a lifetime use of ketamine for non-anesthetic purposes ≥10 times.
6. Has a history of intracerebral hemorrhage.
7. Has cognitive impairment sufficient to impede the ability to complete study tasks.
8. Has had delirium/encephalopathy within 3 months of signing ICF.
9. Has a history of intracranial hemorrhage.
10. Has had a stroke (embolic) within 12 months of signing ICF.
11. Has had a seizure within 6 months of signing ICF.
12. Currently has an intracranial mass (e.g., primary tumor or brain metastasis).
13. Has an advanced stage of a neurologic disease that puts patients at elevated risk for psychosis (e.g., Parkinson or Huntington disease).
14. Has a history of a primary psychotic disorder or primary bipolar disorder I or II (determined by QuickSCID-5).
15. Has a history of dissociative disorder.
16. Has active suicidal ideation with intent in the last 2 months (Suicidal ideation score ≥4 and Reason for ideation >1 on C-SSRS).
    Note: This does not include requesting medical aid in dying.
17. Is currently receiving electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS) or similar somatic therapies.
18. Has baseline hypertension (≥150 SBP or ≥90 DBP), after repeated measurements.
    Note: Participants with hypertension that has been controlled by medication down to <150 SBP and <90 DBP will be allowed to participate.
19. Has a history of aneurysmal vascular disease or dissection (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation.
20. Has had cardiac arrest within 12 months of signing ICF.
21. Has had a myocardial infarction within 12 months of signing ICF.
22. Has QTcf >480msec on 12-lead EKG.
    Note: Participants may qualify for the study if QTc 480-500 msec on one EKG, but then ≤480 msec on repeat EKG taken >1 day later. If QT-prolonging medications are started or increased in dose after enrollment and prior to ketamine administration, a repeat EKG must be done >12-hours after this change in order to assure continued safe enrollment in the trial.
23. Has clinically significant arrhythmia defined as:
    a) Ventricular fibrillation or ventricular tachycardia within 1 year of signing ICF
    b) Bradycardia, severe, within 1 year of signing ICF
       Note: Participants with pacemakers will be considered to be eligible at the discretion of the Principal Investigator.

c) Atrial fibrillation, without rate or rhythm control
d) Supraventricular tachycardia (SVT), without standard treatment
e) Other clinically significant arrhythmias (e.g., Wolf Parkinson White)

24. Has symptomatic congestive heart failure (NYHA Class II-IV)
25. Has severe obstructive intracardiac abnormalities (e.g., aortic stenosis)
26. Has any current condition where physical activity is associated with palpitations, anginal pain or syncope.
27. Is unable to protect their own airway due to dysphagia, difficulty swallowing, or a neurologic disease resulting in a risk of aspiration.
28. Has a history of flash pulmonary edema within 12 months of signing ICF.
29. Has a diagnosis of moderate or severe pulmonary hypertension.
30. Needs supplemental oxygen (intermittent or continuous).
31. Has current intractable nausea/vomiting/diarrhea.
32. Meets the following laboratory parameters:
    a) Asymptomatic ALT or AST ≥5x ULN.
    b) Symptomatic ALT or AST ≥2x ULN.
    c) Total bilirubin > 2x ULN [Gilbert syndrome is allowed]
    d) Alkaline phosphatase >5x ULN
    e) INR > 2.5 for patients with any history of cirrhosis or gastrointestinal bleeding within 6 months of signing ICF. (An INR measurement is otherwise not required).
    f) Renal insufficiency (i.e., eGFR < 30mL/min/1.73 m2 [using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation], CrCl < 30mL/min [using the Cockcroft-Gault Equation], or current dialysis)
33. Is currently pregnant or breastfeeding.
34. Has insulin-dependent diabetes with diabetes-related hospitalization within 6 months of signing ICF.

3.4 Inclusion and Recruitment of Women and Minorities

3.4.1 Eligibility of Women and Minorities

Individuals of any sex/gender, race, or ethnicity are eligible for this study.

The study recruitment strategy aims to achieve representation of minority groups that reflects the demographics of the affected population in the catchment area. This includes consideration of outreach programs to conduct or support recruitment of women and members of minority groups as participants and design of the clinical trial to include a valid analysis plan of whether variables being studied in the trial affect women or minority groups.

3.5 Inclusion Across the Lifespan

3.5.1 Age Range of Participants

Individuals ages 18 and over are eligible for this study. Children are excluded from the study because insufficient data on prospective benefits and/or adverse events for a treatment that includes potentially fatal risks poses unacceptable risk to children.

3.5.2 Study Design/Recruitment Considerations Related to Age Groups

The study design and recruitment strategy aim to achieve representation of age groups that reflect the demographics of the affected population. This includes adults aged 18 or older. GI cancers occur at any age but mostly in patients aged 60 or older. To maximize the generalizability of results,

enrollment should reflect the age distribution of the affected population who is likely to use the investigational drug(s) in clinical practice.

3.6 Duration of Treatment

Ketamine treatment will be given on Day 0. K-MaP therapy will continue from Day -13 to Day 14 (about 28 days) or until:

- Inter-current illness that prevents further administration of treatment;
- Unacceptable adverse event(s);
- Participant decides to withdraw from the study;
- Significant participant non-compliance with protocol;
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the investigator.

3.7 Duration of Follow Up

Participants will be followed for 35 days (+/- 2 days) after treatment with ketamine (on Day 0/Visit 4) or removal from the study, whichever occurs first. Participants removed from the study for unacceptable treatment- or study-related adverse event(s) will be followed until resolution or stabilization (as determined by the investigator), whichever occurs first.

3.8 Randomization Procedures

A total of 12 patients will be randomized on Day 0 at a 1:1 ratio to receive either 0.5 mg/kg of oral ketamine, or 0.5 mg/kg of IM ketamine. Randomization will be in block sizes of 4.

3.9 Primary Completion

Each individual will participate for at least 7 weeks (Day 35) plus [up to 4 weeks] from telephone screening to the baseline study visit (between Day -28 to -7). The expected primary completion date for a sample of 12 participants is 1.5 years after the study opens to accrual.

3.10 Study Completion

The expected on-study completion date is 1.5 years after the study opens to accrual.

4 Investigational Products

4.1 Description, Supply and Storage of Investigational Products

4.1.1 Ketamine

Classification
NMDA-receptor antagonist

Mechanism of Action
Ketamine is a nonselective, noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. The mechanism by which it exerts its antidepressant effect is unknown; a transient dissociative experience correlates with better depression outcomes. The major circulating metabolite norketamine demonstrated activity at the same receptor with less affinity.

Metabolism
Substrate of CYP2B6 (major), CYP2C19 (minor), CYP2C9 (minor), CYP3A4 (minor). Note: assignment of major vs. minor substrate states are based on clinically relevant drug interaction potential

Contraindications
Hypersensitivity to esketamine, ketamine, or any component of the formulation; aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation; history of intracerebral hemorrhage

Formulation, Appearance, Packaging, and Labeling
This study will use commercially available (non-diluted) ketamine (ideally, 50mg/mL - NDC 42023-114-10, manufactured by Par Pharmaceutical). However, if not available due to market inventory, we will substitute with a generic alternative or different concentration of commercially available product (i.e., ketamine 50mg/mL - NDC 0143-9508-10, manufactured by Hikma; ketamine 50mg/mL - NDC 55150-439-10, manufactured by AuroMedics Pharmaceuticals; ketamine 10mg/mL - NDC 42023-113-10, manufactured by Par Pharmaceutical; ketamine 10mg/mL - NDC 55150-438-10, manufactured by AuroMedics Pharmaceuticals; ketamine 100mg/mL - NDC 42023-115-10, manufactured by Par Pharmaceutical; ketamine 100mg/mL - NDC 0143-9509-10, manufactured by Hikma; or ketamine 100mg/mL - NDC - 55150-440-10, manufactured by AuroMedics Pharmaceuticals). Review the FDA approved package labeling for ketamine for more information.

Availability
Ketamine (Ketalar) is an FDA approved product. We will purchase it from AmerisourceBergen, a commercial distributor. If the Par Pharmaceutical formulation is not available, we will substitute with one of the other formulations available [redacted], as described above.

Storage and handling

Store at 20° to 25°C (68° to 77°F). Protect from light.
Review the FDA approved package labeling for ketamine (Ketalar) for more information.

Side Effects
Complete and updated adverse event information is available in the FDA approved package labeling for ketamine (Ketalar).

4.2 Accountability Records for Investigational Product(s)

The Principal Investigator and research team will be responsible for managing investigational product accountability records, including inventory logs, transfer forms, and usage logs in compliance with the UCSF Controlled Substances Program Manual:
[redacted]

After consulting with the UCSF Investigational Drug Service, it was determined that they will not be engaged in this trial due to the non-General Acute Care Hospital (GACH) setting of the study site.

4.3 Ordering Investigational Product

The Principal Investigator will obtain ketamine (Ketalar) directly from a commercial distributor, AmerisourceBergen. If not available through the commercial distributor due to inventory issues, the Principal Investigator has received approval from the Director of the Investigational Drug Pharmacy

Services at UCSF Health to obtain ketamine (Ketalar) through a transfer from the UCSF Parnassus Pharmacy as a DEA coincident activity for research purposes.

5 Treatment Plan

K-MaP will consist of 4 sessions of Meaning and Purpose (MaP) therapy and a single dose of ketamine on day 0. Two MaP sessions will occur prior to ketamine therapy, the 1st session between days -13 and -7, and the second session between days -12 to -1. The two sessions of MaP after ketamine administration will occur on days 3 (+/- 2 days) and 11 (+/- 3 days). MaP sessions may occur in-person at UCSF or via telehealth; however, we will strongly recommend that participants undergo at least one of the first two MaP sessions in-person when doing so is logistically feasible.

MaP is a manualized existential behavioral intervention, in which participants discuss their condition, their thoughts and feelings about their health and life, and are prompted to explore what brings meaning to their life. All MaP sessions and the ketamine administration visits will be video- and audio-recorded on a camcorder with a removable storage chip or PHI-compliant software (i.e., Zoom). The recordings on the chips will be downloaded onto encrypted external hard drives. The camcorders, chips, and hard drives will be stored in locked cabinets in a secure and locked room. The recordings will be securely uploaded to a dedicated UCSF Research Analysis Environment (RAE) workspace for analysis at a later date. Transcripts of recordings will be analyzed to assess treatment fidelity and qualitative assessment of the participant's subjective experiences. MaP sessions will not be billed to participants or their insurance.

After two MaP sessions, participants will receive ketamine on Day 0. This session will last about 4 hours. Participants will arrive to the Neurosciences Clinical Research Unit (NCRU) of the Sandler Building at UCSF Mission Bay, where they will be oriented to the treatment room for this study, which will contain a couch or bed for the participant to lie on in a private setting. Participants will hand over their shoes, keys, wallet, and phone to the study clinicians for safekeeping; these will all be returned to the participant upon completion of the treatment session. They will then complete all pre-randomization assessments described in Section 6 of this study protocol. The ketamine session will be audio and video recorded, but participants will have the option of requesting that the recording be paused momentarily if they wish to discuss matters that are too personal to be recorded. There will be an on-site study physician (MD or DO) with 1) experience in the management of psychiatric emergencies and 2) experience or certification in the management of cardiovascular emergencies. Ketamine, its administration, and the medication visit will be paid for by the study and will not be billed to participants or their insurance.

During the medication session, vital signs (heart rate and blood pressure) will be recorded at 10 minutes prior to ingestion of the oral solution ("Minute -10"), and then 30, 60, 90, 120, and 180 minutes after oral ingestion. If at 180 minutes blood pressure is meaningfully elevated compared to Minute -10, blood pressure will continue to be repeatedly assessed until it has returned to near its Minute -10 measurement. Respiratory rate and oxygen saturation will be assessed as needed.

In the event of elevated blood pressure prior to study drug administration

If the Minute -10 assessment (the mean of at least two readings separated by at least 2 minutes) of blood pressure exceeds either 140 systolic or 90 diastolic, periodic blood pressure readings will be obtained (e.g. at 5-minute intervals) to determine if the elevation may be temporary (e.g. due to anticipatory anxiety). If blood pressure decreases to (or below) 140 systolic and 90 diastolic within 20 minutes, study drug administration will proceed.

If blood pressure continues to exceed either 140 systolic or 90 diastolic, periodic blood pressure readings will be continued, and the study physician will be contacted. The study physician can authorize study drug administration if the study physician believes that it is safe to proceed and if the last two blood pressure readings do not exceed 155 systolic or 95 diastolic. The determination that it is safe to proceed requires that 1) the participant endorses currently feeling anxiety, 2) the participant is <70 years of age, 3) the participant's medical history is negative for stroke, myocardial infarction, heart failure, flash pulmonary edema. The study physician must regularly care for patients with serious medical illness and/or in acute care settings.

The participant will be randomized to ingest liquid ketamine 0.5mg/kg vs. an equivalent mL quantity of normal saline (placebo) mixed with cranberry juice (prepared by unblinded study staff) in a medication administration room located next door to the treatment room. At 10 minutes following oral ingestion of cranberry juice, while sitting in a wheelchair in the medication administration room, all participants will be administered an intramuscular injection (also prepared by unblinded study staff). The injection will be administered either by an RN, NP, or MD/DO involved in the study. Participants who received oral ketamine 0.5mg/kg will be administered normal saline via IM injection while those who received normal saline (placebo) in cranberry juice will receive ketamine 0.5 mg/kg IM. Following this injection, the participant (still in a wheelchair) will be rolled into the treatment room located across the hall from the medication administration room, where they will be supported by the therapy facilitators in transferring from the wheelchair to the couch and instructed to lie down wearing eyeshades and listening to a preselected music playlist via headphones or speakers. The participant will be instructed to focus their attention internally and to attempt to interact minimally with the two facilitators present in the room throughout the drug session. The facilitators will be as non-directive as possible in their interactions with the participant. In the event of a psychologically challenging experience such as significant anxiety or confusion, the facilitators will provide verbal reassurance and, when consented to prior to the session, supportive touch (e.g., brief handholding or hand-on-shoulder). Participants will have been instructed in the preparatory therapy session to notify the study therapists if during the treatment they feel anxiety or fear.

Facilitators will work in dyads (one Lead Facilitator and one Assistant Facilitator) and have licensure or clinical experience according to the following requirements, which the FDA has used for prior studies of medication-assisted talk therapy:

Lead Facilitator: Licensed to provide healthcare with professional training and clinical experience in psychotherapy. They must be licensed to practice independently. Acceptable professional credentials are limited to the following: clinical or counseling psychologist (PhD or PsyD), psychiatrist or other

physician (MD or DO), Master of Social Work (MSW), masters Licensed Clinical Professional Counselor (PCPC), or licensed Psychiatric Nurse Practitioner (Psychiatric NP).

Assistant Facilitator: Must have at least a bachelor's degree and at least one year of clinical experience in a licensed healthcare setting. Their clinical experience may have been in medical care, mental health care, or professional spiritual care (aka, chaplaincy).

In the event of a psychiatric emergency, verbal de-escalation and physical and/or chemical restraint will be used to maintain the safety of the participant and the facilitators, according to the clinical judgment of the on-call study physician. All reasonable efforts will be made to avoid using restraints of any kind. Participants will not be allowed to leave the premises until the drug effects have worn off.

In the event of a medical emergency, participants will be evaluated by the on-call study physician. At least one ACLS-certified study clinician will be on-site for all drug administrations. While expected to be rare, the most likely non-psychiatric serious adverse event to occur would be a hypertensive crisis. If a participant's blood pressure becomes grossly elevated (SBP >180mmHg, DBP >110mmHG) or unsafe (BP elevations with associated symptoms such as chest pain or shortness of breath), blood pressure will be rechecked immediately in both arms and the on-call physician will be notified if s/he is not already in the treatment room. If the participant is clinically suspected of being in hypertensive emergency (with signs of end-organ damage), then the participant will be transported to the nearest Emergency Department for further evaluation and treatment. If the participant is determined to be in hypertensive urgency (without clinical signs of end-organ damage), then blood pressure will be re-assessed with greater frequency while the study physician continues her/his evaluation for signs of clinical instability, and the study staff may attempt to calm the participant with verbal de-escalation, a short-acting blood pressure medication (e.g. clonidine), or an anxiolytic (e.g. lorazepam), as transient hypertension is often due to a challenging psychological experience. If after 30 minutes, the hypertensive urgency has not improved, the study physician will evaluate the need for transporting the participant to the Emergency Department for further evaluation and treatment.

In the case of acute chest pain, the on-call study physician will have available sublingual nitroglycerin to administer to the participant. An automated external defibrillator (AED) will be located in the building, but the goal will be to transport a decompensating patient to the Emergency Department prior to an AED becoming necessary.

As the drug effects begin to wear off at the 1.5-2-hour mark, the facilitators will engage the participant in a therapeutic interview (also video-recorded) to explore the experience. Patient-reported outcomes characterizing the Ketamine experience—the Mystical Experience Questionnaire (MEQ) and the Challenging Experience Questionnaire (CEQ)—will be obtained.
Trained study staff will administer the Columbia suicidality rating scale (C-SSRS) and the Heartbeat Detection (HBD) task. Only once participants are deemed to be free of the acute effects of ketamine, and after at least 3 hours have passed since ingestion of ketamine, will the participant be allowed to leave the premises in the company of a caregiver who has been instructed on how best to support the participant over the coming days.

The participant and caregiver will be given a study clinician's pager or work cell phone number in case of any clinical event off-site that needs further assessment. Participants must agree not to drive themselves home nor to drive later that same day after they arrive home. Participants will be instructed to write a detailed account of their experience as soon as possible over the following week.

Participants will be reminded well before the day of ketamine administration that a caregiver will need to take them to and from the 4-5-hour appointment. In the event that a participant did not arrange a friend/family member to accompany them home, the participant will be required to stay with the study

staff, will be encouraged to eat, and then the participant will be escorted outside by a study team member who will accompany the participant home in a taxi/Lyft/Uber. The taxi/Lyft/Uber fee will be paid for by the study.

5.1 Dosage and Administration

Treatment with ketamine will be administered on an outpatient basis, on Day 0/Visit 4.

This session will last about 4-5 hours. Participants will arrive to the Neurosciences Clinical Research Unit (NCRU) of the Sandler Building at UCSF Mission Bay, where they will be oriented to the treatment room for this study, which will contain a couch or bed for the participant to lie on in a private setting. Participants will hand over their shoes, keys, wallet, and phone to the study clinicians for safekeeping; these will all be returned to the participant upon completion of the treatment session. The session will be audio and video recorded for subsequent behavioral analysis and rating of clinician adherence to the trial protocol. Participants will have the option of requesting that the recording be paused momentarily if they wish to discuss matters that are too personal to be recorded. There will be an on-site study physician (MD or DO) with experience in the management of psychiatric emergencies and experience or certification in the management of cardiovascular emergencies. Ketamine, its administration, and the medication visit will be paid for by the study and will not be billed to participants or their insurance. The participant will be randomized to ingest liquid ketamine vs. an equivalent mL quantity of normal saline (placebo) mixed with cranberry juice (prepared by unblinded study staff) and then be administered an intramuscular injection (prepared by unblinded study staff) 10 minutes later. Participants who received oral ketamine 0.5mg/kg will be administered normal saline via IM injection while those who received normal saline (placebo) in cranberry juice will receive ketamine 0.5 mg/kg IM. Following this injection, participants will be moved from the medication administration room into the treatment room via wheelchair, transferred to the couch, and instructed to close their eyes while wearing eyeshades and listening to a preselected music playlist via headphones and speakers. The participant will be instructed to focus their attention internally and to attempt to interact minimally with the two facilitators, who will be present in the room throughout the drug session but will be as non-directive as possible in their interactions with the participant. In the event of a psychologically challenging experience such as significant anxiety or confusion, the facilitators will provide verbal reassurance and, when consented to prior to the session, supportive touch (e.g., brief handholding or hand-on-shoulder). Participants will have been instructed in the preparatory therapy session to notify the study therapists if during the treatment they feel anxiety or fear.

<u>Ketamine preparation</u>

On Day 0, an unblinded preparer will draw up a 0.5 mg/kg dose of liquid ketamine solution into a syringe. They will also draw up an equivalent mL quantity of normal saline in an identical syringe. Using a computer-generated randomization scheme, they will then mix either the liquid ketamine or normal saline solution into a cup of cranberry juice. This drug-cranberry juice admixture and the second syringe (containing either ketamine or saline solution) will then be handed to a blinded study therapist, who will administer the medications to the study participant.

Investigational Product	Premedication; precautions	Dose	Route	Schedule
Ketamine	N/A	0.5 mg/kg	Oral or Intramuscular	One dose, on Day 0/Visit 4

5.1.1 Rescue Medications

The study site will have rescue medications on-site for use, as needed, during the ketamine administration visit. Rescue medications will be obtained locally. The following rescue medications may be used:

- Benzodiazepine for acute, severe anxiety or agitation not relieved by verbal de-escalation.
- Lorazepam 1-2mg PO or Diazepam 5-10mg PO

- Olanzapine for acute, severe psychosis or agitation not relieved by verbal de-escalation.
- Zyprexa Zydis (olanzapine) 5-10mg SL
- Olanzapine 10mg vial (5mg/mL) IM

- Clonidine for hypertensive urgency not thought to be associated with anxiety.
- Clonidine 0.1-0.2mg PO

- Nitrogylcerin for acute angina pectoris.
- Nitroglycerin 0.4mg SL

- Ondansetron for nausea or vomiting and/or as pre-treatment 30-60 minutes prior to ketamine dosing for participants who report being prone to medication-induced nausea or who regularly experience nausea associated with pre-existing medical conditions.
- Ondansetron 4-8mg SL

Although the use of rescue medications is allowable to protect the safety and well-being of study participants and staff during the ketamine administration visit, the use of rescue medications is not expected to be necessary in this study. If used, the date and time of rescue medication administration as well as the name and dosage of the rescue medication must be recorded.

6 Study Procedures and Schedule of Events

Assessment Plan

Patient-reported outcomes of demoralization (DS-II), depression (PHQ-9), anxiety (GAD-7), Quality of Life (FACIT-Pal-14), pain (BPI-SF), and opioid use (<24hr morphine milligram equivalence (MME), will be obtained at baseline, immediately prior to randomization (on Day 0), and post-ketamine at follow-up assessments on days 7, 14, and 35. In addition, a patient-reported outcome of interoceptive awareness (MAIA-2) will be obtained once immediately prior to randomization (on Day 0) and post-ketamine at follow-up assessment on Day 7.

As an objective measure of cardiac interoceptive accuracy, an 8-minute heartbeat detection (HBD) task will be conducted with participants while measuring their peripheral physiology using electrocardiography (ECG), respiratory rate (RR) and skin conductance (SC) monitoring, twice on Day 0—once at least 15 minutes prior to dosing of the oral solution and a second time at least 3 hours following dosing of the oral solution.

Patient-reported outcomes characterizing the Ketamine experience—the Mystical Experience Questionnaire (MEQ) and the Challenging Experience Questionnaire (CEQ)—will be obtained on Day 0 after the medication effects have worn off (about 1.5-2 hours after Ketamine administration).

Clinician-rated outcomes of global clinical impression of severity (CGI-S), demoralization (DI), and mood symptoms (GRID-HAMD-6) will be assessed at baseline, immediately prior to randomization, and post-ketamine administration on days 14 and 35.

As a safety measure, the Columbia suicidality rating scale (CSSRS) will be given at every study visit (Visits 1-9, starting on Day -28 to Day 35). Trained study staff will assess the participant for onset or exacerbation of suicidal idealization or behavior. If at any time the participant is unwilling to continue the study, they will be allowed to stop (except while under the acute effects of study drug ketamine on Day 0/Visit 2). Support services from therapists and clinicians will be available to the participant at each study visit. The participant will continue receiving their regular medical care, separate from this study.

Patient-reported measures include:

- Demoralization Scale-II (DS-II): A well-validated self-report measure of demoralization [4]. This 16-item, 3-point scale has a 2-week recall period and produces a total score than can range 0-32, with higher scores indicating a greater degree of demoralization. It has also been validated for use with Spanish-speaking patients from both Spain and Latin America [5].
- Patient Health Questionnaire-9 (PHQ-9): A validated and widely-used 9-item, 4-point scale (0 = “Not at all” to 3 = “Nearly every day”) that assesses depression symptom severity with a 2-week recall period [74]. Higher scores indicate worse depression. The scale has also been validated in Spanish [75].
- General Anxiety Disorder-7 (GAD-7): A validated self-report measure for the severity of generalized anxiety disorder (GAD) symptoms. This 7-item, 4-point scale (0 = “Not at all” to “3 = Nearly every day”) scale has 2-week recall period. Item scores are summed to produce a total score that can range 0-21, with higher scores indicating greater severity of symptoms of GAD [76]. The measure has been validated in Spanish [77].
- Functional Assessment of Chronic Illness Therapy Palliative Care 14 Item Version (FACIT-Pal-14): A validated 14-item, self-report measure of quality of life in palliative care patients. The measure has a 7-day recall period and consists of 14-items with a 5-point Likert scale (0 = “Not at all” to 4 = “Very much”) [78]. The measure has good internal consistency with a single underlying latent variable [79], and has been validated for use with Spanish-speaking patients with advanced cancer [80].
- Brief Pain Inventory-Short Form (BPI-SF): A validated and widely-used self-report measure of pain over the last 24-hours in patients with and without cancer [81, 82]. This 15-item measure consists of a 4-item, 11-point subscale measuring pain intensity (Severity); a 7-item 10-point subscale measuring impact on functioning and well-being (Interference); 2 open-ended questions measuring location of pain and type of pain treatment used; and a single-item 11-point subscale measuring the effectiveness of treatment. The BPI-SF Spanish version has been validated for use with patients from Spain with cancer-related [83] and non-cancer-related pain [84].
- Morphine Milligram Equivalents (MME): Calculates the patient’s cumulative daily dose of opioids.
- Multidimensional Assessment of Interoceptive Awareness, Version 2 (MAIA-2): A validated a widely used questionnaire to measure interoceptive awareness [85]. This measure consists of 37-items using a 6-point Likert scale (0 = “Never” to 5 = “Always”). It has demonstrated good internal consistency and reliability for the evaluation of clinical mind-body interventions, with higher scores indicating increased.
- Heartbeat Detection (HBD) Task: Participant’s bodily physiology will be measured with a respiration belt, galvanic skin conductance (SC) sensors, and EKG sensors while they perform an 8-minute heart beating detection task. During the first two 2-minute blocks of this task, they will be instructed to press a button on a keyboard each time they hear a heartbeat on the

speaker. During the last two 2-miute blocks of this task, they will be instructed to press a button on a keyboard each time they think they are having a heartbeat. The physiological sensors are non-invasive and cause minimal discomfort. This task has been validated as a novel index of cardiac interoceptive accuracy [86, 87].

- Mystical Experience Questionnaire (MEQ): A validated self-report, 30-item, 6-point scale of mystical-type experiences, derived from surveys of subjective responses to psilocybin [88, 89]. Participants are asked to "please rate the degree to which at any time during that [medication] session you experienced the following phenomena;" each item is rated from 0 = "none; not at all" to 5 = "extreme (more than any other time in my life and stronger than 4)". The total score is calculated by the sum of all items. A higher score indicates a more mystical-type experience [90].
- Challenging Experience Questionnaire (CEQ): A validated 26-item self-report measure of challenging experiences with psychedelics, the CEQ assesses seven factors: grief (5 items), fear (6 items), subjective experience of death (2 items), insanity (3 items), isolation (3 items), physical distress (5 items), and paranoia (2 items). Each of the 26 items is scored on a 5-point Likert scale (0 = "None; not at all" to 5 = "Extreme [more than ever before in my life]"), with participants asked to "please rate the degree to which at any time during that [medication] session you experienced the following phenomena." A higher total CEQ score indicates greater psychologically adverse reactions to psilocybin [91].

Participants may complete these measures on an electronic tablet (using a REDCap survey) or by paper and pencil, whichever is their preference. In the event the participant opts for a telehealth visit, the study team may email the participant a link to the REDCap survey. Some visits must be in-person (see Study Calendar in Section 6.1 for more details).

Clinician-rated outcomes include:

- The Clinical Global Impressions Scale (CGI): The CGI is a widely-used 3-item clinician-administered measure developed by the NIMH to assess clinical change in patients in psychopharmacology trials [92]. The scale has previously been modified to detect clinical change in specific populations [93, 94]. In this trial we use the Global Impression of Severity item ("Considering your total clinical experience with patients with demoralization, how would you rate this participant's level of demoralization at this time?"), on the scale from "1 = Normal, not at all demoralized" to "7 = Among the most extremely demoralized patients" to assess specifically for change in demoralization as a secondary endpoint.
- Demoralization Interview (DI): A clinician-administered, 14-item structured interview designed from items of the Demoralization Scale-II [95, 96]. The DI has demonstrated good reliability and validity, with a threshold of 6 symptoms supporting a diagnosis of demoralization.
- GRID Hamilton Depression Rating Scale 6 (GRID-HAMD-6): The 6-item Hamilton Depression Rating Scale (HAMD-6) is a validated, brief, clinician-rated measure of the core symptoms of major depression [97, 98]. The measure is highly sensitive to change in pharmacotherapy trials. The GRID version of the Hamilton Depression scale is a structured and highly reliable version of the classic Hamilton Depression scale [99-101]. With permission from the owner of the GRID-HAMD, the International Society for CNS Drug Development, we will use the 6-items of the HAMD-6 in the GRID-HAMD format to create a brief, responsive and reliable measure of core depression symptoms for this trial.
- Columbia Suicidality Severity Rating Scale (C-SSRS): A validated 17-item scale that assesses suicidal ideation and behavior according to the Columbia Classification Algorithm for Suicide Assessment (C-CASA) [102]. The C-SSRS is made up of ten categories, consisting of binary responses (yes/no), to indicate presence or absence of suicidal ideation or behavior (e.g., Wish to be Dead or Aborted Attempt). A numerical score for the C-SSRS is obtained from the aforementioned categories. A validated version of the C-SSRS exists in Spanish [103].

The clinician may complete their assessment in-person or over video conference/phone if the participant opts for a telehealth visit.

On Day 35, the last visit day, participants will be interviewed on the acceptability and tolerability of K-MaP. This interview will be audio-recorded and conducted with study staff, either via phone/teleconference or in-person, depending on participant preference.

The study-specific procedures and assessments are detailed in this section and outlined in the Study Calendar – Section 6.1.

6.1 Study Calendar

	≥7, ≤28 days before Enrollment	Day -28 to -7	Day -13 to -4	Day -12 to -1	Day 0	Day 3 +/- 2 days	Day 7 +/- 2 days	Day 11 +/- 2 days	Day 14 +/-2 days	Day 35 +/- 2 days
	Phone Screening	V1 [Enrollment/ Baseline]	V2 [MaP Session 1]	V3 [MaP Session 2]	V4 [Randomization/ Ketamine]	V5 [MaP Session 3]	V6	V7 [MaP Session 4]	V8	V9
Verbal Waiver of Consent; Phone Screen	x									
Informed Consent Form		x								
Brief Clinical Interview[1]		x			x					
Interview on Acceptability and Tolerability										x
Demographics		x								
C-SSRS		x	x	x	x	x	x	x	x	x
Physical exam		x								
Vitals (BP, HR)[2]		x			x					

1 Partcipants will be briefly interviewed by the study team at baseline. The baseline interview will asses for clinical fit for K-MaP by evaluating participant expectations and prior experiences of altered states of consciousness . On Day 0/Visit 4, around 1.5-2 hours after ketamine administration (when the drug effects wear off), the facilitators will engage the participant in a therapeutic interview to explore the experience they had. The Day 0/Visit 4 interview will be video and audio recorded.

2 Vitals will be taken at baseline, and prior to ketamine administration on Day 0/Visit 4. On Day 0, vital signs (heart rate and blood pressure) will be recorded at 10 minutes prior to drug ingestion (“Minute -10”), and then 30, 60, 90, 120, and 180 minutes after drug ingestion. If at 180 minutes blood pressure is meaningfully elevated compared to Minute -10, blood pressure will continue to be repeatedly assessed until it has returned to near its Minute -10 measurement. Respiratory rate and oxygen saturation will be assessed as needed.

	≥7, ≤28 days before Enrollment	Day -28 to -7	Day -13 to -4	Day -12 to -1	Day 0	Day 3 +/- 2 days	Day 7 +/- 2 days	Day 11 +/- 2 days	Day 14 +/-2 days	Day 35 +/- 2 days
	Phone Screening	V1 [Enrollment/ Baseline]	V2 [MaP Session 1]	V3 [MaP Session 2]	V4 [Randomization/ Ketamine]	V5 [MaP Session 3]	V6	V7 [MaP Session 4]	V8	V9
Height and Weight		x								
Medical/Psychiatric Hx		x								
PPSv2		x								
Eligibility Verification		x								
Randomization					x					
LFTs, Creatinine, Electrolytes, PT/INR[3]		x								
12-lead EKG[4]		x								
DS-II[5]	x	x			x		x		x	x

3 The following laboratory tests are required at baseline:

- Electrolytes: Sodium, potassium, carbon dioxide, and chloride.
- Liver function tests: Total bilirubin, ALT, AST, and alkaline phosphatase.
- Cogulation tests: PT/INR (for patients with a history of cirrhosis or GI bleed within past 6 months)
- Renal function: Creatinine.

4 EKG is required at baseline.

5 DS-II will be measured two times before enrollment. Once over the phone after verbal waiver of consent, and tagain, ≥7 days apart, after the participant has signed the informed consent form and started screening procedures. DS-II will also be measured at Visits 4 (before Ketamine administration), 6, 8, and 9.

	≥7, ≤28 days before Enrollment	Day -28 to -7	Day -13 to -4	Day -12 to -1	Day 0	Day 3 +/- 2 days	Day 7 +/- 2 days	Day 11 +/- 2 days	Day 14 +/-2 days	Day 35 +/- 2 days
	Phone Screening	V1 [Enrollment/ Baseline]	V2 [MaP Session 1]	V3 [MaP Session 2]	V4 [Randomization/ Ketamine]	V5 [MaP Session 3]	V6	V7 [MaP Session 4]	V8	V9
PHQ9, GAD7, BPI-SF, <24hr MME,		x			x		x		x	x
MAIA-2					x		x			
FACIT-Pal14		x			x		x		x	x
CGI-S, DI, GRID-HAMD6		x							x	x
MEQ, CEQ					x					
MaP Therapy Session[6]			x	x		x		x		
Ketamine therapy (day of administration)[7]					x					
HBD Task[8]					x					

6 It will be recommended that att least one MaP session prior to Day 0/Visit 4 occur in-person (i.e., MaP sessions on Visit 2 or 3)..

7 The ketamine administration visit will last approximately 4-5 hours. Patients will leave the premises once they are deemed to be free of the acute effects of ketamine, at least 3 hours have passed since ingestion of the oral drug-cranberry juice solution, and the study team confirms they are in the presence of a caregiver. In the event that a participant did not arrange a caregiver to accompany them home, the participant will be required to stay with the study staff and will be escorted outside by a study team member who will accompany them home in a taxi, Lyft, or Uber.

8 The Heartbeat Detection (HBD) task will be administered by a trained provider twice on the day of ketamine dosing. The tasks takes about 8 minutes to complete and will administered once a least 15 minutes prior to receipt of the oral drug-cranberry juice solution and again at least 3 hours after receipt of this oral solution.

	≥7, ≤28 days before Enrollment	Day -28 to -7	Day -13 to -4	Day -12 to -1	Day 0	Day 3 +/- 2 days	Day 7 +/- 2 days	Day 11 +/- 2 days	Day 14 +/-2 days	Day 35 +/- 2 days
	Phone Screening	V1 [Enrollment/ Baseline]	V2 [MaP Session 1]	V3 [MaP Session 2]	V4 [Randomization/ Ketamine]	V5 [MaP Session 3]	V6	V7 [MaP Session 4]	V8	V9
Concomitant Meds.		x	x	x	x	x	x	x	x	x
Adverse Events			x	x	x	x	x	x	x	x

7 Participant Registration

A verbal waiver of consent will be obtained to collect only information essential for the screening call that will be conducted by phone or teleconference.

At the Enrollment study visit (Visit 1), a written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All participants consented to the study will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

7.1 Use of Concomitant Medications

The use of the medications listed below are not exclusionary in and of itself; rather their use will be evaluated by the Principal Investigator, treating physician, and/or a pharmacist on a case-by-case basis.

- Participants receiving chemotherapy or immunotherapy should be receiving a regimen that will allow them to schedule their Ketamine session (Day 0/Visit 4) at least 5-7 days after the end of a treatment cycle and at least 5-7 days before the beginning of the next treatment cycle.
- NMDA receptor antagonists (e.g., memantine, amantadine, dextromethorphan, methadone)
- Chronic benzodiazepine use can be continued as a stable, scheduled regimen, except for the morning of the ketamine administration visit (Day 0/Visit 4)
- Chronic antidepressant and serotonergic supplement use can be continued as a stable, scheduled regimen
- Drugs that may increase the risk of hypertension and tachycardia (e.g., levothyroxine, monoamine oxidase inhibitors [MAOIs]) [104, 105]
- Drugs that may increase the risk of seizures (e.g., metrizamide, theophylline and bupropion)
- Drugs that may increase the risk of neuromuscular blockade (e.g., atracurium and tubocurarine)
- Inhibitors or inducers of CYP 2B6, 2C9, 3A4 (e.g., clopidogrel and ticlopidine)**

**Cytochrome P450 Inhibitors and Inducers
After careful consideration, participants may qualify for the trial if they are taking medications that are inhibitors or inducers of CYP 2B6, 2C9, or 3A4. Drug-drug interactions will be assessed against the evidence for the strength of the interaction using peer-reviewed literature (e.g., Flockhart Table https://drug-interactions.medicine.iu.edu/MainTable.aspx), and the participant's medical status, co-morbidities, and concomitant medications will be taken into consideration.

7.2 Dietary Restrictions

Participants will be asked to adhere to the following guidelines before receiving their ketamine dose (on Day 0/Visit 4):

- Consume no more than a modest quantity (e.g., 1 cup) of caffeine or xanthine-containing products (e.g., coffee or tea)
- Abstain from nicotine for at least 3 hours before ketamine administration
- Abstain from alcohol and any other non-prescribed substances for 24 hours before receiving ketamine

- If cannabis products are used regularly, participants will be asked to maintain their regular amount but will be asked not to use cannabis within 24 hours prior to receiving ketamine.

7.3 Prohibited Medications

The medications below may not be used during the study. If participants require these medications, they will be taken off-study (except for when anxiolytics as rescue medications ar used during the ketamine medication visit on Day 0/Visit 4).

- Anxiolytics, as needed
- Lithium

7.4 Evaluation of Safety

The safety parameters for this study include all laboratory tests, physical findings, and spontaneous reports of adverse events reported to the investigator by participants.

Safety will be assessed according to the NCI CTCAE version 5.0.

Safety analyses will be performed for all participants who receive ketamine treatment in the trial (V2).

8 Safety Parameters

8.1 Definitions

8.1.1 Adverse Event (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.1.2 Serious Adverse Event (SAE)

An adverse event is considered *serious* if, in the view of either the investigator or Sponsor-Investigator, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
    - An adverse event is considered life-threatening if, in the view of either the investigator or Sponsor-Investigator, its occurrence places the participant at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.1.3 Unanticipated Problem (UP)

An unanticipated problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2) related or possibly related to participation in the research; and

3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

Only a small subset of adverse events occurring in human subjects participating in research will meet these three criteria for an unanticipated problem. Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

8.2 Classification of Adverse Events

8.2.1 Severity

Adverse events are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

8.2.2 Attribution

Following expert guidance in adverse event assessment [106] and reporting [107], all serious adverse events (SAEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. However, relatedness to study intervention will not be assessed for non-serious adverse events (AEs). The degree of certainty about causality for SAEs will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The SAE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the SAE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the SAE. In summary, the SAE is more likely related to the study intervention than to other causes.
- **Unrelated** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study

intervention and event onset, or an alternate etiology has been established. In summary, the SAE is more likely related to other causes than to the study intervention.
- **Unknown** – It is equally likely that the SAE is related to the study intervention as to other causes.

8.2.3 Expectedness

An adverse event is considered unexpected if the nature, severity, or frequency of the event is not listed in the study protocol, product inserts, investigator brochure or informed consent document.

8.3 Recording of Adverse Events

Refer to the Data Safety Monitoring Plan, located in Appendix 2.

8.4 Expedited Reporting

8.4.1 Reporting to the HDFCCC Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the UCSF PI or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

8.4.2 Reporting to Institutional Review Board

The UCSF PI must report events to the IRB according to institutional guidelines.

8.4.3 Expedited Reporting to the FDA

If the study is being conducted under an IND, the Sponsor (or the Sponsor-Investigator) is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with federal regulations (21 CFR §312.32).

The Sponsor (or Sponsor-Investigator) must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor needs to ensure that the event meets all three definitions:

- Suspected adverse reaction
- Unexpected
- Serious

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

8.5 Follow-up of Adverse Events

All participants who experience adverse events will be followed with appropriate medical management until resolved or stabilized, as determined by the investigator. For selected adverse events for which administration of the study drug/intervention was stopped, a re-challenge of the subject with the study drug/intervention may be conducted if considered both safe and ethical by the investigator.

8.6 Adverse Events Monitoring

Refer to the Data Safety Monitoring Plan, located in Appendix 2.

9 Statistical Considerations and Evaluation of Results

9.1 Sample Size Considerations

9.1.1 Sample Size and Power Estimate

No formal power analysis was conducted, and no formal tests of efficacy will be conducted. This N=12 pilot study has a sample size sufficient for assessing the feasibility and preliminary safety of a novel behavioral-pharmaceutical intervention, at two different dose levels and routes of administration of the study drug.

If the 0.5mg/kg PO dose of ketamine is well-tolerated (i.e., zero treatment-related SAEs) and demonstrates mean clinical improvement in demoralization assessed by DS-II that endures beyond 7 days post-drug, then this would suggest a fully powered study is warranted using the 0.5mg/kg PO dose.

If the 0.5mg/kg IM dose of ketamine is well-tolerated (i.e., zero treatment-related SAEs) and demonstrates mean clinical improvement in demoralization assessed by DS-II that endures beyond 7 days post-drug, then this would suggest a fully powered study is warranted using the 0.5mg/kg IM dose.

If the either dose is well-tolerated and fails to demonstrate mean clinical improvement in demoralization assessed by DS-II that endures beyond 7 days post-drug, then this would suggest that the dose is an appropriate control for other psychoactive investigational drugs whose clinical effects are expected to have greater durability.

9.1.2 Randomization

Participants will be randomized 1:1, without stratification, in block sizes of 4.

9.1.3 Accrual Estimates

We estimate an enrollment rate of 1-2 participants per month, for an enrollment period lasting 6 months. It is expected that approximately 50% of patients being referred to the study will meet eligibility criteria at the time of screening. The study team thus aims to screen approximately 24 or more potential participants.

9.2 Analyses Plans

9.2.1 Population for Analysis

Descriptive analyses will be prepared based on the Modified Intention-to-Treat study populations, including all participants who received a dose of either oral or intramuscular ketamine on Day 0 (at 0.5 mg/kg).

9.2.2 Primary Analysis (or Analysis of Primary Endpoints)

The primary objective of this pilot study is to assess the feasibility and preliminary safety of administering Meaning and Purpose therapy combined with oral vs. intramuscular ketamine (K-MaP) in demoralized patients with stage 3 or 4 GI cancers (i.e., pancreatic, colorectal, hepatocellular, biliary, or gastro-esophageal). Pre-determined criteria for success of feasibility include:

- A recruitment rate of 50% among referred/screened participants and those ultimately found to be fully eligible and enrolled in the study.
- Completion rates of (i) 75% for participation in 4 Meaning and Purpose therapy sessions and (ii) 80% of 5 on-study DS-II assessments (Visits 1, 4, 6, 8, and 9), in addition to receipt of ketamine.
- Qualitative assessment of clinician fidelity to manualized K-MaP intervention.
- Qualitative assessment of acceptability of the intervention and assessments by participants at the end of the study, with at least 60% of included participants completing this assessment.

9.2.3 Secondary Analysis (or Analysis of Secondary Endpoints)

Secondary Objective #1: To characterize the preliminary safety and tolerability of K-MaP in patients with stage 3 or 4 GI cancers (i.e., pancreatic, colorectal, hepatocellular, biliary, or gastro-esophageal), we will analyze:

- Rates and types of adverse events (AEs), unexpected AEs, and serious AEs will be summarized by arm. Pre-determined criteria for assessment of tolerability to K-MaP include zero treatment-related serious adverse events.
- Across each study arm, changes in individual participant and mean heart rate (HR), systolic (SBP) and diastolic blood pressure (SBP) measurements from 10 minutes prior to ingestion of the oral solution to 30, 60, 90, 120, and 180 minutes post-oral ingestion, using random effects models that account for correlated outcomes within participants. The below thresholds will be used as indications of potential concern for patient safety. These estimates have been determined on the basis of established human safety thresholds and findings from a recent meta-analysis of hemodynamic responses to sub-anesthetic ketamine doses in patients with psychiatric conditions.[109]
    - An increase in HR baseline of greater than 25 BPM in any patient
    - An increase in SBP of greater than 40 mm Hg in any patient
    - An increase in DBP of greater than 25 mm Hg in any patient

- Mean CEQ scores on the day of ketamine administration will be compared between the two study arms using ANCOVA models, discussed in the next objective.

Secondary Objective #2: To assess the magnitude and durability of improvement from randomization in psychosocial distress associated with K-MaP, we will measure mean trends in patient-reported outcomes (DS-II, PHQ9, GAD7, FACIT-PAL-14 scores) in each study arm from baseline visit (Day -28 to -7) to post-ketamine (on Days 7, 14, and 35). In addition, we will calculate the proportion of participants per arm who no longer meet criteria for moderate-to-severe demoralization (i.e., DS-II > 10) post-ketamine. We will also measure mean trends in clinician-rated outcomes (CGI-S, DI, and GRID-HAMD-6 scores) per arm as above. ANCOVA models of follow-up endpoints as a function of study arm, adjusted for endpoints at baseline and randomization, will be conducted [110]. ANCOVA results will be presented graphically via mean trends per arm overlaid on individual trends, and via the mean (95% CI) difference between arms at Day 35. Cohen's d will be calculated at each follow-up time to estimate effect sizes. Any missing data will be estimated through the use of single imputation with baseline observations carried forward.

Secondary Objective #3: We will evaluate BPI-SF scores analogously to DS-II scores.

Secondary Objective #4: We will evaluate opioid analgesia use analogously to DS-II scores.

Secondary Objective #5: We will be using pair t-tests to measure mean changes in MAIA-2 scores in each study arm from prior to ketamine administration (on Day 0) to post-ketamine (on Day 7).

Secondary Objective #6: To assess how participants' subjective experiences with ketamine may be related to clinical outcomes, subjective reports of each participant's ketamine experience (videorecorded from Day 0) will be transcribed, inductively coded, and qualitatively analyzed to identify phenomenological content. In addition, participant MEQ and CEQ scores, which provide summary measures of the intensity of ketamine's acute effects, will be evaluated for potential correlation with trends in DS-II, BPI-SF, and opioid use.

Secondary Objective #7: To assess how participants' changes in measures of cardiac interoceptive accuracy may be related to subjective experiences with ketamine, we will assess for correlations between changes in scores on the Heartbeat Detection (HBD) task following the receipt of ketamine (measured pre- and post-dosing on Day 0) and MEQ scores (measured post-dosing on Day 0). We will also evaluate for potential correlation of changes in HBD task scores following receipt of ketamine with post-intervention trends in MAIA-2, DS-II, BPI-SF, and opioid use.

9.3 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the PI will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to participants before any protocol-related procedures are performed on any participants.

The PI must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed, or the FDA has determined that the study is exempt from IND requirements.

9.4 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant-facing materials related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the IRB of record. Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review and Monitoring Committee (PRMC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.5 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB -approved informed consent form prior to participation in any study-specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.6 Changes in the Protocol

Once the protocol has been approved by the IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the PI and approved by PRMC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to participants, an amendment may be implemented prior to IRB approval. In this circumstance, however, the PI must then notify the IRB according to institutional requirements.

9.7 Handling and Documentation of Clinical Supplies

The PI will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs at the site. The date, quantity and batch or code number of the drug, and the identification of participants to whom the investigational product has been dispensed by participant number and initials will be included.

The PI shall not make the investigational drug available to any individuals other than to qualified study participants. Furthermore, the PI will not allow the investigational product to be used in any manner other than that specified in this protocol.

9.8 Case Report Forms (CRFs)

The PI and/or designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study-specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. Study personnel will complete the CRFs; the PI will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the participant's medical records maintained by study personnel. All source documentation should be kept in separate research files for each participant.

In accordance with federal regulations, the PI is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

The PI will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the PI and the trial statistician.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

9.9 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring/auditing entity for this study. The UCSF DSMC will monitor or audit the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and serious adverse events (SAEs). The DSMC will review study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC monitoring/auditing review will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 2 - Data and Safety Monitoring Plan.

9.10 Record Keeping and Record Retention

The PI is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The PI is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

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

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

In accordance with FDA regulations, the PI shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication until 2 years after the investigation is discontinued and FDA is notified.

9.11 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the Sponsor-Investigator and collaborators.

10 References

1. Kissane, D.W., et al., *Meaning and Purpose (MaP) therapy II: Feasibility and acceptability from a pilot study in advanced cancer.* Palliat Support Care, 2019. **17**(1): p. 21-28.
2. Robinson, S., et al., *A Review of the Construct of Demoralization: History, Definitions, and Future Directions for Palliative Care.* Am J Hosp Palliat Care, 2016. **33**(1): p. 93-101.
3. Kissane, D.W., D.M. Clarke, and A.F. Street, *Demoralization syndrome--a relevant psychiatric diagnosis for palliative care.* J Palliat Care, 2001. **17**(1): p. 12-21.
4. Robinson, S., et al., *Refinement and revalidation of the demoralization scale: The DS-II-internal validity.* Cancer, 2016. **122**(14): p. 2251-9.
5. Belar, A., et al., *Multicenter Study of the Psychometric Properties of the New Demoralization Scale (DS-II) in Spanish-Speaking Advanced Cancer Patients.* J Pain Symptom Manage, 2019. **57**(3): p. 627-634.
6. Siegel, R.L., et al., *Cancer statistics, 2022.* CA: A Cancer Journal for Clinicians, 2022. **72**(1): p. 7-33.
7. Jemal, A., et al., *Cancer statistics, 2008.* CA Cancer J Clin, 2008. **58**(2): p. 71-96.
8. Ushio, J., et al., *Pancreatic Ductal Adenocarcinoma: Epidemiology and Risk Factors.* Diagnostics (Basel), 2021. **11**(3).
9. Zabora, J.R., et al., *The prevalence of psychological distress by cancer site.* Psycho-Oncology, 2001. **10**.
10. Mehnert, A., et al., *Four-week prevalence of mental disorders in patients with cancer across major tumor entities.* J Clin Oncol, 2014. **32**(31): p. 3540-6.
11. Akizuki, N., et al., *Prevalence and predictive factors of depression and anxiety in patients with pancreatic cancer: a longitudinal study.* Jpn J Clin Oncol, 2016. **46**(1): p. 71-7.
12. Boyd, C.A., et al., *The effect of depression on stage at diagnosis, treatment, and survival in pancreatic adenocarcinoma.* Surgery, 2012. **152**(3): p. 403-13.
13. Turaga, K.K., et al., *Suicide in patients with pancreatic cancer.* Cancer, 2011. **117**(3): p. 642-647.
14. Misono, S., et al., *Incidence of suicide in persons with cancer.* J Clin Oncol, 2008. **26**(29): p. 4731-8.
15. Carvajal, G., *Pancreatic Cancer Related Pain: Review of Pathophysiology and Intrathecal Drug Delivery Systems for Pain Management.* Pain Physician, 2021. **24**(5): p. E583-E594.
16. Aman, M.M., et al., *The American Society of Pain and Neuroscience (ASPN) Best Practices and Guidelines for the Interventional Management of Cancer-Associated Pain.* J Pain Res, 2021. **14**: p. 2139-2164.
17. Carmichael, A.N., L. Morgan, and E. Del Fabbro, *Identifying and assessing the risk of opioid abuse in patients with cancer: an integrative review.* Subst Abuse Rehabil, 2016. **7**: p. 71-9.
18. Barlass, U., et al., *Opioid use as a potential risk factor for pancreatic cancer in the United States: An analysis of state and national level databases.* PLoS One, 2021. **16**(1): p. e0244285.
19. Suarez-Roca, H., et al., *Contribution of Baroreceptor Function to Pain Perception and Perioperative Outcomes.* Anesthesiology, 2019. **130**(4): p. 634-650.
20. Critchley, H.D. and S.N. Garfinkel, *Interoception and emotion.* Curr Opin Psychol, 2017. **17**: p. 7-14.
21. Avery, J.A., et al., *Major depressive disorder is associated with abnormal interoceptive activity and functional connectivity in the insula.* Biol Psychiatry, 2014. **76**(3): p. 258-66.
22. Robinson, S., et al., *Refinement and revalidation of the demoralization scale: The DS-II—external validity.* Cancer, 2016. **122**(14): p. 2260-2267.

23. Robinson, S., et al., *Refinement and revalidation of the demoralization scale: The DS-II—internal validity.* Cancer, 2016. **122**(14): p. 2251-2259.
24. Kissane, D.W., D.M. Clarke, and A.F. Street, *Demoralization syndrome—a relevant psychiatric diagnosis for palliative care.* Journal of palliative care, 2001. **17**(1): p. 12-21.
25. Robinson, S., et al., *A systematic review of the demoralization syndrome in individuals with progressive disease and cancer: a decade of research.* J Pain Symptom Manage, 2015. **49**(3): p. 595-610.
26. Bovero, A., et al., *Exploring demoralization in end-of-life cancer patients: Prevalence, latent dimensions, and associations with other psychosocial variables.* Palliat Support Care, 2019. **17**(5): p. 596-603.
27. Ignatius, J. and R. De La Garza, 2nd, *Frequency of demoralization and depression in cancer patients.* Gen Hosp Psychiatry, 2019. **60**: p. 137-140.
28. Caruso, R., et al., *Depressive spectrum disorders in cancer: prevalence, risk factors and screening for depression: a critical review.* Acta Oncol, 2017. **56**(2): p. 146-155.
29. Juliao, M., B. Nunes, and A. Barbosa, *Prevalence and factors associated with demoralization syndrome in patients with advanced disease: Results from a cross-sectional Portuguese study.* Palliat Support Care, 2016. **14**(5): p. 468-73.
30. Mehnert, A., et al., *Demoralization and depression in patients with advanced cancer: validation of the German version of the demoralization scale.* J Pain Symptom Manage, 2011. **42**(5): p. 768-76.
31. Fang, C.K., et al., *A correlational study of suicidal ideation with psychological distress, depression, and demoralization in patients with cancer.* Support Care Cancer, 2014. **22**(12): p. 3165-74.
32. Vehling, S., et al., *The association of demoralization with mental disorders and suicidal ideation in patients with cancer.* Cancer, 2017. **123**(17): p. 3394-3401.
33. Robinson, S., et al., *A systematic review of the demoralization syndrome in individuals with progressive disease and cancer: A decade of research.* J Pain Symptom Manage, 2015. **49**: p. 595–610.
34. Mangelli, L., et al., *Assessing demoralization and depression in the setting of medical disease.* The Journal of clinical psychiatry, 2005. **66**(3): p. 0-0.
35. Caruso, R., et al., *Depressive spectrum disorders in cancer: prevalence, risk factors and screening for depression: a critical review.* Acta Oncologica, 2017. **56**(2): p. 146-155.
36. Gan, L.L., S. Gong, and D.W. Kissane, *Mental state of demoralisation across diverse clinical settings: A systematic review, meta-analysis and proposal for its use as a 'specifier' in mental illness.* Australian & New Zealand Journal of Psychiatry, 2021: p. 00048674211060746.
37. Ignatius, J. and R. De La Garza II, *Frequency of demoralization and depression in cancer patients.* General Hospital Psychiatry, 2019. **60**(Sep -Oct): p. 137-140.
38. Liu, J.-Y., et al., *Demoralization and depression in pancreatic cancer patients.* Journal of Clinical Oncology, 2020. **38**(4_suppl): p. TPS778-TPS778.
39. Bauereiß, N., et al., *Effects of existential interventions on spiritual, psychological, and physical well-being in adult patients with cancer: Systematic review and meta-analysis of randomized controlled trials.* Psycho-oncology, 2018. **27**(11): p. 2531-2545.
40. Park, C.L., et al., *Effects of psychosocial interventions on meaning and purpose in adults with cancer: A systematic review and meta-analysis.* Cancer, 2019. **125**(14): p. 2383-2393.
41. Breitbart, W., et al., *Individual meaning-centered psychotherapy for the treatment of psychological and existential distress: a randomized controlled trial in patients with advanced cancer.* Cancer, 2018. **124**(15): p. 3231-3239.

42. Kissane, D.W., et al., *Meaning and Purpose (MaP) therapy II: Feasibility and acceptability from a pilot study in advanced cancer.* Palliative & Supportive Care, 2019. **17**(1): p. 21-28.
43. Rodin, G., et al., *Managing Cancer and Living Meaningfully (CALM): A randomized controlled trial of a psychological intervention for patients with advanced cancer.* Journal of Clinical Oncology, 2018. **36**(23): p. 2422.
44. Thase M, C.K., *Ketamine and esketamine for treating unipolar depression in adults: Administration, efficacy, and adverse effects.* UpToDate, Inc, 2022.
45. Fond, G., et al., *Ketamine administration in depressive disorders: a systematic review and meta-analysis.* Psychopharmacology (Berl), 2014. **231**(18): p. 3663-76.
46. Xu, Y., et al., *Effects of Low-Dose and Very Low-Dose Ketamine among Patients with Major Depression: a Systematic Review and Meta-Analysis.* Int J Neuropsychopharmacol, 2016. **19**(4).
47. Balzer, N., et al., *Low-dose Ketamine For Acute Pain Control in the Emergency Department: A Systematic Review and Meta-analysis.* Acad Emerg Med, 2021. **28**(4): p. 444-454.
48. Wilkinson, S.T., et al., *The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation: A Systematic Review and Individual Participant Data Meta-Analysis.* Am J Psychiatry, 2018. **175**(2): p. 150-158.
49. Goldman, N., M. Frankenthaler, and L. Klepacz, *The Efficacy of Ketamine in the Palliative Care Setting: A Comprehensive Review of the Literature.* J Palliat Med, 2019. **22**(9): p. 1154-1161.
50. Iglewicz, A., et al., *Ketamine for the treatment of depression in patients receiving hospice care: a retrospective medical record review of thirty-one cases.* Psychosomatics, 2015. **56**(4): p. 329-37.
51. Irwin, S.A., et al., *Daily oral ketamine for the treatment of depression and anxiety in patients receiving hospice care: a 28-day open-label proof-of-concept trial.* J Palliat Med, 2013. **16**(8): p. 958-65.
52. Irwin, S.A. and A. Iglewicz, *Oral ketamine for the rapid treatment of depression and anxiety in patients receiving hospice care.* J Palliat Med, 2010. **13**(7): p. 903-8.
53. Vollenweider, F.X. and M. Kometer, *The neurobiology of psychedelic drugs: implications for the treatment of mood disorders.* Nat Rev Neurosci, 2010. **11**(9): p. 642-51.
54. Witkin, J.M., et al., *Rapid-Acting Antidepressants.* Curr Pharm Des, 2018. **24**(22): p. 2556-2563.
55. Irwin, S.A., et al., *Daily oral ketamine for the treatment of depression and anxiety in patients receiving hospice care: a 28-day open-label proof-of-concept trial.* Journal of palliative medicine, 2013. **16**(8): p. 958-965.
56. Iglewicz, A., et al., *Ketamine for the treatment of depression in patients receiving hospice care: a retrospective medical record review of thirty-one cases.* Psychosomatics, 2015. **56**(4): p. 329-337.
57. Irwin, S.A. and A. Iglewicz, *Oral ketamine for the rapid treatment of depression and anxiety in patients receiving hospice care.* Journal of palliative medicine, 2010. **13**(7): p. 903-908.
58. Irwin, S.A., *NCT05086250 Feasibility Study of Oral Ketamine Versus Placebo for the Treatment of Anxiety in Patients With Pancreatic Cancer*. 2022: https://clinicaltrials.gov/ct2/show/NCT05086250.
59. Blonk, M.I., et al., *Use of oral ketamine in chronic pain management: a review.* European journal of pain, 2010. **14**(5): p. 466-472.
60. Chilukuri, H., et al., *Acute antidepressant effects of intramuscular versus intravenous ketamine.* Indian J Psychol Med, 2014. **36**(1): p. 71-6.

61. Loo, C.K., et al., *Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression.* Acta Psychiatr Scand, 2016. **134**(1): p. 48-56.
62. Zanicotti, C.G., D. Perez, and P. Glue, *Mood and pain responses to repeat dose intramuscular ketamine in a depressed patient with advanced cancer.* J Palliat Med, 2012. **15**(4): p. 400-3.
63. Grant, I.S., W.S. Nimmo, and J.A. Clements, *Pharmacokinetics and analgesic effects of i.m. and oral ketamine.* Br J Anaesth, 1981. **53**(8): p. 805-10.
64. Clements, J.A., W.S. Nimmo, and I.S. Grant, *Bioavailability, pharmacokinetics, and analgesic activity of ketamine in humans.* J Pharm Sci, 1982. **71**(5): p. 539-42.
65. McIntyre, R.S., et al., *Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation.* American Journal of Psychiatry, 2021. **178**(5): p. 383-399.
66. O'Brien, B., S.T. Wilkinson, and S.J. Mathew, *An update on community ketamine practices.* American Journal of Psychiatry, 2022. **179**(5): p. 393-394.
67. Ahuja, S., et al., *Real-world depression, anxiety and safety outcomes of intramuscular ketamine treatment: a retrospective descriptive cohort study.* BMC Psychiatry, 2022. **22**(1): p. 634.
68. Bonnett CJ, J.R., Ross CN, Wallington DA, Schock TR. *Intramuscular Ketamine to Treat Major Depressive Disorder: A Case Series of Forty Patients*. 2021 [cited 2023 10/27/2023]; Available from: https://www.sciforschenonline.org/journals/psychiatry-mental-health/JPMH145.php.
69. Barbosa, M.G., et al., *Efficacy and safety of ketamine for the treatment of depressive symptoms in palliative care: A systematic review.* Braz J Psychiatry, 2023. **45**(2): p. 182-195.
70. Dore, J., et al., *Ketamine Assisted Psychotherapy (KAP): Patient Demographics, Clinical Data and Outcomes in Three Large Practices Administering Ketamine with Psychotherapy.* J Psychoactive Drugs, 2019. **51**(2): p. 189-198.
71. Shram, M.J., et al., *Evaluation of the abuse potential of lorcaserin, a serotonin 2C (5-HT2C) receptor agonist, in recreational polydrug users.* Clin Pharmacol Ther, 2011. **89**(5): p. 683-92.
72. Kamp, J., et al., *Pharmacokinetic and pharmacodynamic considerations for NMDA-receptor antagonist ketamine in the treatment of chronic neuropathic pain: an update of the most recent literature.* Expert Opin Drug Metab Toxicol, 2019. **15**(12): p. 1033-1041.
73. Calvert, M., et al., *SPIRIT-PRO Extension explanation and elaboration: guidelines for inclusion of patient-reported outcomes in protocols of clinical trials.* BMJ open, 2021. **11**(6): p. e045105.
74. Kroenke, K., R.L. Spitzer, and J.B. Williams, *The PHQ-9: validity of a brief depression severity measure.* J Gen Intern Med, 2001. **16**(9): p. 606-13.
75. Merz, E.L., et al., *A multigroup confirmatory factor analysis of the Patient Health Questionnaire-9 among English- and Spanish-speaking Latinas.* Cultur Divers Ethnic Minor Psychol, 2011. **17**(3): p. 309-316.
76. Spitzer, R.L., et al., *A brief measure for assessing generalized anxiety disorder: the GAD-7.* Arch Intern Med, 2006. **166**(10): p. 1092-7.
77. Garcia-Campayo, J., et al., *Cultural adaptation into Spanish of the generalized anxiety disorder-7 (GAD-7) scale as a screening tool.* Health Qual Life Outcomes, 2010. **8**: p. 8.
78. Zeng, L., et al., *Preliminary results of the generation of a shortened quality-of-life assessment for patients with advanced cancer: the FACIT-Pal-14.* J Palliat Med, 2013. **16**(5): p. 509-15.

79. Shinall, M.C., et al., *Psychometric Properties of the FACIT-Pal 14 Administered in an Outpatient Palliative Care Clinic.* Am J Hosp Palliat Care, 2018. **35**(10): p. 1292-1294.
80. Molina, B., Rodríguez, L., Valdelamar, A. & Sánchez, R., *Traducción y adaptación transcultural de la escala FACIT-Pal para medir la calidad de vida en pacientes con cáncer avanzado en Colombia.* Revista Colombiana de Cancerología, 2020. **24**: p. 18-25.
81. Cleeland, C.S.R., K, *The brief pain inventory.* Pain Research Group, 1991: p. 143-147.
82. Keller, S., et al., *Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain.* Clin J Pain, 2004. **20**(5): p. 309-18.
83. Badia, X., et al., *[Validation of the Spanish version of the Brief Pain Inventory in patients with oncological pain].* Med Clin (Barc), 2003. **120**(2): p. 52-9.
84. de Andres Ares, J., et al., *Validation of the Short Form of the Brief Pain Inventory (BPI-SF) in Spanish Patients with Non-Cancer-Related Pain.* Pain Pract, 2015. **15**(7): p. 643-53.
85. Mehling, W.E., et al., *The Multidimensional Assessment of Interoceptive Awareness, Version 2 (MAIA-2).* PLoS One, 2018. **13**(12): p. e0208034.
86. Fittipaldi, S., et al., *A multidimensional and multi-feature framework for cardiac interoception.* Neuroimage, 2020. **212**: p. 116677.
87. de la Fuente, A., et al., *Multimodal neurocognitive markers of interoceptive tuning in smoked cocaine.* Neuropsychopharmacology, 2019. **44**(8): p. 1425-1434.
88. MacLean, K.A., M.W. Johnson, and R.R. Griffiths, *Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness.* Journal of Psychopharmacology, 2011. **25**(11): p. 1453-1461.
89. Pahnke, W., et al., *The Experimental Use of Psychedelic (LSD) Psychotherapy.* JAMA, 1970. **212**: p. 1856-1863.
90. Barrett, F.S., M.W. Johnson, and R.R. Griffiths, *Validation of the revised mystical experiences questionnaire in experimental sessions with psilocybin.* J Psychopharmacology, 2015. **29**(11): p. 1182-90.
91. Barrett, F.S., et al., *The Challenging Experience Questionnaire: Characterization of challenging experiences with psilocybin mushrooms.* Journal of Psychopharmacology, 2016. **30**(12): p. 1279-1295.
92. Guy, W., *CDEU Assessment Manual for Psychopharmacology Revised*. 1976, Kensington, MD.
93. Schneider, L.S.O., J.T, *Clinical Global Impression of Change.* International Psychogeriatrics, 1996. **8**.
94. Schneider, L.S., et al., *Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study.* Alzheimer Dis Assoc Disord, 1997. **11 Suppl 2**: p. S22-32.
95. Fava, G.A., F. Cosci, and N. Sonino, *Current Psychosomatic Practice.* Psychother Psychosom, 2017. **86**(1): p. 13-30.
96. Bobevski I, et al. T*he Demoralization Interview: Reliability and validity of a new brief diagnostic measure among medically ill patients.* Gen Hosp Psychiatry, 2022. 79: p. 50-59.
97. Timmerby, N., et al., *A Systematic Review of the Clinimetric Properties of the 6-Item Version of the Hamilton Depression Rating Scale (HAM-D6).* Psychother Psychosom, 2017. **86**(3): p. 141-149.
98. Bech, P., et al., *The Hamilton Depression Scale (HAM-D) and the Montgomery-Asberg Depression Scale (MADRS). A psychometric re-analysis of the European genome-based therapeutic drugs for depression study using Rasch analysis.* Psychiatry Res, 2014. **217**(3): p. 226-32.

99. Carrozzino, D., et al., *The Hamilton Rating Scales for Depression: A Critical Review of Clinimetric Properties of Different Versions.* Psychother Psychosom, 2020. **89**(3): p. 133-150.
100. Williams, J.B., et al., *The GRID-HAMD: standardization of the Hamilton Depression Rating Scale.* Int Clin Psychopharmacol, 2008. **23**(3): p. 120-9.
101. Tabuse, H., et al., *The new GRID Hamilton Rating Scale for Depression demonstrates excellent inter-rater reliability for inexperienced and experienced raters before and after training.* Psychiatry Res, 2007. **153**(1): p. 61-7.
102. Posner, K., et al., *The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults.* Am J Psychiatry, 2011. **168**(12): p. 1266-77.
103. Al-Halabi, S., et al., *Validation of a Spanish version of the Columbia-Suicide Severity Rating Scale (C-SSRS).* Rev Psiquiatr Salud Ment, 2016. **9**(3): p. 134-42.
104. Katz, R., et al., *Concurrent use of ketamine and monoamine oxidase inhibitors in the treatment of depression: a letter to the editor.* General hospital psychiatry, 2018. **54**: p. 62.
105. Ludwig, V.M., et al., *Cardiovascular effects of combining subcutaneous or intravenous esketamine and the MAO inhibitor tranylcypromine for the treatment of depression: a retrospective cohort study.* CNS drugs, 2021. **35**(8): p. 881-892.
106. George, G.C., et al., *Improving attribution of adverse events in oncology clinical trials.* Cancer treatment reviews, 2019. **76**: p. 33-40.
107. Lineberry, N., et al., *Recommendations to improve adverse event reporting in clinical trial publications: a joint pharmaceutical industry/journal editor perspective.* bmj, 2016. **355**.
108. Lu, Z., et al., *Opioid use and associated factors among pancreatic cancer patients diagnosed between 2007 and 2015.* Cancer medicine, 2022.
109. Vankawala, J., et al., *Meta-analysis: Hemodynamic responses to sub-anesthetic doses of ketamine in patients with psychiatric disorders.* Frontiers in Psychiatry, 2021. **12**: p. 549080.
110. Vickers, A.J., *The use of percentage change from baseline as an outcome in a controlled trial is statistically inefficient: a simulation study.* BMC Med Res Methodol, 2001. **1**(6).
111. Anderson, F., et al., *Palliative performance scale (PPS): a new tool.* J Palliat Care, 1996. **12**(1): p. 5-11.

Appendix 1 Palliative Performance Scale v. 2 (PPSv2)[111]

PPS Level	Ambulation	Activity & Evidence of Disease	Self-Care	Intake	Conscious Level
100%	Full	Normal activity & work No evidence of disease	Full	Normal	Full
90%	Full	Normal activity & work Some evidence of disease	Full	Normal	Full
80%	Full	Normal activity *with* Effort Some evidence of disease	Full	Normal or reduced	Full
70%	Reduced	Unable Normal Job/Work Significant disease	Full	Normal or reduced	Full
60%	Reduced	Unable hobby/housework Significant disease	Occasional assistance necessary	Normal or reduced	Full or Confusion
50%	Mainly Sit/Lie	Unable to do any work Extensive disease	Considerable assistance required	Normal or reduced	Full or Confusion
40%	Mainly in Bed	Unable to do most activity Extensive disease	Mainly assistance	Normal or reduced	Full or Drowsy +/- Confusion
30%	Totally Bed Bound	Unable to do any activity Extensive disease	Total Care	Normal or reduced	Full or Drowsy +/- Confusion
20%	Totally Bed Bound	Unable to do any activity Extensive disease	Total Care	Minimal to sips	Full or Drowsy +/- Confusion
10%	Totally Bed Bound	Unable to do any activity Extensive disease	Total Care	Mouth care only	Drowsy or Coma +/- Confusion
0%	Death				

Appendix 2 Data and Safety Monitoring Plan

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for auditing data quality and participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Annual auditing (depending on trial accrual)
- Review of serious adverse events
- Minimum of biennial regulatory auditing

2. Monitoring and Reporting Guidelines

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the results of each participant's treatment are discussed and documented in the site committee minutes.
The DSMC DSA will audit up to a maximum of five cycles of treatment for each participant selected for the annual audit. A total of twenty percent of the participants enrolled in the study will be reviewed until the study is closed by the IRB. For example, if there are 10 participants enrolled in the trial, then only 2 participants will be required to be reviewed by the DSA.

The DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 20 business days after the monitoring visit is complete for the study team to resolve all action items from the Action Item Report (AIR) report within 8 weeks. The due date for the completion of the action items may be extended for up to an additional 2 months for extenuating circumstances, if approved by the DSMC. The AIR report must be completed by the study team prior to the next monitoring review of this study. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment (or a total of 10 participants have been reviewed). However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of the

investigational agent(s) or study procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to investigational agent or study procedure. Attribution categories are:

- **Definite** – clearly related to the investigational agent(s) or study procedure.
- **Probable** – likely related to the investigational agent(s) or study procedure.
- **Possible** – may be related to the investigational agent(s) or study procedure.
- **Unrelated** –clearly not related to the investigational agent(s) or study procedure.

All Grade 3-5 adverse events entered into OnCore will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and attribution assignment.

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death,
- Life-threatening adverse experience*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event that changes the risk/benefit ratio of the study.

* A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:
https://irb.ucsf.edu/adverse-event
Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore, as well as submitted to the IRB (per IRB guidelines). The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE is sent to all required reporting agencies will be documented in OnCore®.

If the SAE involves a subject death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair (or Vice Chair) and DSMC Director within one business day.

3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC via report at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.
If at any time the Investigator voluntarily holds enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified as per IRB reporting regulations.

Data and Safety Monitoring Committee Contacts:

Katie Kelley, MD (DSMC Chair)
[redacted]
UCSF HDFCCC
San Francisco, CA 94158

John McAdams (DSMC Director)
[redacted]
UCSF HDFCCC
San Francisco, CA 94158