CLINICAL STUDY PROTOCOL

Psilocybin-assisted Psychotherapy in the Management of Anxiety Associated With Stage IV Melanoma.

Version**: Final** IND**: [79,321]**

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Study Period	2008

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Introduction

Background

This protocol is for a Multidisciplinary Association for Psychedelic Studies (MAPS),-sponsored, randomized, active-placebo controlled pilot study of the safety and efficacy of psilocybin-assisted psychotherapy in nine people experiencing anxiety in association with a diagnosis with stage IV melanoma. Preliminary results are promising from Dr. Charles Grob's active pilot study of psilocybin-assisted psychotherapy in twelve subjects with anxiety associated with advanced-stage cancer, taking place at Harbor-UCLA. These findings suggest that following this line of research is worthwhile.

Psilocybin, or 4-phosphoryloxy- N,N-dimethyl-tryptamine, is a psychedelic (hallucinogenic) "mind-manifesting" compound that is one of a few active constituents contained in a variety of mushrooms, most in the family psilocybe and referred to as "magic mushrooms." These mushrooms, indigenous to Central and South America, were used as sacraments in religious ceremonies for millennia prior to the discovery of their pharmacological properties in the 1950s. In humans, psilocybin can produce profound changes in thought, perception and emotion, including the facilitation of mystical or transformative experiences. Albert Hofmann, the inventor of LSD, first isolated and synthesized psilocybin in 1958. Soon after its discovery, psychotherapists used psilocybin in therapy, employing similar methods to those used by researchers and psychotherapists working with LSD (Passie 2005). Therapists used psilocybin and other similar compounds to produce insight or positive changes in views about the self or the world. Psilocybin-assisted psychotherapy included psycholytic and psychedelic therapy, with psycholytic psychotherapy involving a number of weekly sessions with moderate doses of psilocybin, and psychedelic therapy consisting of a smaller number of sessions with higher doses (Passie 2005). This research was almost completely shut down by the early 1970s and is only recently being resumed.

The first wave of human psilocybin research occurred in the 1950s and 1960s, and included basic research and use as adjunct to psychotherapy. This research was halted in the US soon after psilocybin was placed in Schedule 1, the most restrictive category of controlled substance, and in most cases human psilocybin research halted in Europe as well. However, a second wave of studies began investigating psilocybin in the mid to late 1990s, indicating a renewal of interest in the potential therapeutic effects of serotonergic hallucinogen (psychedelic) drugs.

Though there are no published reports of psilocybin-assisted psychotherapy in people with life-threatening illnesses, examining the history of past use of psilocybin suggests that psychiatrists used it in similar settings and with similar procedures as those used with the related psychedelic (serotonergic hallucinogen) LSD (Passie 2005). LSD appeared to reduce anxiety and depression in people with advanced-stage cancer (Grof et al. 1973), with improvement in quality of life seen in two-thirds of participants who received LSD-assisted psychotherapy (Grof et al. 1973; Kurland 1973; Pahnke 1969). People experiencing anxiety as a result of facing the threat of continued deterioration in health

and impending death may similarly be able to use psilocybin in concert with psychotherapy to promote emotional catharsis and powerful mystical or transformative experiences that enable them to confront or make peace with their fears in a manner that reduces anxiety. Following an examination of these early reports, Charles Grob MD, Harbor UCLA, is currently conducting a study of psilocybin-assisted psychotherapy in people with advanced-stage cancer. Preliminary data from this study appears promising.

Disease History and Related Research

Melanoma is a cancer arising from pigment-producing cells, or melanocytes. These cells are chiefly located in the skin, but they can also be found in other parts of the body, including eyes, ears and GI tract. While melanoma accounts for 4% of all skin cancers, it is associated with 77% of mortality due to skin cancer. The development of melanoma is likely due to multiple factors, including sun exposure and blistering sunburn, fair skin complexion, and increased numbers of moles. Untreated melanoma is an aggressive cancer. Oncologists categorize melanomas into four stages, subdividing several of the early stages into further categories, with later stages indicative of greater tumor depth and metastases. A stage IV melanoma has often metastasized to other parts of the body, including skin, the major organ systems, and lymphatic vessels. The five-year survival rate is extremely high for all Stage 1 and most Stage II melanomas (63% to 100%), but five-year survival rate for Stage IV melanoma is far lower (7% to 19%), and people diagnosed with Stage IV cancer are likely to live no longer than nine months after diagnosis. Sometimes progression to death is even more rapid. As a direct result of disease process and cytokine based therapies, patients with Stage IV melanoma are very likely to experience fatigue, pain, and psychosocial distress.

A diagnosis of life-limiting illness such as Stage IV melanoma carries with it a tremendous psychosocial burden on patients and their caregivers. In addition to the limitations in daily functioning brought by advanced disease, many patients report that their existential uncertainty and accompanying emotional distress have a detrimental effect on overall quality of life. Therefore, psychotherapies that aim to reduce anxiety can be seen to have the dual purpose of also improving quality of life at life's end. Recent data also show that reduced anxiety in people with advanced stage cancer may also have a beneficial effect on immune funtioning and caregiver distress (Grunfeld et al. 2004; Reiche et al. 2004). Providing psychotherapy in combination with psychedelic drugs, compounds that induce sometimes profound changes in thought, perception and perspective, may hold promise as a means of anxiety reduction in this population. Historically, some psychiatrists and psychotherapists performed psychotherapy in combination with lysergic acid diethylamide (LSD). However, as mentioned above, research ended after the scheduling of LSD.

Consistent with palliative care guidelines for the treatment of all people with advanced, life-threatening cancers, the management of distress in patients with advanced melanoma forms a crucial component of care. It has previously been shown that for most patients with advanced medical illnesses such as metastatic melanoma, spiritual and existential concerns become greater contributors to overall quality of life as illness advances (Chibnall et al. 2002; McCullough et al. 2000). Additionally, a greater sense of existential well-being has been associated with lower levels of self-reported anxiety and depression

(McCoubrie and Davies 2006). The Institute of Medicine has called on researchers to discover and develop innovative strategies and methods of palliative care (Institute of Medicine 1997).

Tackling the spiritual or existential concerns of people with advanced stage cancer through intensive psychotherapy in combination with psilocybin is an innovative means of reducing distress and improving quality of life. A greater sense of existential well-being has been associated with lower levels of self-reported anxiety and depression (McCoubrie and Davies 2006). Women with metastatic breast cancer who reported a greater sense of meaning and peace exhibited increased T-cell activation (Sephton et al. 2001). Unfortunately, most patients report that medical care all too frequently does not address the increasingly salient spiritual concerns of dying patients ((Balboni et al. 2007). The need for greater proficiency in addressing spiritual concerns is bolstered by findings indicating the potential for spiritual well-being to buffer against the often profound existential despair and distress that accompanies dying (McClain et al. 2003).

Preliminary results from an ongoing pilot study of psilocybin-assisted psychotherapy in twelve advanced-stage cancer patients with anxiety conducted by Dr. Charles Grob at Harbor-UCLA are reported to be promising. These findings suggest that following this line of research is worthwhile. Psilocybin produces profound dose-dependant alterations of consciousness lasting approximately four to six hours that include perceptual changes, changes in cognition including novel or non-sequential thought, and amplification and release of emotion, often with spiritual/mystical elements. Psilocybin can occasion profound spiritual experiences in people with some previous religious or spiritual practice, with some reporting the experience to be one of the most profound in their lives (Griffiths et al. 2006). The effects of psilocybin are hypothesized to enhance psychotherapy in people struggling with end-of-life issues by catalyzing catharsis and insight, and through the inspiration or cognitive restructuring provided by the spiritual/mystical experience, if obtained.

Historically, psychedelic-assisted psychotherapy demonstrated tremendous promise in directly addressing the spiritual concerns of patients suffering from advanced cancer (Grof et al. 1973). This therapeutic modality utilized a limited number of structured therapeutic sessions typically including lysergic acid diethylamide (LSD), psilocybin, and dipropyltryptamine (DPT) in a safe, clinical environment. Sessions last for the duration of the drug effects, and subsequent sessions of non-drug psychotherapy help in further integrating and developing the material generated during each drug-assisted session. “Psychedelic” in this case refers to any of the “classical” or “serotonergic” hallucinogens such as lysergic acid diethylamide (LSD), psilocybin and mescaline that share similar pharmacological profiles, such as at least partial agonism at 5HT2A receptors, and that produce sometimes intense changes in perception, cognition and emotion (Nichols 2004).

Soon after its synthesis by Hofmann in 1943, psychiatrists and psychotherapists began using LSD in psychotherapy (Stoll 1947; 1949), and fifteen to twenty years later, researchers had begun using LSD to improve quality of life in people with advanced stage cancer. Therapists performing LSD-assisted psychotherapy administered moderate to high doses in a supportive environment and encouraged introspection that might lead

toward greater processing of emotional and transformative experiences. At least two-thirds of people with advanced stage cancer enrolled in psychotherapy using doses of 200 mcg or more exhibited improved quality of life (Grof et al. 1973; Kurland 1973; Pahnke 1969). Initial reports of the efficacy of LSD-assisted psychotherapy appeared promising, but early studies did not employ methods, controls or measures featured in modern psychiatric and psychotherapy research, making it difficult to interpret these findings.

Rationale

The Multidisciplinary Association for Psychedelic Studies (MAPS), the sponsor of the proposed study, plans on following the path of the first therapists and researchers who reported benefits from psychedelic-assisted psychotherapy in people with life-threatening illnesses. MAPS has previously helped design, obtain full approval, and arrange the funding for a randomized, double-blind, placebo-controlled pilot study of MDMA-assisted psychotherapy in twelve advanced-stage cancer patients with anxiety. This study will be conducted by Dr. John Halpern, McLean Hospital, Harvard Medical School, and is currently in the subject recruitment stage. MAPS is also working to sponsor a pilot study of LSD-assisted psychotherapy in twelve subjects with anxiety associated with any life-threatening illness, to be conducted by Dr. Peter Gasser in Switzerland, with the protocol having already been approved by a Swiss ethics committee and by Swissmedic. MAPS will use the data gathered from these three pilot studies to inform its decision about whether to initiate Phase 3 studies and, if so, with which subject population, drug and dosing schedule. The sponsor hopes to develop one or more of these substances as psychotherapeutic adjuncts for people with anxiety in relation to a potentially fatal illness.

Summary

This protocol is for a randomized, active-placebo controlled pilot study of the safety and efficacy of psilocybin-assisted psychotherapy as a means of managing anxiety in association with stage IV melanoma. The active placebo in this study consists of a low dose of the investigational drug that is expected to induce only slight alterations in consciousness without producing the therapeutic effects. Study participants will have an estimated life expectancy of less than 12 months and elevated anxiety as indicated through Structured Clinical Diagnostic Interview (SCID) or Hospital Anxiety and Depression (HADS) score of 8 or above. Six of nine participants will be assigned to receive 25 mg psilocybin in combination with psychotherapy in two day-long experimental sessions scheduled seven to 14 days apart, and three of nine participants will be assigned to receive 4 mg psilocybin. In addition, all participants will receive introductory/preparatory non-drug psychotherapy sessions prior to each experimental session, and non-drug integrative psychotherapy sessions on the morning of the day after psilocybin-assisted sessions, or approximately 23 hours after psilocybin administration, and again during one non-drug psychotherapy session occurring between the first and the second psilocybin-assisted sessions.

Anxiety, depression, quality of life, and spiritual beliefs will be assessed at baseline, prior to each experimental session and two weeks after the second experimental session. The two-week follow-up marks the end of the randomized phase of the study and the breaking

of the blind. Upon completion of the active treatment phase of the study, participants who received full dose psilocybin (25 mg) will not receive any further therapy and will have the opportunity to take part in a similar follow-up assessment two months after their second psilocybin-assisted session. Participants assigned to receive active placebo have the opportunity to undergo an open-label study phase that will use nearly identical procedures except that the participants will receive 25 mg psilocybin during two day-long psychotherapy sessions with the same number of non-drug preparation and integration sessions. The same battery of measures will be re-administered two weeks and two months after the second open-label experimental session. We estimate that it will take approximately one to two years to complete this study.

Anxiety will be assessed by the Hospital Anxiety and Depression Scale (HADS), the State-Trait Anxiety Inventory (STAI) and the Hamilton anxiety scales. The HADS will serve as a primary outcome measure. Depression will be assessed with the HADS and the Hamilton Depression Rating Scale (HAM-D). Daily pain levels will be assessed throughout the study. The researchers will also assess participant quality of life with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ), feelings about life purpose and spirituality with the Functional Assessment of Chronic Illness Therapy-spirituality (FACIT-Sp), and spirituality in relation to the self with the Self-Expansiveness Level Form (SELF). The researchers will assess natural killer (NK) cell activity through diagnostic flow cytometry, assessing blood drawn at baseline, on the morning of the day after each psilocybin-assisted session and two weeks after the second psilocybin session. The researchers will assess the nature and extent of psilocybin effects related to producing a mystical or peak experience through the States of Consciousness Questionnaire, administered 24 hours after each experimental session.

Ethics

The trial will not be initiated until appropriate Institutional Review Board (IRB) approval of the protocol and the informed consent document has been obtained. In addition, all documents will be submitted to other authorities in compliance with local jurisdictions. The IRB and, if applicable, other authorities must be informed of protocol amendments in accordance with local legal requirements.

This trial will be conducted in accordance with the most recently acceptable version of the Declaration of Helsinki, Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines, and applicable standard operating procedures (SOPs). The trial will be conducted under a protocol reviewed and approved by an IRB; the trial will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the trial do not find the hazards to outweigh the potential benefits; each subject, or where applicable, each subject's legally acceptable representative(s) will give his or her written informed consent before any protocol-driven tests or evaluations are performed.

Informed Consent of Subject

The investigator is responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial.

The information about the trial must be given orally and in an understandable form. Written information about the trial will also be provided. In addition to the explanation of the trial and of subject's legal rights, the information should include that access to original medical records and processing of coded personal information must be authorized. The informed consent discussion must be conducted by a person who is qualified according to applicable local regulations. The subject should have the opportunity to inquire about details of the trial and to consider participation.

The informed consent form (ICF) must be signed and dated by the subject and must be countersigned by the person who conducted the informed consent discussion (according to local laws and GCP).

The investigator or an appropriate individual from CCOP at the same institution as the investigator will provide a copy of the signed informed consent to the subject, and will maintain the original in the investigator's study file.

The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive approval from an IRB before use.

The subject should be informed in a timely manner if new information becomes available that may affect the decision to participate in the clinical trial. The communication of this information should be documented.

Subject names will not be supplied to the sponsor. Only the subject numbers and subject identification codes will be recorded in the case report form (CRF), and if a subject's name appears on any other document (e.g., pathologist report), it will be obliterated before the copy of the document is supplied to the sponsor.

Written consent to take part in this study includes giving the investigators permission to view the participant's recent medical records to assess study eligibility. Information necessary for study participation includes physical examination, tests of metabolic and liver function, CBC within the last two weeks prior to referral, and a recent brain MRI.

Recruitment and Screening

Participants will be patients receiving care at the study site. The treating physician will provide prospective participants with printed consent material for the prospective participant and a primary caregiver, and contact information for at least one of the investigators. Consent material and contact information will be provided to people who express an interest in taking part in the study during the course of a regular examination or routine physician visit. Prospective participants will take these materials home to review and discuss with others. An individual with stage IV melanoma can only enroll in

this study if he or she has one primary caregiver who will take part in the study and will transport the participant to and from the cancer center for the two experimental sessions.

If a prospective participant and a primary caregiver both remain interested in taking part in the study, they will contact Community Clinical Oncology Program (CCOP) staff to schedule a meeting or further contact to review consent material. Members of the CCOP staff will also review and discuss consent materials for this study and the related study in caregivers. If prospective participants and their primary caregivers remain interested in taking part in these studies, they and the CCOP staff will schedule a meeting with one of the study investigators. Prospective participants and selected primary caregivers will then meet with the investigator, and they will give written informed consent after further discussion of the study with the investigator, and after ensuring that they have had the opportunity to receive answers to their questions about the study.

Study Objectives

Primary Efficacy and Safety Objectives

The primary objective of this pilot study is to gather preliminary data about the safety and efficacy of psilocybin-assisted psychotherapy in people diagnosed with anxiety arising from a diagnosis of Stage IV melanoma. Changes in anxiety will be assessed at baseline and two weeks after the second psilocybin-assisted session via self-report and clinician-administered instruments. Changes in anxiety will be assessed in all participants in an open-label study phase two weeks after the second open-label session. Changes in anxiety will also be assessed two months after the second experimental or open-label session. Safety will be assessed through recording adverse events and serious adverse events.

Secondary Objectives

The secondary objectives of this study include assessing depression, spirituality, quality of life, perceived self-boundaries, pain and natural killer (NK) cell activity in participants, and examining possible relationships between measures of the psilocybin experience and anxiety and spiritual beliefs.

> *Depression:* We will assess the effects of psilocybin-assisted psychotherapy on symptoms of depression. Changes in depression will be assessed via clinician-administered and self-report instruments at baseline and two weeks after the second psilocybin-assisted session. When applicable, changes in depression will be assessed two weeks after the second open-label session and two months after the second open label or experimental session.
>
> *Quality of Life, Beliefs about Spirituality and Self-Boundaries*: We will investigate the effects of psilocybin-assisted psychotherapy on beliefs about life purpose, spirituality, self-boundary and quality of life. Changes in spiritual beliefs and quality of life will be assessed via self-report measures at baseline and two weeks after the second psilocybin session. When applicable, changes in spiritual

beliefs and quality of life will be assessed two weeks after the second open-label session and two months after the second open label or experimental session.

Pain: A third secondary objective is to learn whether psilocybin-assisted psychotherapy produces at least transient changes, as analgesia or reduction in physical pain. Changes in pain will be assessed via daily diaries using visual analog scales and via daily diaries of medication use. When applicable, changes in pain will be assessed two weeks after the second open-label session and on the day two months after the second open label or experimental session.

Immune function: We wish to investigate the short-term and continued effects of psilocybin-assisted therapy on immune system function. Changes in immunological function will be assessed by NK cell counts made at baseline, 24 hours after each experimental session and two weeks after the second psilocybin-assisted session. When applicable, NK cell counts will occur 24 hours after each open-label session and two weeks after the second open-label session.

Mystical Experience and Anxiety: Finally, we wish to examine the association between undergoing a peak or mystical experience during psilocybin-assisted psychotherapy and subsequent reduction in anxiety. Presence and features of mystical experiences will be measured via a self-report instrument administered 24 hours after each experimental session, and self-boundary changes will be assessed via a self-report instrument administered at baseline, 24 hours after each experimental session and two weeks after the second experimental session. When applicable, occurrence of mystical experiences and changes in self-boundary will be assessed 24 hours after each open-label session.

General Investigational Plan

Drug Description and Doses

Participants will either receive 4 or 25 mg psilocybin (4-phosphoryloxy- N,N-dimethyl-tryptamine) in opaque capsules on two separate psilocybin-assisted psychotherapy sessions to occur seven to 14 days apart.

The full experimental intervention dose of psilocybin was chosen on the basis of early psilocybin psychotherapy research (Passie 2005) and recent studies of psilocybin's ability to produce mystical or spiritual experiences in healthy individuals with prior spiritual practice (Griffiths et al. 2006; Hasler et al. 2004). The dose is slightly lower on average than Griffiths and colleagues' dose of 30 mg/70 kg and is expected to produce all the cardinal effects of serotonergic hallucinogens, including changes in visual perception, rapid and sometimes profound changes in mood, derealization and depersonalization (feeling as if the world or the self are not real, feeling "as if in a dream") and unusual experiences relating to the body and the self. These effects are expected to facilitate therapeutic effects, including generation of a peak or mystical experience, reassessment of world view, perception of the body or the self, and re-appraisal or feelings of mastery over anxiety. This dose is also expected to overcome any potential blunting of effects arising from concurrent use of opiates in pain management medication (Grob 2007).

The active placebo in this study will be a low dose of the investigational drug. Active placebo dose of psilocybin was chosen on the basis of early and recent studies of psilocybin in humans (Hasler et al. 2004; Isbell 1959; Moreno et al. 2006; Passie et al. 2002). This dose was chosen for its ability to produce a few of the effects of psilocybin without producing any of the potentially therapeutic effects. People may perceive lights or colors as being brighter and sounds as being different, and they may experience slight changes in mood, cognition or perception. A 4 mg dose of psilocybin is not expected to generate a mystical or transformative experience.

Sample Population and Subjects

The study will enroll nine (9) individuals with the following criteria listed below. Study drop-outs or withdrawals will be replaced until nine participants have completed the randomized phase of the study. Study completion will be defined as attending visits from screening up through the follow-up two weeks after the second psilocybin-assisted session. Participants who are unable to complete or withdraw from the open-label phase or before the two-month follow-up phase will not be replaced. Inclusion Criteria

Inclusion Criteria

Prospective participants must meet the following inclusion criteria listed below to be eligible for study enrollment.

1. Have been diagnosed with Stage IV melanoma with a life expectancy of one year or less
2. Meet diagnostic criteria for anxiety on the SCID, or a score of 8 or higher on the HADS Anxiety score.
3. Diagnosis must be a new diagnosis of anxiety subsequent to diagnosis with melanoma.
4. Are 18 years or older,
5. Live with another adult who is their primary caregiver, who can also provide transportation to and from the cancer center for each experimental session and who also consents to take part in a parallel investigation of anxiety and depression in primary caregivers. The same caregiver may remain overnight with participants after each psilocybin session.
6. Have a Mini-Mental State Exam score of 27 or higher.
7. Are willing to commit to medication dosing, experimental sessions with overnight stay, traveling to follow-up sessions, and to complete the evaluation instruments.
8. Are willing to refrain from taking any anti-depressants during the study period.
9. Are willing to refrain from taking any benzodiazepines during the 24 hours preceding each scheduled psilocybin, placebo, or open label session.
10. Are able to communicate in English.

Exclusion Criteria

Prospective participants with the following conditions will be excluded:

1. Meet DSM-IV criteria for bipolar disorder, schizophrenia, or other psychotic disorders.

2. Meet DSM-IV criteria for abuse of or dependence on any substance (other than caffeine or nicotine) in the past 60 days.
3. Have first-degree relatives (as parent or full sibling) with past or present psychiatric disorders, including schizophrenia, bipolar affective disorder and other psychoses, but excluding mood disorders.
4. Cannot have a current diagnosis of anxiety disorder that predates diagnosis with melanoma.
5. Have used psilocybin or psilocybin-containing mushrooms within the past year.
6. Require concomitant treatment with anti-psychotic medications, prescribed for the management of either psychiatric symptoms or nausea. The restriction on 5HT2C/5HT3 antagonists is applicable for 24 hours before and including the day of the study.
7. Are cachectic as indicated by loss of 10% or greater of their total weight.
8. Have been diagnosed with primary or metastatic cancer of the CNS confirmed by MRI, within 6 weeks of participation in the study.
9. Have uncontrolled hypertension.
10. Have baseline laboratory values indicative of severely compromised hepatic function, indicated by unacceptable levels of alkaline phosphatase (ALP) above 750 U/L. Participants must also have laboratory blood screening indicating ALP below 750 U/L immediately prior to administration of psilocybin.
11. Are women who are pregnant or nursing, or of child bearing potential and are not practicing an effective means of birth control.
12. Are reasonably judged to present a serious suicide or homicide risk or who are likely to require psychiatric hospitalization during the course of the study.
13. Are unable to fully understand the potential risks and benefits of the study and give informed consent.

Planned Duration of the Study

The duration of the randomized study phase is from consent until two weeks after the second psilocybin session is approximately six weeks. All participants who received the full 25 mg dose of psilocybin and participants who received 4 mg psilocybin and declined to take part in the open-label session will, if able to do so, complete the two-month follow-up approximately three months (or 12 weeks) after consenting to take part in the study. From potential baseline to follow-up two weeks after the second psilocybin session, the open-label study phase lasts approximately one more month, so that subjects finish in 3.5 months (14 weeks). While it is exceedingly unlikely that participants who complete the open-label phase will take part in a follow-up two months after the second open-label psilocybin session, doing so would make the study last five months. On average, it is expected that participants will remain in the study for approximately three months, either completing the follow-up two months after the second experimental session or the follow-up two weeks after the second open-label session.

Method

The study will enroll nine people with stage IV melanoma diagnosed with anxiety or with HADS anxiety scores of 8 or higher. This study will use a randomized, active-placebo controlled, double-blind design to examine the effects of two day-long sessions of

psilocybin-assisted psychotherapy with either full (25 mg) or active placebo (4 mg) dose psilocybin, given along with non-drug preparatory and integrative psychotherapy sessions. Participants must have a primary caregiver who consents to be assessed as part of a related protocol examining caregiver anxiety. After participants and a selected caregiver give written consent, participants will undergo psychiatric screening and a selective drug screen to confirm study eligibility. If subjects are eligible, they and their caregiver will be administered baseline evaluations by an independent rater.

Psychotherapy will be performed by one male and one female psychotherapist. The study consists of at least two introductory sessions with the investigator-psychotherapists, two experimental sessions scheduled within a seven to 14-day interval that include an overnight stay at the clinic, psychotherapy follow-ups 24 hours after each psilocybin-assisted session, a second interim and preparatory non-drug psychotherapy session scheduled between the first and second psilocybin sessions, and evaluation two weeks after the second experimental session. Due to the short life expectancy of subjects in this study, subjects will be considered to have completed the study if they complete the outcome measures scheduled 2 weeks after the second experimental session.

Participants in the active placebo condition are eligible for an open-label study continuation. Participants will be re-screened no later than a week after the blind is broken to make sure they still meet study criteria. If they are ineligible, or choose not to enroll in the open-label study, they will be scheduled for another follow-up assessment two months after the second psilocybin-assisted session. If they are eligible and choose to enroll in the open-label continuation, they may do so, undergoing psilocybin-assisted sessions occurring within another seven to 14 day period. Participants in the full experimental dose condition are ineligible for the open label study phase.

The open-label phase of the study will follow nearly identical procedures to those used in the randomized phase. Participants will be re-assessed on all study measures two weeks after their second psilocybin session and again at two months, should participant health permit it. Subjects need not complete any portion of the open-label phase or the two-month follow up phase for their participation in the study to be considered completed.

Time and Events

Time and Events P-CA1	Baseline and Screening			Therapy and Evaluation 1					Therapy and Evaluation 2		
Visit #	V1	V2	V3	V4	V4.5	V5	V6	V7	V8	V9	V10
Type of Visit	Screening	IC Review	Psychiatric Eval	Intro Psychotherapy	Intro psychotherapy2	Psilocybin Session1	Therapy follow-up	Non-drug psychotherapy	Psilocybin Session 2	Therapy follow-up	2 wk follow-up
Approximate Study Day			0	7	10	14	15	21	29	30	43
Visit Timing and Windows				Post psych eval	Post psych eval	post V4	24 h post-psilo session 1	Between V5 & V8	7-14 days post V5	24 h post psilo session 2	2 weeks post V8
Study Staff	Jose	CCOP	Sameet	Sameet and Irene	Sameet and Irene	Sameet and Irene	Sameet and Irene	Sameet and Irene	Sameet and Irene	Sameet and Irene	Sameet and Irene
Medical Examination	X										
Liver FCT	#					X			X		
Drug Screen			X			X			X		
Pregnancy Screen						X			X		
KPRS			X	X				X			X
Psychiatric examination			X								
Provide consent materials	X										
Study informed consent		X									
Caregiver consent		X									
Baseline evaluation			X								
Study Enrollment			X								
Psychotherapy				X	X	X	X	X	X	X	
Give hypnotic induction CD				X							
Daily Pain Diary			X	X	X	X	X	X	X	X	X
Daily Medication Diary			X	X	X	X	X	X	X	X	X
FACIT-Sp			X		X	X		X	X		X
EORTC-QLQ-C15			X		X	X		X	X		X
HAM-A			X					X			X
HAM-D			X					X			X
SCID			X								
MMSE			X	X		X		X	X		X
SELF			X				X			X	X
STAI			X	X		X		X	X		X
HADS			X*	X		X		X*	X		X*
Mystical Experience Questionnaire							X			X	
Administer Psilocybin						X			X		
Blood Pressure						X			X		
Pulse						X			X		
Overnight stay						X			X		
Natural Killer cell count			X				X			X	X
Serious Adverse Events			X	X	X	X	X	X	X	X	X
Adverse Events Requiring Dr Visit				X	X	X	X	X	X	X	X
Unblinding											X
RRPQ											X
Common Side Effects						X			X		X
End Randomized phase											X

* = administer to subject's Caregiver

administer if not in recent subject's medical history

&=only full dose participants

Open-Label Study Phase									
Time and Events P-CA1			Open Label Therapy and Evaluation 1				Open Label Therapy and Evaluation 2		
Visit #	V10	V11	V12	V13	V14	V15	V16	V17	V18
Type of Visit	"Baseline"	Screening	Intro Psychotherapy	Psilocybin Session 1	Therapy follow-up	Non-drug psychotherapy	Psilocybin Session 2	Therapy follow-up	2 wk follow-up Psychotherapy
Approximate Study Day	43	44	52	59	60	67	72	73	86
Visit Timing and Windows	v10 else post v10	0-5 d post V10	0-5 d post screening	Post V12	24 h post-stage 2 psilo 1	Between V13 & V16	7-14 days post V13	24 h post stage2 psilo session 2	2 weeks post V16
Study Staff	Sameet	Sameet	Sameet and Irene	Sameet and Irene	Sameet and Irene	Sameet and Irene	Sameet and Irene	Sameet and Irene	Sameet and Irene
Medical Examination		X^							
Liver FCT		X^		X			X		
Drug Screen		X							
Pregnancy Screen				X			X		
KPRS	X	X	X			X			X
Psychiatric examination		X							
Study Enrollment		X							
Psychotherapy			X	X	X	X	X	X	X
Daily Pain Diary	X		X	X	X	X	X	X	X
Daily Medication Diary	X	X	X	X	X	X	X	X	X
EORTC-QLQ-C30	X		X			X			X
FACIT-Sp	X		X			X			X
HAM-A	X					X			X
HAM-D	X					X			X
MMSE	X	X	X	X		X	X		X
Daily Pain Diary			X	X	X	X	X	X	X
SELF	X	X			X			X	X
STAI	X	X	X			X	X		X
HADS	X*	X*	X	X		X*	X		X*
States of Consciousness Questionnaire					X			X	
Administer Psilocybin				X			X		
Blood Pressure				X			X		
Pulse				X			X		
Overnight stay				X			X		
Natural killer cell count	X				X			X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X
Adverse Events Requiring Dr Visit			X	X	X	X	X	X	X
Common Side Effects				X			X		X
RRPQ									X^
End open label phase									X
* = administer to subject's Caregiver				^=Admin prior to withdrawal if deterioration evident					
"Baseline" scores = 2-week followup									

Two-month Followup		
Time and Events P-CA1		2-month follow-up
Visit #	**F/U Screening**	**F/U 1**
Type of Visit	Screen 2-month follow-up	2-month follow-up
Approximate Study Day	88/131	89/132
Visit Timing and Windows	0-5 day pre F/U 2	2 months post v8 or V18
Study Staff	Sameet and Irene	Sameet and Irene
Medical Examination	X*	
KPRS		X
Psychiatric examination	X	
Assess HPPD	X	
Daily Pain Diary		X
Daily Medication Diary		
EORTC-QLQ-C30		X
FACIT-Sp		X
HAM-A		X
HAM-D		X
STAI		X
MMSE	X	X
VAMS		
SELF		
HADS		X
Serious Adverse Events		X
Adverse Events Requiring Dr Visit		X
Study Termination		X
***=review recent medical records**		

Assessments and Measures

All outcome measures selected for this study were chosen because they are well-recognized in the literature and because they are or will be used in related pilot studies, allowing comparison across these investigations. The primary outcome measure for this study will be the HADS anxiety score. The investigators will also measure anxiety with the STAI and the HAM-A. The investigators will assess depression with HADS depression scores and with the HAM-D. Participant beliefs about life purpose and spirituality will be measured with the FACIT-Sp, spirituality in relation to self-concept by the SELF, and quality of life will be assessed with the EORTC-QLQ-C15. Daily pain levels will be assessed via participant response on a visual analog scale, and daily pain and anxiety medication use will serve as an indirect measure of anxiety and experienced pain. Natural killer cell counts will serve as a measure of innate immune system function.

All participants will be screened via SCID and HADS, as described above in "Screening". The investigators will also use MMSE scores to assess study eligibility and mental competence throughout the course of the study.

The SCQ will serve as a process measure, assessing presence and degree of effects of psilocybin, and the SELF will serve as a process measure of self-boundary change. The KRPS, a measure frequently employed in studies of people with cancer, will serve as a means of rating performance status.

Table 1: List of assessments for use in this study. Time listed in minutes.

Assessment	Abbreviation	Measure of	Time needed	Clinician rated	Participant Self-rated	Purpose of Assessment/ Measure
Daily Medication Diary	--	Anxiolytic & pain management meds	5 min		X	Outcome
Daily Pain Level Diary	--	Daily pain levels	5 min.		X	Outcome
Europ. Organiz. For Research and Treatment of Cancer; Quality of Life Questionnaire-C15	EORTC QLQ-C15	Global quality of life	5-10 minutes.		X	Outcome
Functional Assessment of Chronic Illness Therapy-spirituality	FACIT-Sp	Spiritual or life purpose beliefs	5 min.		X	Outcome
Hamilton Anxiety Rating Scale	HAM-A	Anxiety	5-10 min	X		Outcome
Hamilton Depression Rating Scale	HAM-D	Depression	5-10 min	X		Outcome
Hospital Anxiety and Depression Scale#	HADS	Anxiety + Depression	5-10 min.		X	Screening & Outcome
Karnofsky Performance R___ Scale	KPRS	Everyday life function	5 minutes	X		Supplemental
Mini Mental State Examination	MMSE	Mental status / competency	15 minutes	X		Screening, continued eligibility
Natural Killer (NK) cell count*	NK count	Immunological function	5 minutes	X*		Outcome
Reactions to Research Participation Questionnaire	RRPQ	Experience of being participant	5-10 minutes		X	Process
Self-Expansiveness Level Form	SELF	Self-boundary	5 min.		X	Process
Spielberger State Trait Anxiety Inventory [a]	STAI	Anxiety	5-10 min.		X	Outcome
States of Consciousness Questionnaire	SCQ	Rating of altered states of consciousness	25 min		X	Process
Structured Clinical Interview for DSM-IV	SCID	Past and present psychiatric health	50-120 min.	X		Screening

#Primary outcome measure *Assessed via blood draw

Visit Descriptions: Psychotherapy and Assessment

Subject Numbering

Prior to enrollment, subjects will be tracked with their initials and a screening number assigned sequentially starting at "001". Subjects who meet the study admission criteria will be enrolled into the study and will be assigned a 4-digit subject number. The first two digits identify the study site. The next two digits identify the subject within the site and will be assigned sequentially, with 01 corresponding to the first subject enrolled, e.g. the first enrolled subject will be 0101, second 0102, etc.

Screening and Baseline evaluation (Visits #1 to #3)

After giving written consent, participants will be screened for presence of anxiety and for the presence of any psychiatric conditions that preclude study participation, such as psychosis. The principal investigator will conduct the screening evaluation in his office. The Structured Diagnostic Clinical Interview (SCID) will be used for diagnosing anxiety and detecting any conditions that preclude study participation, and the Mini Mental State Evaluation (MMSE) will be used to determine mental state and competency to take part in the study. Only participants with MMSE scores of 27 or higher will be eligible for study participation. The Hospital Anxiety and Depression Scale (HADS) will be used to quantify anxiety. Only people who are diagnosed with anxiety via SCID or who have a HADS Anxiety score of eight (8) or higher will be eligible for study participation. Once it is determined that participants meet study eligibility criteria, participants will complete or undergo additional assessments of anxiety and depression, quality of life and functional status, described above. The primary caregivers will complete the HADS. The investigators will also provide participants with daily pain and medication diaries and instructions on how to complete them. Participants will begin completing daily pain and medication diaries starting after baseline analysis.

Randomized blinded Study phase

Randomization

Upon enrollment into the study, participants will be assigned to one of two conditions, active placebo (4 mg psilocybin) or full experimental intervention (25 mg psilocybin). Active placebo in this study is a low dose of the investigational drug that will not produce the unique effects of psilocybin. Participants have a 66% chance of assignment to the full experimental intervention, with six of nine participants will be assigned to receive the full experimental intervention and three will be assigned to receive active placebo. The internal review committee coordinator at the study site will generate and maintain the randomization code and procedure. Condition assignment will be maintained from study enrollment up through the course of the study, as there is no crossover design. If there is an adverse event or other emergency requiring knowledge of participant's condition assignment, as when pharmacological intervention is necessary, the blind may be broken for an individual participant.

Introductory Psychotherapy Session (Visits #4 and #4.5)

Psychotherapy

The therapist-investigators will conduct at least one introductory psychotherapy session no later than seven days after the baseline evaluation. Introductory sessions will provide up to six hours of preparation, including one to two sessions of psychotherapy that will last from 90 to 120 minutes, and working with a hypnotic induction CD. Introductory sessions may be presented by one or both of the investigator-therapists. Introductory psychotherapy will occur after participants are assessed for continued study eligibility and complete measures of anxiety and depression.

After introductions are shared between the participant and the therapist-investigators, at least one and possibly both of the investigators will discuss the participant's lifespan and psychological development, any goals or desires they have, their spiritual beliefs or world-view and any beliefs about death or the afterlife, and any past experiences that share some similarities with psilocybin-assisted psychotherapy, such as any past use of classical hallucinogens/psychedelics and any past mystical or transformative experiences. The therapist-investigators will teach mindfulness techniques, such as diaphragmatic breathing with cognitive-behavioral stress management in a spiritual context. The therapist-investigators will inform participants of what to expect during a psilocybin-assisted psychotherapy session and they will address any specific hopes, fears or specific goals the participant has in respect to the upcoming psilocybin-assisted psychotherapy sessions. The investigators will also provide participants with a CD containing procedures for hypnotic induction, and if there is time available, one or both therapist-investigators will review and discuss the content of the hypnotic induction CD. The investigators will present participants with instructions and food, alcohol or medication restrictions for the time starting 24 hours prior to a psilocybin-assisted psychotherapy session, and the participant will be encouraged to ask questions about these instructions. A second introductory session will occur if the investigators deem it necessary. The investigators will meet with any significant other who plans to accompany the participant for part of a psilocybin-assisted session and the overnight stay, if applicable.

Introductory psychotherapy sessions will be recorded to audio and video. No identifying information save assigned participant subject number will be written on any session recordings. Participants will have an opportunity to review session recordings.

Assessment

Participants will undergo assessment with MMSE to ensure their continued eligibility prior to each introductory psychotherapy session. They will complete the HADS and STAI prior to the first introductory session, and the FACIT-SP and EORTC-QLQ-C15 prior to the second introductory session. They will complete daily pain and medication diaries during this time period.

Psilocybin-Assisted Psychotherapy (Visit #5, Visit #8)

Psychotherapy

There will be two psilocybin-assisted psychotherapy sessions scheduled to occur seven to fourteen (14) days apart, on study visits #5 and #8. Both psilocybin-assisted psychotherapy sessions will take place at the study site and will be staffed by the two investigator-therapists, one male and one female. Procedures for the two drug-assisted sessions will be identical. During the second experimental session, the participant and therapist-investigators may discuss material or experiences from the first psilocybin-assisted session.

Participants will arrive at the Cancer Center at approximately 9:00 AM. Participants will be instructed to refrain from alcoholic beverages starting 12:00 on the night prior to each psilocybin-assisted session, and to eat only a light breakfast on the morning of the

session. On arrival, they will have a blood draw for the assessment of liver function and metabolism, and they will have urinary drug and pregnancy screens. After undergoing these screens, one of the investigators will conduct the MMSE, and the participant will complete outcome measures. He or she may return completed daily pain and medication diaries at this point. Results from laboratory tests will be available approximately 45 minutes after the blood draw, and significantly abnormal results will result in rescheduling of psilocybin session or withdrawing the subject from the study. Positive pregnancy screen will result in withdrawal from the study.

If there is no reason to discontinue the session, the principal investigator will administer a capsule of psilocybin p.o. along with a glass of water, at approximately 10:00 AM. Participants assigned to active placebo will receive 4 mg psilocybin and participants in the experimental (full dose) condition will receive 25 mg psilocybin. The session will take place in a comfortably furnished room that will be prepared and decorated for these sessions. Participants will be encouraged to sit or lie down while listening to music, and be instructed to utilize relaxation techniques previously discussed in preparatory, non-drug psychotherapy sessions, with a specific emphasis on addressing spiritual concerns. Eyeshades will be available if desired. Both therapist-investigators will remain with the participant and will offer support or help if requested to do so while minimizing direct verbal interaction with the participant during the period of peak drug effects. This model of psychotherapy is based on that described by Grof (Grof 2000; 1980).

The investigators will periodically assess blood pressure and pulse, with measurements occurring immediately prior to psilocybin administration, hourly for the next three hours after drug administration, and with more frequency if in their judgment the investigators conclude that more frequent measurements are needed. If the participant remains silent for over an hour, the participants will check in with him or her. The therapist-investigators will remain with the participant for the expected six-hour duration of drug effects, and until the participant appears to be stable and all or most drug effects have dissipated. If the participant has selected a significant other to remain with him or her for part of the psilocybin-assisted session and, if applicable, for the overnight stay, then this person should arrive at least 30 minutes before the end of the psilocybin session.

During their overnight stay, participants will remain in appropriately furnished rooms, and a significant other will be able to remain with them throughout the night. An overnight nurse and medical assistant will also be provided for the duration of the overnight stay until regular nursing staff arrive at the cancer center in the morning. Prepared meals or food will be available to the participant and significant other. At least one of the therapist-investigators will be available via 24-hour pager in case of any emerging difficulties that occur throughout the night, and one or both of the investigators can return to the cancer center if necessary to be with the participant.

The first and second psilocybin-assisted sessions will be recorded to audio and video in the same manner as all the non-drug-assisted sessions. The privacy of participants will be ensured and appropriate HIPPA regulations will be followed. Participants will have an opportunity to review these recordings.

Assessment

The investigator will assess each participant for continued study eligibility via MMSE. Participants will complete the HADS and STAI to measure anxiety and depression. They will complete the FACIT-Sp and the EORTC-QLQ-C15 to assess spirituality and quality of life. All these measures will occur prior to the start of psilocybin-assisted psychotherapy.

Integrative Non-Drug Psychotherapy (Visits #6, #7 and #9)

Psychotherapy

Participants will engage in non-drug psychotherapy with both therapists at 9:00 AM on the morning after each psilocybin session and during one session scheduled to occur between the first and second psilocybin-assisted sessions. During these sessions, the participant and the therapist-investigators will discuss the feelings, thoughts and experiences that occurred during the psilocybin session, seeking to integrate this material. During these sessions, the participant and therapists may also consider whether the participant attained his or her initial goals. Psychotherapy will occur after participants complete process or outcome measures. These sessions will be recorded to audio and video, and participants will have an opportunity to review session recordings.

The participant and therapists will continue to work with material from the first psilocybin-assisted session and will discuss ways in which the participant has integrated this material into his or her everyday life. There will also be more explicit preparation for the second psilocybin session, including discussing any changes or elaborations in plans or goals and addressing participant concerns raised during the first session. They will review hypnotic induction and mindfulness techniques during this interim non-drug psychotherapy session.

Assessment

On the morning of the day after each psilocybin-assisted session, participants will complete the SELF and the SCQ prior to undergoing integrative psychotherapy. They will also undergo a blood draw for the assessment of natural killer (NK) cell numbers on the morning of the day after each psilocybin-assisted session. Prior to integrative psychotherapy scheduled between the first and the second psilocybin-assisted psychotherapy session, participants will be assessed for continued study eligibility with MMSE. After undergoing the MMSE, participants will be assessed for anxiety and depression with the HADS, STAI, HAM-A and HAM-D, and they will be assessed for spirituality and quality of life with the FACIT-Sp and EORTC-QLQ-C15.

Final Evaluation in Randomized Phase (Visit #10)

Psychotherapy

Psychotherapy will not be conducted during the evaluation and assessment occurring two weeks after the second psilocybin-assisted session.

Assessment

Two weeks after the second psilocybin-assisted psychotherapy session, participants and a primary caregiver will arrive at the cancer center. Participants will undergo a comprehensive evaluation, including administration of KPRS, MMSE, HAM-A and HAM-D, STAI, FACIT-Sp, EORTC-QLQ and SELF. Participants and primary caregivers will complete the HADS. After this evaluation, participants will briefly meet with the investigators and the study blind will be broken, as described below.

Participants will complete the Reactions to Research Participation Questionnaire (RRPQ), an instrument examining reasons and feelings related to taking part in research studies, including reasons for taking part in the study and positive and negative feelings related to research participation.

Unblinding and Opportunity to Enter the Open-Label Study Segment or Two-Month Follow-up (Visit 10)

Unblinding will occur after each participant has undergone the evaluation described above. Participants who learn that they received active placebo have the opportunity to take part in an open-label phase of this study. This segment will contain two sessions of psilocybin-assisted psychotherapy with 25 mg psilocybin. Active placebo participants will be immediately entered into the open label study segment, screened for eligibility and scheduled for preparatory psychotherapy and the first psilocybin-assisted session.

All participants have the opportunity to take part in an additional follow-up assessment. The assessment will take place two months after the second psilocybin-assisted session (six weeks after the two-week follow-up) for all full-dose participants and for any active placebo participants who choose not to enroll in the open-label phase, and two months after the second open-label psilocybin session if enrolled in the open-label study phase.

Open-Label Study Phase (Visits #11-18)

Procedures and methods for the open label study phase will be nearly identical to those for the randomized, double-blind study phase except that psilocybin-assisted sessions will be open-label and it is unlikely that there will be more than one introductory psychotherapy session.

Psychotherapy

Once enrolled in the open-label study phase, participants will undergo an introductory psychotherapy session with the therapist-investigators. The participant and the investigators will re-assess participant goals, desires and spiritual beliefs, and participants will be reminded of study procedures and what to expect during psilocybin-assisted psychotherapy. The investigators will conduct psilocybin-assisted psychotherapy in a manner nearly identical to that used during the randomized study phase, except that all participants in the open-label phase will receive 25 mg psilocybin. Participants will undergo integrative psychotherapy on the morning of the day after each open-label psilocybin session, and there will be an integrative psychotherapy session scheduled between the first and second psilocybin-assisted sessions. During integrative psychotherapy, participants will discuss any thoughts, feelings or experiences that arose

during the psilocybin session with the investigators in order to integrate this material into everyday life.

Assessment

The investigators will assess each participant prior to starting the open label phase to make sure they still meet study criteria by reviewing medical records and performing the MMSE. Participants will continue to complete daily pain and medication diaries. Participants will complete HADS, STAI, FACIT-SP and EORTC-QLQ-C15 at the introductory session, prior to each psilocybin-assisted session, prior to psychotherapy in between the two psilocybin sessions and two weeks after the second open-label session. The investigators will administer the HAM-A and HAM-D during the introductory psychotherapy session, prior to psychotherapy scheduled between the first and second psilocybin sessions and two weeks after the second psilocybin session. Participants will complete the SELF prior to the introductory session, prior to psychotherapy taking place between the first and the second psilocybin session and two weeks after the second open-label psilocybin session. Participants will complete the RRPQ two weeks after the second open-label psilocybin-assisted session. If it appears and is fairly certain that a participant will be unable to complete the entire open-label phase prior to the assessment two weeks after the second open-label psilocybin session, then he or she will be encouraged to complete the RRPQ immediately before withdrawing from the study.

Two-Month Follow-up (Follow-up Screening and Follow Up 1)

The two-month follow-up will occur two months after the second experimental session for all participants who received 25 mg psilocybin and any who received active placebo but who declined to take part in the open-label session, and it will occur two months after the second open-label session for all active placebo participants who completed the open label study phase. The principal investigator will screen all participants prior to their taking part in the two-month follow-up.

Psychotherapy

The investigators may interview or discuss participant experiences to assess response to taking part in the study. However, there will be no further psychotherapy during the two-month follow-up.

Asessment

Participants must be able to complete self-report measures and understand and answer items in clinician-administered measures. The investigators will perform the MMSE to assess mental status and review medical records for indicators of subsequent metastasis or other CNS disease since the end of the randomized or open-label phase. Only participants with MMSE scores of 27 or higher and without any signs of serious CNS disease will undergo assessments at this time. Participants will complete the HADS, STAI, FACIT-Sp, EORTC-QLQ-C15 and SELF, and the investigators will administer the HAM-A and HAM-D and a pain level measurement for the day of the two-month follow-up. The investigator will assess participants for symptoms of HPPD by asking about cardinal symptoms of perceptual disturbances and distress at their occurrence.

Visit by Visit Description

Participants who consent to take part in the study will undergo the following sequence of events:

The randomized, blinded study phase:

- **Psychiatric Evaluation and Baseline (Visit 3):** A two-hour long psychiatric evaluation. The principal investigator will diagnose psychiatric disorders via SCID. Mental status will be assessed with MMSE. Participants will also complete measures of anxiety (HADS anxiety, STAI), depression (HADS depression), spirituality (FACIT-SP) and quality of life (EORTC-QLQ-C15). The investigators will also administer observer-scored measures of anxiety (HAM-A), depression (HAM-D), and ability to perform everyday life functions (KPRS). If a participant meets study eligibility criteria after psychiatric evaluation, he or she will be scheduled for an introductory psychotherapy session.
- **Introductory Psychotherapy (Visits 4-4.5):** Two 90 to 120-minute introductory psychotherapy sessions. The participant will complete measures of anxiety and depression (HADS, STAI), spirituality and quality of life (FACIT-Sp and EORTC-QLQ-C15). Psychotherapy takes place with both investigator-therapists following assessment, with a particular emphasis on the participants' chief religious and spiritual beliefs, as well as existential concerns. Introductory sessions will be recorded to audio and video, and participants will have an opportunity to review the recordings. The investigators will provide participants with instructions on mindfulness and self-hypnosis, and they will provide participants with a self-hypnosis CD during one introductory session. If there are two introductory sessions, participants will complete anxiety measures prior to the first introductory session and the spirituality and quality of life measures in the second session. Participants will also receive instructions and restrictions relating to food and drug consumption for the night before and morning of the psilocybin-assisted session.
- **Psilocybin-Assisted Psychotherapy Session 1 (Visit 5):** First day-long psilocybin-assisted psychotherapy session. On arrival, the participant will undergo blood draw for assessing liver function, assessment of mental competency through MMSE and urinary drug and pregnancy screen, with positive tests from these tests resulting in either delaying or rescheduling the session to withdrawal from the study. The participant will next complete measures of anxiety and depression (HADS, STAI), spirituality (FACIT-Sp) and quality of life (EORTC-QLQ-C15). The session will be recorded to audio and video, and participants will have an opportunity to review the recordings. After these measures are completed, a capsule of 4 or 25 mg psilocybin will be administered, and the participant will be encouraged to sit or lie comfortably for the duration of the session. Blood pressure will be measured immediately

before, and hourly for the first three hours. The investigators will remain with the participant for up to six hours later or until drug effects have waned. A significant other may stay with the participant during part of the therapy. All participants will remain overnight.

- **Integrative Psychotherapy 1 (Visit 6):** A 60 to 90 minute long integrative psychotherapy session occurring at approximately 9:00 AM on the morning after the first psilocybin-assisted psychotherapy, or approximately 23 hours post-psilocybin. Psychotherapy will begin after participants complete a measure of alterations in consciousness (SCQ) and spiritual identity and self-boundary (SELF) and after a blood draw for assessing NK cell numbers. The participant will meet with both therapists, and all three will work on discussing experiences, thoughts, feelings and memories that arose during the psilocybin-assisted session. The session will be recorded to audio and video. Participants will have a chance to review the recordings.
- **Integrative Psychotherapy Session 2 and Evaluation (Visit 7):** A 120 minute interim psychotherapy and evaluation scheduled to occur in between the first and second psilocybin-assisted sessions. Participants first undergo or complete measures of anxiety and depression (HADS, HAM-A, STAI, HAM-D), spirituality (FACIT-SP) and quality of life (EORTC-QLQ-C15). The investigators will assess participants for mental competence. This session will be recorded to audio and video, and participants will have an opportunity to review the recordings. The participant will meet with both psychotherapist-investigators, and they will prepare for the second psilocybin-assisted psychotherapy session.
- **Psilocybin-Assisted Psychotherapy Session 2 (Visit 8):** The second day-long experimental psilocybin-assisted session will occur seven to 14 days after the first psilocybin-assisted session. The second psilocybin-assisted session will follow the same sequence of events as the first psilocybin-assisted session, including administering measures and blood draw, drug administration, psychotherapy with both therapist-investigators, and overnight stay.
- **Integrative Psychotherapy Session 3 (Visit 9):** A 60 to 90-minute long integrative psychotherapy follow-up will take place at approximately 9:00 AM on the morning after the second experimental session, following the same sequence of events and procedures occurring during the integrative follow-up 24 hours after the first psilocybin-assisted session, including administration of process measures, blood draw and psychotherapy.
- **Final Evaluation-Randomized Phase (Visit 10):** A 90-minute follow-up evaluation will occur two weeks after the second psilocybin-assisted psychotherapy session. This visit marks the end of the randomized phase of the study. Participants will be assessed for mental competence with the MMSE before any other measures are administered. The evaluation includes administering measures of anxiety and depression (HADS, STAI, HAM-A, HAM-D), spirituality (FACIT-Sp), quality of life

(EORTC-QLQ-C15), and response to being a research participant (RRPQ). The participants will briefly meet with the investigators but will not undergo psychotherapy.

- **Study Blind Broken for Individual Subject (Visit 10):** The blind will be broken for each participant after completing all measures and assessments, and participants who received active placebo can enter into the open-label phase of the study. After blind is broken, only active placebo participants are permitted to take part in open label study phase. Those who withdraw from this phase of the study can take part in the follow-up assessment two months after the second experimental psilocybin-assisted psychotherapy session. All experimental dose participants will not enroll in the open-label phase.

Open-label study phase

- **Open Label Baseline (Visit 10-11):** A 90-minute screening and baseline session; in most cases, all assessments from the two-week follow-up ending the randomized phase will be treated as baseline for the open-label phase.
- **Open Label Screening (Visit 10-11):** A 20 to 30 minute screening visit; this may take place on the same day as the baseline visit described above. The investigators will review any new medical information and screen to ensure the participant can continue to enroll in the study, including assessment for mental competency. The investigators will perform blood draw to assess liver function and a urinary drug screen.
- **Introductory Psychotherapy 2 (Visit 12):** A 90 to 120 minute long introductory psychotherapy session will occur no later than five days after baseline. Prior to assessment and psychotherapy, the investigators will assess mental competence with MMSE. The participant will complete measures of anxiety, depression, spirituality and quality of life (HADS, STAI, FACIT-SP and EORTC-QLQ-C15). The investigators will re-acquaint themselves with the participant and his or her hopes, desires, and fears, and they will re-introduce the participant to psilocybin-assisted psychotherapy. The session will be recorded to audio and video. Participants will have a chance to review the recordings.
- **Psilocybin-Assisted Psychotherapy Session 3 (Visit 13):** A day-long open-label psilocybin-assisted psychotherapy session that will commence with the investigator assessing participant mental competence via MMSE, followed by a urinary drug and pregnancy screen and a blood draw to assess liver function. Participants will complete measures of anxiety and depression (HADS and STAI) spirituality (FACIT-Sp) and quality of life (EORTC-QLQ-C15. Participants will receive 25 mg psilocybin. The investigators will remain with the participant throughout the duration of drug effects. Blood pressure will be assessed once prior and hourly for three hours post-drug. A selected significant other may arrive during the latter part of the psilocybin-assisted psychotherapy session. Participants will remain at the site overnight.

- **Integrative Psychotherapy Session 4 (Visit 14):** A 60 to 90-minute long integrative therapy session occurring at approximately 9:00 AM on the morning after the psilocybin-assisted psychotherapy session. Participants will first complete measures of alterations in consciousness (SCQ) and spiritual identity and self-boundary (SELF), and they will have a blood draw to assess NK cell numbers. After these assessments are complete, the participant will meet with both investigator-therapists for integrative psychotherapy. The session will be recorded to audio and video, and study participants will have an opportunity to review the recordings.
- **Integrative Psychotherapy Session 5 and Evaluation (Visit 15):** A 120-minute long integrative assessment and integrative psychotherapy session scheduled to occur between the first and second open-label psilocybin sessions. The investigators will assess mental competency with MMSE. Participants will complete measures of anxiety, depression, spirituality and quality of life (HADS, STAI, FACIT-SP and EORTC-QLQ-C15) and the investigators will administer measures of anxiety and depression (HAM-A and HAM-D). The participant and investigators will continue to integrate any insights, thoughts or feelings from the first psilocybin session. This session will be recorded to audio and video, and study participants will have an opportunity to review the recording.
- **Psilocybin-Assisted Psychotherapy Session 5 (Visit 16):** A second day-long open-label psilocybin-assisted psychotherapy session will occur seven to 14 days after the first psilocybin-assisted session, and will follow the same sequence of events and procedures as the first psilocybin-assisted session, including all assessments, measures, urinary tests blood work, and session recording. Psychotherapy will last up to six hours or as long as drug effects remain, and a significant other may arrive during the psilocybin-assisted session. All participants will remain at the site.
- **Integrative Psychotherapy Session 5 (Visit 17):** A 60 to 90 minute long integrative psychotherapy session will occur at approximately 9:00 AM on the morning of the day after the second psilocybin session, following the same sequence of events and procedures as the integrative psychotherapy visit 24 hours after the first psilocybin-assisted session, including assessments of alterations in consciousness a blood draw for assessing NK cell numbers prior to beginning integrative psychotherapy and session recording.
- **Final Evaluation-Open Label Study Phase (Visit 18):** A 90-minute long evaluation will occur two weeks after the second psilocybin-assisted session. The investigators will first assess participant mental competence with the MMSE. Participants will complete measures of anxiety, depression, spirituality and quality of life (HADS, STAI, FACIT-Sp, EORTC-QLQ-C15) and the investigators will administer measures of anxiety and depression (HAM-A, HAM-D). Participants may meet with the investigators but will not undergo further

psychotherapy. Participants will complete a measure of their feelings and experience as a research participant (RRPQ).

Two-month follow-up

- **Two Month Follow Up Visit(s):** A 90 to 120 minute long follow up occurring two months after the second experimental psilocybin-assisted session for all full (experimental) dose participants and any active-placebo participants who did not take part in the open-label study phase, and two months after the second open-label psilocybin-assisted psychotherapy session for active placebo participants who enrolled in the open-label study phase. Only participants who are willing and able to complete study measures will take part in the two-month follow-up. Participants will complete all the measures of anxiety, depression, spirituality and quality of life described above. In addition, they will complete the daily pain and medication diaries for the day of the two-month follow-up, and the investigators will assess them for HPPD occurrence. There are no more visits for any participants after completing the two-month follow-up. Participants may briefly meet with the investigators, but they will not undergo any further psychotherapy.

Removal of Subjects from Therapy or Assessment

The participant, or where applicable, the participant's legally acceptable representative(s) can withdraw consent for participation in the study at any time without prejudice. The investigator can withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.

The subject will be clinically monitored after withdrawal, the cause of which will be recorded on the "Study Termination" CRF and, where appropriate, on the subject's medical records. Where the withdrawal of a subject resulted from an adverse event, this will be documented in accordance with the procedures in section.

Whenever possible, the tests and evaluations listed for the termination and outcome visits will be carried out.

Premature Discontinuation of the Study

The sponsor or the investigator (following consultation with the sponsor) has the right to discontinue this study at any time. If the trial is prematurely terminated, the investigator is to promptly inform the study subjects and she or he should assure appropriate therapy and follow-up. If the trial or study is prematurely discontinued, all procedures and requirements pertaining to the archiving of the documents will be observed. All other study materials will be returned to the sponsor, will be treated in accordance with federal and local regulations. DEA requires destruction of unused schedule 1 drugs in studies.

Data Analysis

The primary analyses for this study will be a repeated measures analysis of variance (ANOVA) with condition (active placebo versus experimental dose) as a between-subject

factor and time of administration (baseline versus two weeks after the second experimental psilocybin-assisted session) as a repeated measure. The investigators will employ separate repeated measures ANOVAs to examine the effects of psilocybin-assisted psychotherapy on all outcome variables, including the primary outcome variable. Separate analyses will be performed for HADS, HAM-A and STAI anxiety scores, HADS and HAM-D depression scores, EORTC-QLQ-C15 scores, FACIT-Sp scores and NK cell counts. The investigators will perform post-hoc tests (as Tukey's test) on any statistically significant interactions. Probability of rejecting the null hypothesis will be set at 0.05. Because of the pilot nature of this study and small sample size, we will not employ Bonferroni corrections for when examining analyses results for measures of anxiety. In the case of pain levels measured by daily diary, the investigators will perform two repeated measures ANOVAs comparing average pain levels at baseline versus average pain levels for the weeks immediately after the first and after the second experimental sessions, with p. set at 0.05. The investigators are interested in discovering whether there are differences in pain level between active placebo and experimental dose participants immediately after undergoing psilocybin-assisted psychotherapy.

If at least four participants complete measures during the follow-up two months after the second experimental or open-label psilocybin-assisted therapy session, then the investigators will perform separate repeated-measures ANOVAs on the anxiety, depression, quality of life and spirituality scores listed above, with p. set at 0.05. The investigators are chiefly interested in differences between baseline and two-month follow-up scores. If a sufficient number of participants complete pain measures on the date of the two-month follow-up session, then the investigators will perform a t-test to compare VAS pain ratings on the day of the two-month follow-up with the average pre-psilocybin pain rating.

Given that only three participants will be eligible for the open-label phase of the study, the investigators do not plan to perform formal comparisons between anxiety, depression, spirituality or quality of life across the randomized and open-label study phases. However, the investigators will perform informal observations and present descriptive statistics for all outcome variables two weeks after the second open-label psilocybin-assisted session.

Before analyzing differences between degree of mystical experiences or changes in spiritual identity for active placebo and experimental dose participants, the investigators will first perform a matched-sample t test to determine whether there were significant differences between mystical experience (SCQ) and self-concept boundary/spiritual identity (SELF) scores measured after each of the two psilocybin-assisted sessions. If there are no significant differences between SCQ and SELF scores after the first and the second psilocybin session, then the investigators will compute the average between the two scores and employ the average SCQ and SELF score in nearly all subsequent analyses of these scores. Subsequent analyses will include an analysis of variance comparing SCQ and SELF scores in active placebo and full-dose participants, and correlational analyses of anxiety (HADS and STAI) and depression (HADS) scores as related to SCQ and SELF scores, with p. set at 0.05. The investigators may also compare

SCQ scores and NK cell counts made from blood sampled approximately 23 hours after each psilocybin-assisted session to see whether there are associations between presence and degree of mystical experience changes in immunological function.

The investigators may describe any patterns of change in SCQ and SELF scores between the randomized study and the open label study segment.

The investigators will record occurrence of spontaneously reported and observed side effects, adverse events, and any serious adverse events in participants in each condition. Descriptive statistics will be gathered for type of side effect. A serious adverse event that is possibly or probably related to the study drug will be considered an indicator that psilocybin-assisted psychotherapy is not safe for this population. The investigators will not formally analyze side effects or adverse events but will record all observations of this data.

Statistical Power

Before conducting an analysis of estimated statistical power, it should be noted that this is a pilot study and as such will enroll a very small sample of participants, and that condition assignment is unequal. Hence it is very likely that estimated statistical power will be very low. It is likely that this study possesses more power for assessing the safety of psilocybin-assisted psychotherapy than assessing potential efficacy.

To date, no one has published results from controlled studies specifically assessing psilocybin-assisted psychotherapy in people experiencing anxiety related to advanced stage cancer. However, there is a history of previous research into treatment of anxiety and quality of life in advanced stage cancer with LSD-assisted psychotherapy. At least two-thirds of people with advanced stage cancer enrolled in psychotherapy using doses of 200 mcg or more exhibited improved quality of life (Grof et al. 1973; Kurland 1973; Pahnke 1969). On the other hand, there is a wide degree of inter-individual variation in response to psychedelic drugs such as LSD and psilocybin, and the studies described above did not follow modern research methods. Assuming the actual effect size for detecting efficacy fell somewhere between 0.4 and 0.7, the analysis of estimate power used an effect size of 0.6.

Using the software provided on Russ Lenth's site for estimating statistical power (Lenth 2006), using a two-sample t-test and estimated effect size of 0.6, the ability to detect differences between a sample of six and a sample of three, estimated power was exceedingly low, or 0.1143, and when power was estimated for a balanced ANOVA with five per condition and an estimated effect size of 0.6, the power estimate was still low, though slightly higher, at 0.2199.

Monitoring for Risks

According to the most recent and comprehensive review, serotonergic hallucinogens "are generally considered to be physiologically safe molecules" that chiefly alter consciousness (Nichols 2004). Recent reviews and searches of the literature indicate that psilocybin is not associated with harm or damage to any organ or system in the body

(Nichols 2004; Passie et al. 2002), for more details see "Chemistry and Pharmacology" section in this protocol and sections of the Investigator's Brochure. Psilocybin can produce changes in blood pressure and heart rate, but these changes are not as strong or as consistent as those seen after psychostimulants or entactogens (MDMA-like drugs), and sometimes these changes only occur at one time point (Griffiths et al. 2006; Hasler et al. 2004). More consistently, psilocybin can produce rapid and intense changes in mood, including periods of anxiety or panic. Both these physiological and psychological effects are transient and do not last beyond the duration of drug effects. Psilocybin is not expected to interact with opiate pain management medication, except to blunt some subjective effects (Grob 2007).

Researchers studying the effects of 30 mg psilocybin took precautions similar to the ones we will use in this study (Griffiths et al. 2006), and no reactions requiring pharmacological intervention occurred.

The investigators will perform a liver panel prior to each psilocybin session to ensure that any recent cancer medications or disease processes have not significantly impaired liver function to the point wherein a participant might have higher than expected psilocybin or psilocin levels. The investigators may reschedule the psilocybin session or withdraw the participant from the study in response to liver panel results.

Acute Psychological Distress

The investigators will discuss possible effects of the study drug with participants during introductory psychotherapy sessions and immediately before each experimental session to reduce the likelihood of a panic response. The intent of psilocybin-assisted psychotherapy sessions is to allow the participant whenever possible to confront and move through intense emotional changes or experiences evinced by psilocybin. Participants will be prepared for confronting emotionally intense thoughts, memories or experiences during the introductory psychotherapy sessions. Preparation includes learning hypnotic induction and diaphragmatic breathing. Both investigator-therapists will remain with the participant for up to six hours after drug administration, or until the participant is mentally stable or has returned nearly or wholly to baseline.

If after eight hours the participant continues to exhibit extreme psychological distress, paranoia or lack of insight into his or her condition, at least one and possibly both therapist-investigators will remain with the participant until his or her anxiety and mental status has returned to baseline. If appropriate, the participant will receive a rescue medication, but with a preference for supportive care first, as described below.

If a participant exhibits signs of psychological distress, panic or psychotic response as described above, the investigators will first remind the participant that he or she has taken a psychoactive drug and that he or she can first stay with and work through the anxiety. The investigators can offer support and reassurance, and they may help reduce anxiety through reminding the participant of the techniques learned prior to the experimental session. Intravenous lorazepam (1 - 3 mg) will also be available for on-site treatment of extreme acute anxiety if needed. Benzodiazepines may be prescribed in the days

following the experimental session, as a supplement to other non-drug methods of reducing anxiety. Sublingual olanzapine (Zyprexa®, 10 mg) will be available for treatment of psychosis or extreme distress that does not resolve with supportive care. At least one of the investigators will be available by telephone throughout the night after each drug administration.

Rescue medication will only be used if an individual is endangering him or herself or others, or at the discretion of the investigator. The use of prescribed rescue medicines during an experimental session is contraindicated because it can interrupt the therapeutic process, although it would not be expected to cause any physical harm to the subject. The goal of the process is to confront fears and to experience them fully as a means of coping with them, and participants are likely to feel anxious during the course of the experimental session.

The investigators will query subjects about suicidal ideation or intent during screening, and prior to each psilocybin session. Participants who evidence suicidal ideation or intent will be withdrawn from the study and referred to appropriate psychiatric care.

If a psychiatric hospitalization is necessary, participants will be admitted to the study site, which is on the same campus as the clinic. The hospital will be informed in advance about the study.

Medical Emergencies

Basic emergency equipment is available in the cancer center. The principal investigator's office is located in the study site, on the same grounds as the clinic. The hospital will be informed in advance about the nature of this study.

The investigators will assess blood pressure at least five times during the experimental session; immediately prior to drug administration, and hourly for the next three hours. The investigators will make more frequent measures if in their judgment these are warranted. The clinic will have the appropriate medications and equipment to treat hypertension or cardiac problems if they should arise. The slight elevations in blood pressure or heart rate after psilocybin are not expected to cause any problems or cause any adverse events requiring medical intervention.

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes concurrent illnesses or injuries and exacerbation of pre-existing conditions.

An *unexpected adverse event* is one that is not listed in the current Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

All AEs will be monitored until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the investigator and Medical Monitor as to whether continued follow-up of the AE is warranted.

The severity of events reported on the "Adverse Events" CRF will be determined by the investigator as:

Mild: no limitation in normal daily activity.
Moderate: some limitation in normal daily activity.
Severe: unable to perform normal daily activity.

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

1. Not Related

The AE is not related if exposure to the investigational product has not occurred, **or** the occurrence of the AE is not reasonably related in time, **or** the AE is considered unlikely to be related to use of the investigational product, i.e. there are no facts (evidence) or arguments to suggest a causal relationship, or the AE is more likely related to the subject's pre-existing condition.

2. Possibly Related

The administration of the investigational product and AE are considered reasonably related in time **and** the AE could be explained by causes other than exposure to the investigational product.

3. Probably Related

Exposure to the investigational product and AE are reasonably related in time **and** the investigational product is more likely than other causes to be responsible for the AE, **or** is the most likely cause of the AE.

The relationship of the study treatment to an AE will be determined by the investigator.

Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

Results in death

Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.

Requires or prolongs inpatient hospitalization

Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions)

Results in a congenital anomaly/birth defect

Requires intervention to prevent permanent impairment or damage

Is an important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events which do not fall into these categories are defined as **non-serious**. It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the medical history. The hospitalization would not result in the event or condition being reported as an on study SAE unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition. This is because the onset of the event (the reason for the procedure) occurred before the subject was entered in the trial. Hospitalization for cosmetics, non-emergency prophylaxis or abortion does not result in an SAE report unless, in the view of the investigator, hospitalization for these procedures was prolonged as a result of participation in the clinical trial.

Adverse Event Collection

All serious adverse events will be collected for the duration of the study. All SAEs which occur during the course of the trial, whether considered to be associated with the study IP or not, have to be reported **within 24 hours** or at the latest on the following working day by telephone or fax to either of the following:

Medical Monitor:	Michael C Mithoefer	Mmit@bellsouth.net	843-849-6899
Study Monitor:	Valerie Mojeiko	valerie@maps.org;	831 336 4325

Adverse events that will be collected for the duration of the study are:

Pain using the VAPS.
Events requiring a physician visit or an intervention, not related to planned treatments for baseline conditions.
Any adverse event leading to withdrawal from the study.

Additional adverse events collected for seven days after each experimental session are:

Common side effects.
Exacerbation of anxiety.

Collection of Concomitant Medications

All prescription concomitant medications will be recorded at baseline. During the study participants will keep a daily log of medications taken while actively enrolled in the study protocol. Only changes to anxiolytic and pain management baseline medications will be recorded on the CRF.

Laboratory Assessments

Before the study, the investigator will supply the sponsor with a list of the normal ranges for clinical laboratory assessments. All abnormal laboratory values require a comment from the investigator on the laboratory report, regardless of the clinical significance.

After reviewing the laboratory report and evaluating any results that are outside the normal range, the investigator must sign and date the laboratory report. Any abnormal laboratory test result that warrants further investigation to guard the subject's safety will be repeated as appropriate and reviewed by the investigator.

Study Monitoring, Auditing and Documentation

Investigators and/or their study staff will be trained during the initiation visit. During each monitoring visit, source data verification will be performed by qualified staff representing the sponsor. A CRF collation supplied by the sponsor will be completed for each subject. The entries will be checked by trained delegates of the sponsor.

Monitoring and auditing procedures of the sponsor will be followed, in order to comply with GCP guidelines and to ensure validity of the study data.

The sponsor will review the study documentation used for planning, conduct and monitoring of the study in order to ensure compliance with GCP and local regulations. This documentation includes as a minimum: the Investigator's Brochure, the Study Protocol, the Case Report Forms and the Subject Information and Consent Form.

Risks to Participants

Risks and Discomforts Related to Screening and Baseline Examination

All participants must first give permission for the investigators to review medical records and later undergo a psychiatric evaluation and a urinary drug screen to ensure that participants are eligible to be in the study. Permitting the investigators to view their medical test results slightly increases the likelihood of a potential breach of confidentiality, but doing so is necessary for screening appropriate candidates for the study. The investigators will store any information in locked file cabinets within a locked office, as described in "Confidentiality." Participants may find discussing their anxiety and their illness during the psychiatric evaluation upsetting, or they may find screening boring or tiring. Screening is necessary to assess participant eligibility. Participants will have to provide urine for a drug screen, and they may be embarrassed or uncomfortable about the procedure. The urinary drug screen is necessary for verifying the participant's report of current substance use.

Participants will complete self-report and clinician-administered measures of anxiety, depression, quality of life, and spirituality at baseline and during nearly every visit throughout the course of the study, including prior to each psilocybin session and the follow-up two weeks after the second experimental session. Participants may find completing these measures upsetting, or they may find them boring or tiring. The measures are necessary to assess anxiety and depression, quality of life and changes in world view, self-concept and presence of mystical experiences.

Risks and Discomforts of Psychotherapy

During non-drug and experimental sessions, participants will be asked to think about and discuss their thoughts and emotions about their illness, including anxiety and the impact the illness has had on their lives. They may experience intense emotional responses to speaking about these thoughts, feelings and concerns. Even in a therapeutic context, thinking about and discussing serious illness and impending death or the effects of disease progression on life function can produce distress during and immediately after psychotherapy. Psychotherapy is conducted as part of the research study, including the experimental intervention (psilocybin-assisted psychotherapy), and people undergoing psychotherapy are expected to confront unpleasant thoughts, feelings and memories in the process of therapy. They will also learn to use several procedures in coping with anxiety and distress as part of psychotherapy. Because psychotherapy is an integral part of the research study design, the potential distress arising from psychotherapy is unavoidable.

Risks and Discomforts of Procedures Prior to Psilocybin Session

Participants will undergo a blood draw for a standard liver panel prior to each psilocybin session to ensure that they possess sufficient liver function to metabolize psilocybin. The blood draw may produce temporary discomfort as a result of sampling blood. Participants may also experience temporary discomfort at the blood drawing site. There is also a remote possibility of inflammation or infection at the blood drawing site. Liver panel results will allow the investigators to detect poor metabolism, which could produce higher than expected levels of psilocybin. Higher levels of psilocybin may produce prolonged duration or greater intensity of subjective effects. Weighing the risks and benefits of a blood draw versus potentially unpredictable levels of psilocybin, the liver panel conveys more benefits than risks.

Participants will also undergo urinary pregnancy and drug screens. Some participants may be uncomfortable with this procedure or discussing the test results. However, it is necessary to assess pregnancy to avoid the risk of unintended psilocybin exposure in utero. The urinary drug screen is necessary to verify that people have abstained from cocaine or nonprescription stimulants upon study enrollment or prior to each psilocybin session.

Risk of the Experimental Drug (psilocybin)

Psilocybin given at the full dose can be expected to alter affect (mood), cognition (thought) and perception. Common side and adverse effects of psilocybin are listed in “Safety Pharmacology” in the Pharmacology section, and include anxiety, changes in

thought speed or content, depersonalization, derealization, dizziness, fatigue, inattention, impaired concentration, labile mood, nausea, parasethesias, altered time perception, altered visual perception, and unusual thoughts. Psilocybin also produces pupillary dilation and can produce changes in blood pressure and heart rate. These effects are transient and are generally gone approximately six hours after drug administration. People in previous human studies have tolerated doses of psilocybin equal to or greater than the doses employed in this study.

Like other serotonergic psychedelics, psilocybin can produce a number of psychological adverse events, most of them related to increased anxiety or psychological distress. The likelihood of these effects occurring during a controlled study is far lower than during nonmedical use (Halpern and Pope 1999; Hasler et al. 2004). However, the investigators will whenever possible take the steps below to further reduce or prevent their occurrence.

Panic attacks, severe generalized anxiety, or persisting insomnia

Psilocybin can produce anxiety and/or panic response, and less commonly, a prolonged unpleasant experience (or "bad trip"), as can other serotonergic psychedelics, such as LSD. Medical case reports and case series specific to consumption of psychedelic mushrooms (Hyde et al. 1978; Musha et al. 1986; Peden and Pringle 1982) report that emergency department admissions after use of psilocybin-containing mushrooms report transient anxiety or panic. The most commonly reported adverse events described in a survey of 44 individuals admitted to hospital after psilocybin use were dysphoria that lasted for an average of 3.8 hours, followed by nausea or vomiting, occurring in almost half the admissions (Peden and Pringle 1982).

The occurrence and intensity of anxiety or panic responses can be reduced through providing participants with information on potential drug effects, supervision and monitoring of participants for the duration of drug effects, and using ascending dose designs. The goal in this study is to treat participants undergoing anxiety or panic reactions first by verbal and psychological interventions, and using anxiolytic medication only after verbal and psychological interventions have failed, and if participants are endangering themselves or others.

In case of insomnia the investigator may prescribe a benzodiazepine or zolpidem as a "rescue medication" for the day or night after an experimental session. Residual symptoms will be addressed during the frequent follow-up psychotherapy visits with the investigators.

Reckless or self-injurious behavior

People who have taken serotonergic psychedelics, as LSD, in uncontrolled settings may engage in reckless behavior, such as driving while intoxicated. The risk of reckless behavior occurring during controlled studies can be prevented or greatly reduced through continued supervision by the researchers and requiring all participants to remain at the practice for 23 hours after each drug administration.

Psychosis, suicidal thoughts or impulses

As is true of the pharmacologically similar compound LSD, psilocybin use is associated with transient and sometimes prolonged psychotic states in users (Benjamin 1979; Halpern and Pope 1999). Researchers who reviewed case series and reports that associated LSD or serotonergic psychedelics more generally with subsequent occurrence of psychosis note that diagnosis of psychosis is made only after drug use, and not prior to it (Strassman 1984). After examining the literature, Strassman concluded that LSD might trigger psychotic episodes in people already vulnerable to psychosis but that it did not directly cause psychosis in people not susceptible to it. Two large studies surveyed clinicians or researchers who had conducted LSD research or LSD-assisted psychotherapy (Cohen 1960; Malleson 1971) and found the prevalence of psychiatric symptoms after participation to be very low. None of the participants in recent psilocybin studies experienced psychotic states, though some participants exhibited transient paranoia or some loss of insight into the situation during the course of psilocybin effects (Gouzoulis-Mayfrank et al. 1999b; Griffiths et al. 2006; Vollenweider et al. 1997). These findings suggest that while psilocybin can provoke psychosis or other psychiatric symptoms in a very small percentage of people, it does not do so often, and that receiving a psychedelic drug as part of a research study is extremely unlikely to trigger transient or persistent psychosis. The occurrence of transient or persistent psychosis can be prevented or further reduced by screening subjects on the basis of past and current mental health. Subjects with a personal or family history in first-degree relatives of psychosis (bipolar disorder or schizophrenia), or suicide attempts will be excluded from this study.

If a participant should become psychotic or suicidal for a time exceeding the duration of drug effects and the investigators are unable to ameliorate these symptoms, arrangements will be made for him or her to be admitted to the nearest inpatient psychiatric facility at the clinic.

Chronic neuropsychological effects

Earlier studies found changes in personality or neuropsychological function after frequent chronic LSD use. However, a review of these studies concluded that they all shared a number of methodological flaws (Halpern and Pope 1999) that included retrospective study design, failure to account for effects of other drugs, possible pre-existing morbidity, and the association of LSD with subcultures that valued specific personality types. In their review and analysis, Halpern and Pope concluded that long-term changes in personality or psychological function, if they existed at all, were liable to be subtle or not clinically significant (Halpern and Pope 1999). It is notable that two months after psilocybin administration, investigation in psilocybin-naïve individuals, investigators found that friends or relatives of the study participants stated that after participants received psilocybin, they underwent positive changes in their attitudes and behavior (Griffiths et al. 2006).

Some people who have used serotonergic psycedelics, such as LSD or psilocybin, experience persistent and distressing alterations in mostly visual perception that last from weeks to years after use. This condition is now diagnosed as hallucinogen persistent perception disorder (HPPD), and is not referred to by the term “flashbacks,” which better

describes an experience more akin to traumatic recall of an intensely upsetting experience, as a "bad trip." By contrast, HPPD involves changes in visual perception rather than a re-experiencing of feelings or memories first experienced while under the influence of a psychedelic. There is a paucity of data concerning the prevalence of HPPD due to psilocybin use.

To date, there are no reports describing prevalence of HPPD in the general population, but an examination of previous reports and estimates of use of LSD and other serotonergic hallucinogens use in the US suggests that HPPD is very rare (Halpern and Pope 2003; Johnston et al. 2003). Halpern and Pope note that many to most previous studies were affected by selection bias. These reports also contained information supporting alternative explanations of flashbacks or HPPD, such as use of other drugs or the presence of other mental disorders, and these same reports found some people who had not used psychedelics also reported experiencing similar perceptual disturbances. In a 2003 NSDUH survey, 9.7% of respondents reported at least some lifetime use of LSD, (Johnston and O'Malley 2004), and 0.2% reported using LSD at least once in the past year (NSDUH, 2004), suggesting that if HPPD were a common outcome of LSD use, it would be reported more often in the literature. Preliminary data collected by Baggott suggests that no more than 1% of 1000 hallucinogen users surveyed experience HPPD (Baggott 2006).

The risk of HPPD occurring after psilocybin administration can be reduced by screening participants for potential risk factors such as substance dependence and through excluding people reporting HPPD after prior use of hallucinogens.

Reproductive and Developmental Risks

Pregnant women will be excluded from participation in the proposed study. Women of childbearing potential enrolled in the study must practice a reliable method of birth control, and they must have a negative pregnancy screen before undergoing each experimental session. Although there is no evidence that psilocybin is teratogenic or mutagenic (see below under "reproductive toxicity" in "Chemistry and Pharmacology" and in the IB), the exclusion of women who can become pregnant from this study is a general ethical commitment.

Potential for Drug/ Drug Interactions

There is scant literature on potential drug-drug interactions between psilocybin and other medications or psychoactives, and a review addressing the pharmacology of psilocybin fails to mention any interactions of note (Passie et al. 2002). Research studies in humans demonstrated that drugs that antagonize the $5HT_{2A}$ receptor may attenuate or eliminate most of the subjective effects of psilocybin, very likely including therapeutic effects (Carter et al. 2007; Vollenweider et al. 1998) and that D_2 receptor antagonists, as haloperidol, attenuate effects on positive mood and increased anxiety (Vollenweider et al. 1998). Surveys of recreational users of serotonergic psychedelics, including psilocybin, suggests that selective serotonin uptake inhibitors (SSRIs) may at first enhance psychedelic effects, but that chronic SSRI treatment attenuates drug effects, and that treatment with MAOIs also attenuates the effects of LSD in humans (Bonson et al. 1996).

By contrast, a chronic course of tricyclic antidepressants may amplify the psychedelic effects of serotonergic psychedelics, likely including psilocybin (Bonson and Murphy 1996).

Early research in rats found that opioid agonists attenuated LSD-associated behavior in rats, such as changes in body posture and disruption of operant conditioning for food reward, while opioid antagonists enhanced these behaviors (Domino 1986; Ruffing and Domino 1981). As noted in "Drug Description and Dose" above, Charles Grob MD, the principal investigator conducting the study of psilocybin-assisted psychotherapy in people with advanced stage cancer, reported that opiates attenuated the effects of psilocybin, but otherwise produced no adverse drug-drug interactions (Grob 2007). This pilot study of psilocybin-assisted psychotherapy may contribute to knowledge of the safety of psilocybin in a medical setting, but based on the existing literature, we are taking appropriate cautions.

Abuse Liability

Currently psilocybin has been placed in the most restrictive schedule of drugs in the US (Schedule 1), defined as having no medical use and having high abuse liability. Despite this designation, examining use patterns in humans and self-administration and conditioned aversion in nonhuman primates suggest that psilocybin possesses little abuse potential. See the section on drug dependence and abuse potential in "Additional Information" for research findings on abuse potential and self-administration of psilocybin.

Risks of Active Placebo dose of Psilocybin

The 4 mg dose of psilocybin used in this study is expected to produce some but not most of the effects of the full 25 mg dose. These include slight changes in perception, cognition or mood, such as slight increases in positive or negative mood or lights or colors seeming brighter. This dose is not expected to produce potentially therapeutic effects, such as amplifying or generating intense mystical or transformative experiences. When combined with psychotherapy, the active placebo dose is not expected to reduce anxiety to the same degree as the experimental intervention dose. It is necessary to employ an active placebo so as to have a controlled study and to maintain the blind concerning condition assignment. Participants who learn they received active placebo will have the opportunity to consent to undergo an open-label study continuation immediately upon learning that they received active placebo.

Alternative Treatments and Procedures

The primary alternative to study participation is not to take part in the study. There are a number of recognized treatments for anxiety arising from diagnosis with a potentially fatal illness such as stage IV melanoma. Treatment often includes both psychotherapy and medication. Most commonly recommended psychotherapeutic treatments include stress management, cognitive therapy, exposure therapy, and psychodynamic psychotherapy. Medications that may ameliorate symptoms of anxiety include

antidepressants (SSRI or tricyclic), benzodiazepines, and mood stabilizers. Participation in this study is entirely voluntary, and refusing to take part in this study will not affect the care the participant is already receiving for anxiety arising from advanced stage illness. Nor will declining to participate affect any care he or she is receiving for stage IV melanoma. Participants will not be penalized for withdrawing from the study.

Confidentiality

Every effort will be made to strictly safeguard the confidentiality of all participants. Despite this, privacy cannot be guaranteed. Prior to and upon entry into the study, participants will be assigned a unique subject number (see "Subject numbering" above). Data collected from each participant will be identified only by the participant's initials and subject number on source documents. All communication concerning the participants, including communications relating to statistical data gathering from the tests and measurements, will use subject number only and not the participant's name. All data, measures, records and recordings, and information linking subject numbers to the names of participants will remain at the office of the principal investigator within a locked file cabinet. Access to measures will be limited to regulatory agencies and researchers assessing the participant for changes in symptoms and individuals analyzing data. Researchers with access to data will not be provided with any information that would identify participants by name or by other means.

Costs to Participants

There will be no costs to participants for any of the study procedures, including receiving the study drug or remaining at the practice site for the duration of the experimental session and staying overnight after each drug administration day. The sponsor, MAPS, will pay for all study drugs and study procedures. Participants will not be paid for their participation in this study.

Risk/Benefits Analysis

Anxiety arising from diagnosis with Stage IV melanoma places an additional burden on people who already face a short estimated life expectancy and who must also deal with the sometimes debilitating side effects of cancer treatments. Coping with anxiety in addition to the strains of contending with an aggressive cancer reduces quality of life and may interfere with maintaining relationships and completing life goals. Existing treatments for anxiety may not help everyone, and some treatments, such as benzodiazepines, come with unwanted side effects such as sedation, memory impairment and physical dependence. Given that people with an aggressive cancer may already be taking several different medications to treat their cancer, pain arising from the cancer, and nausea arising from cancer treatments, people with stage IV melanoma may not wish to take additional medications for anxiety.

Psilocybin, like other psychedelic compounds, can powerfully alter affect (mood, feelings), cognition and perception. Psilocybin can produce life-changing experiences that reduce anxiety in the face of imminent death, but it can also produce severe anxiety, panic reactions and transient psychotic states in some individuals. While intense, these experiences are for the most part transient and treatable, and relatively rare. Psilocybin

likely produces intensely beautiful or moving and transformative experiences through the same processes as produce anxiety and panic. Psilocybin has minimal toxicity, and no one has reported a verifiable fatality from psilocybin. The substance has been used in psychotherapy during the 1960s, with psychiatrists and researchers administering psilocybin to thousands of people. Psychotherapists stopped conducting psilocybin-assisted therapy when the drug was made illegal, and not because of any untoward events that occurred during therapy.

Currently, several studies that were just completed in the US and Europe (Griffiths et al. 2006; Hasler et al. 2004; Moreno et al. 2006) have reported safely administering psilocybin in healthy people and in people with OCD, and an ongoing study continues to administer psilocybin to people with advanced stage cancer (Grob 2005). Careful screening, offering a supportive environment and teaching means of dealing with intense anxiety will reduce the likelihood and severity of the adverse effects of psilocybin. Despite psilocybin's capacity to generate profound alterations in consciousness, it possesses little to no physiological risks, has low abuse liability, and also has the capacity to attenuate anxiety and facilitate positive changes in attitude and behavior.

A third of the study participants will receive "active placebo" doses of psilocybin, with "active placebo" connoting a dose that is not expected to produce therapeutic effects. However, these participants will still undergo up to four non-drug psychotherapy sessions plus psychotherapy conducted during each experimental session with active placebo. Once the blind has been broken for each individual, participants who received active placebo may immediately enroll in an open-label study continuation wherein they receive a fully active dose of psilocybin as soon as such a session can be scheduled. An active placebo group is required in order to properly assess the efficacy of study drugs, and an active placebo is required when dealing with strong psychoactives such as psilocybin. Because serotonergic psychedelics produce a unique array of effects that are hard to replicate through other means, the active placebo in this study is a low dose of psilocybin expected to produce some but not all of the drug's cardinal effects.

After taking into consideration the costs and benefits associated with the current study versus alternative treatments available for people with anxiety relating to their cancer diagnosis, we conclude that the benefits of conducting the proposed study outweigh the risks, as the risks are minimal and this innovative treatment, if found to be efficacious, has the potential to help many people experiencing intense anxiety in addition to an aggressive cancer.

Patient's Rights/Insurance

All patients will receive the Informed Consent before enrolling in the study. In the first investigational interview, the investigators will ensure that participants understood the study design as described in consent documents. The investigators will let participants know that they can stop their participation at any point of the study without negative consequences for them and without giving any reason for their decision.

The sponsor will pay for all study-related assessments and therapy. The sponsor will be responsible for payment in treating study-related injuries. Participants will pay for any care not related to the study.

Record Retention

Investigators must retain all study records required by MAPS and by the applicable regulations in a secure and safe facility. The investigator must consult a MAPS representative before disposal of any study records. "Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Chemistry, Manufacturing and Control Information

The study drug is psilocybin, 4-phosphoryloxy-N,N-dimethyltryptamine), a tryptamine first isolated from psilocybe mushrooms by Albert Hofmann, the discoverer of LSD, in 1957, and later synthesized by him in 1958 (Passie 2005). Psilocybin will be administered orally in the form of opaque capsules. The supplier of psilocybin is Organix. The psilocybin is from the same batch manufactured for Dr. Francisco Moreno for his study of psilocybin in people with obsessive-compulsive disorder. This manufacturer has supplied psilocybin to Dr. Charles Grob for the ongoing study of psilocybin-assisted psychotherapy in people with advanced stage cancer. A Certificate of Analysis issued by the manufacturer to the sponsor on November 14, 2007 states that the sample is 100% pure.

Psilocybin will be compounded by the pharmacy at the University of Arizona. The pharmacist will pre-randomize all capsules. Full (25 mg) and placebo (4 mg) doses of psilocybin will be placed in opaque capsules of identical size. An inert substance, such as lactose, will be added to placebo capsules so that they weigh the same as full dose capsules. All psilocybin will be handled and stored in accordance with federal and state regulations concerning Schedule 1 substances.

MAPS claims categorical exclusion from the requirement to submit an environmental assessment (21 CFR 25.15[a]). MAPS claims categorical exclusion (under 21 CFR 25.31[e]) for the study under this IND. To its knowledge, no extraordinary circumstances exist.

Pharmacokinetics and Pharmacodynamics

Primary Pharmacology

Psilocybin (4-phosphoryloxy-N,N-dimethyltrypatmine, also referred to as 3-[2-(Dimethylamino)ethyl]-1H-indol-4-ol dihydrogen phosphate ester), one of the chief psychoactive compounds found in mushrooms in the genus psilocybe (as psilocybe cubensis, p. semilanceata, p. mexicana). Its chemical formula is $C_{12}H_{17}N_2O_4P$.

It is likely that psilocybin and LSD both alter consciousness through similar mechanisms of action (Aghajanian and Marek 1999; Nichols 2004), acting as $5HT_{2A}$ agonists. Psilocybin acts upon several serotonin receptors, including $5HT_{1A}$, $5HT_{2A}$ and $5HT_{2C}$ receptors (McKenna et al. 1990; Passie et al. 2002). Psilocybin does not act directly on dopamine receptors, and there is no current information on its actions on newly discovered serotonin receptors, as $5HT_{5A}$ or $5HT_7$. Large doses of psilocybin (25 mg/kg) increased the presence of a norepinephrine metabolite (Stolk et al. 1974), but it is unclear if this action occurs at typical human doses.

Primary Pharmacodynamics

Drug Activity Related to Proposed Action

Research conducted during the 1950s and 1960s found that psilocybin, like LSD, can be used in combination with psychotherapy (Passie 2005; see for example (Fontana 1961; Leary et al. 1963). Therapists used some of the subjective effects of these serotonergic hallucinogens to stimulate or uncover unconscious feelings or memories and to facilitate breaks with routine or habitual behavior. In the psychotherapy context, potentially therapeutic effects of psilocybin include changes in ego boundary, stimulating unusual thoughts and views of the self and the world, and mood lability. From a traditional psychodynamic viewpoint, a less rigid or more expanded ego boundary and viewing the self or the world in a new perspective can offer a chance for insight, and profound changes in mood and can facilitate confrontation with these emotions. Furthermore, psychotherapy utilizing serotonergic hallucinogens consistently contained spiritual elements which in and of themselves seemed to have profound, positive effects on patients (Griffiths et al. 2006; Pahnke 1963). All three combined may help produce mystical or transformative experiences. These effects of psilocybin may help reduce anxiety when experienced in a safe and supportive environment. However, none of these early studies sought to examine the pharmacological bases of these effects, and to date, there are still no studies that tie a specific putative therapeutic effect of psilocybin with a specific pharmacological action. All serotonergic hallucinogens appear to share activity at $5HT_{2A}$ receptors, suggesting that these receptors are necessary, but not sufficient, for producing alterations in affect, cognition and perception (Nichols 2004). Psilocybin exhibits an affinity for $5HT_{2A}$ receptors (McKenna et al. 1990) and it has a stronger affinity for human than rat $5HT_{2A}$ receptors (Gallaher et al. 1993). Administration of the $5HT_{2A}$/$5HT_{2C}$ antagonist ketanserin attenuated subjective effects of psilocybin (Vollenweider et al. 1998) and reduced psilocybin effects on visual perception (Carter et al. 2005a). It is possible that psilocybin alters consciousness through compound-specific alterations in secondary messenger signaling upon activating $5HT_{2A}$ receptors ("allosteric receptor trafficking"), as both psilocybin and LSD stimulate the arachidonic acid pathway when activating rat $5HT_{2A}$ receptors (Kurrasch-Orbaugh et al. 2003). While a study chiefly comparing LSD with the non-hallucinogenic compound lisuride in mice suggests that serotonergic hallucinogens produce at least some of their subjective effects through selective stimulation of secondary messengers, researchers have not examined psilocybin in similar studies. Finally, it is possible that some of the potentially therapeutic effects of psilocybin are the result of changes in gene expression stimulated by $5HT_{2A}$ receptor activation (Gonzalez-Maeso et al. 2003; Nichols and Sanders-Bush 2002). It is not clear

what significance these changes in gene expression have on the generation of subjective effects.

Table 1
Psilocybin Binding Data

Receptor	Ki (nM)	Hot Ligand	Species	Source	Reference
5HT1A	190	3H-8-OH-DPAT			
5HT2A	6	3H-DOI	Rat/cow	Brain	(McKenna et al. 1990)
5HT2C	410	3H-Ketanserin	Rat/cow	Brain	(McKenna et al. 1990)

Table 2
Psilocin binding Data

Receptor	Ki (nM)	Hot Ligand	Species	Source	Reference
5-HT1A	49	3H-8-OH-DPAT	Human	Cloned	(Blair et al. 2000)
5-HT2A	25	125I-DOI	Rat or bovine	Cloned	(Blair et al. 2000)
5-HT2C	10	1251-DOI	Rat	Cloned	(Blair et al. 2000)

Some neuroscientists hypothesize that serotonin $5HT_{1A}$ and $5HT_{2C}$ receptors play a role in producing at least some and perhaps most of the effects of serotonergic hallucinogens (Nichols 2004). It is notable that most $5HT_{2A}$ agonists also act on $5HT_{2C}$ receptors, making it difficult to single out only one of the two receptors as key for producing the effects of psychedelics. To date, work has not specifically studied the effects of psilocybin or psilocin on $5HT_{2C}$ receptors. Psilocybin activates $5HT_{1A}$ receptors. Direct application of psilocybin to dorsal raphe nucleus (DRN) neurons reduces firing of DRN neurons (Aghajanian et al. 1968; Aghajanian and Hailgler 1975), an effect attributed to $5HT_{1A}$ activity. Administering the $5HT_{2A/2C}$ antagonist ketanserin along with psilocybin reduced most psychedelic effects in humans without reducing self-reported fatigue or inattention, and without preventing psilocybin from altering binocular rivalry (Carter et al. 2005b), findings suggesting that $5HT_{1A}$ receptor activation may produce or modulate some, but not all, psilocybin effects.

Previous research has reported that LSD produced analgesia that outlasted its subjective effects (Kast 1966). It is possible that psilocybin shares this effect with the related serotonergic hallucinogen. The pharmacological mechanisms for LSD-induced analgesia remain unclear, and researchers do not know if psilocybin produces analgesia. If LSD causes analgesia as a result of activating $5HT_2$ or $5HT_{1A}$ receptors, then psilocybin may share these effects as well.

Secondary Pharmacology

Safety Pharmacology

Studies in humans and nonhuman animals indicate that psilocybin has very low toxicity (Nichols 2004; Passie et al. 2002). LD_{50} ranged from 285 mg/kg in rats and mice to 12.5 mg/kg in rabbits (Usdin and Efron 1972), cited in Merck Manual, 12th Edition). The full dose of psilocybin that will be administered in this study is approximately 20 times smaller than the LD_{50} in rabbits.

Psilocybin is not associated with disease or damage to any organ or system (Nichols 2004). A recent extensive search conducted by Lisa Jerome on the PubMed database in September, 2005 using the words "psilocybin" and various organs or medical terms ("heart," "cardiac," "liver") and "adverse event" uncovered only a single case of liver problems. An additional search using the word "psilocybin" alone conducted on August, 2006 also failed to turn up any new cases of adverse events after psilocybin. More commonly, damage or disease to organs (as renal failure) is associated with mistakenly consuming poisonous mushrooms under the belief that they are psilocybin-containing varieties (see for example (Franz et al. 1996). There have been no fatalities directly related to consumption of psilocybin-containing mushrooms or to use of psilocybin. Given the long history of research in humans with psilocybin and the continued use of psilocybin-containing mushrooms in various nonmedical settings for perhaps thousands of years, the lack of serious adverse events or fatalities is especially notable.

Common side effects

Common acute side effects of psilocybin are almost all psychological, and include anxiety, changes in thought (experiencing thinking speeding up or slowing down), changes in motion perception, changes in time perception (time slowing down or speeding up), depersonalization (feeling as if one is "outside oneself"), derealization (feeling as if the world is unreal or as if one is "in a dream"), dizziness, fatigue, impaired concentration, inattention, mood lability (rapid and sometimes profound changes in mood), nausea, nervousness, parasthesias (strange bodily sensations or feelings), perceptual alterations (general), altered time perception, alteration in visual perception (distortions, illusions and imagery seen with eyes open or closed), and unusual thoughts or feelings about the self or the world (Carter et al. 2004; Carter et al. 2005b; Fischer 1966; Gouzoulis-Mayfrank et al. 1999b; Griffiths et al. 2006; Hasler et al. 2004; Hollister 1961; Hollister and Sjoberg 1964; Umbricht et al. 2002; Vollenweider et al. 1997) . Most of these effects are acute and last no longer than six hours (Hasler et al. 2004; Hollister 1961; Passie et al. 2002; Vollenweider et al. 1998). For the most part, people receiving psilocybin maintained insight concerning the nature and source of their experience. However, some participants occasionally exhibited paranoid ideation or temporarily lost insight into the experimental situation (Gouzoulis-Mayfrank et al. 1999b; Griffiths et al. 2006; Vollenweider et al. 1998).

Psilocybin produces slight sympathetic system activation. Physiological effects include pupillary dilation and detectable but moderate increases in blood pressure or heart rate (Griffiths et al. 2006; Hasler et al. 2004). Researchers sometimes detected changes in blood pressure and heart rate only at one point in time, as sixty minutes after drug administration (Hasler et al. 2004). It is notable, however, that a 26-year old man with obsessive compulsive disorder (OCD) exhibited an elevation in diastolic blood pressure from 91 to 104 mm Hg after receiving 0.2 mg/kg psilocybin in the absence of self-reported anxiety (Moreno et al. 2006).

Acute Adverse Effects

Common acute adverse effects are all psychological and include anxiety or panic response and a prolonged unpleasant experience (or "bad trip"). Less frequently, people experience transient psychotic reactions. These effects are nearly identical to the acute adverse events associated with other psychedelic compounds, such as LSD. Medical case reports and case series specific to consumption of psychedelic mushrooms (Hyde et al. 1978; Musha et al. 1986; Peden and Pringle 1982) report the occurrence of usually transient anxiety or psychosis-like symptoms similar to those reported for LSD. The most commonly reported adverse events described in a survey of 44 individuals admitted to hospital after psilocybin use were dysphoria lasting an average of 3.8 hours, followed by nausea or vomiting, occurring in almost half the admissions (Peden and Pringle 1982). As might be expected to occur in people taking psychedelic compounds (Nichols 2004; see "Previous Human Experience" below), Peden and Pringle found that the people surveyed also reported experiencing alterations in perception and parasthesias (unusual body sensations), such as numbness or tingling. These experiences and reactions typically resolved spontaneously with supportive care, or, on some occasions, with the use of sedative medications such as benzodiazepines. In most cases, emergency room admissions related to anxiety or psychological distress after psilocybin did not require hospitalization.

Some individuals enter transient and at times prolonged psychotic states after use of serotonergic hallucinogens, including psilocybin (Benjamin 1979; Halpern and Pope 1999; Strassman 1984). Because in nearly all cases, there are no reported evaluation of psychological state prior to hallucinogen use, drawing conclusions about causality is difficult. After examining the literature, Strassman concluded that psychedelic drugs such as psilocybin might trigger psychotic episodes, but in a non-specific and non-etiologic manner, and that they did not cause psychosis (Strassman 1984). Cohen examined the prevalence of psychiatric morbidity by sending questionnaires to researchers who had conducted controlled studies with the related serotonergic psychedelic LSD, and found that 0.08% of 5000 study volunteers experienced psychiatric symptoms that lasted more than two days (Cohen 1960). Psychiatric symptoms occurred at the slightly higher rate of 0.18% in psychiatric patients given LSD. Another survey of a separate sample of 4300 research volunteers who took part in LSD studies reported that 0.9% of the sample experienced serious, persistent psychiatric reactions (Malleson 1971). These findings suggest that participating in a research study involving the administration of a psychedelic compound is extremely unlikely to trigger transient or persistent psychosis. Past research with LSD and other psychedelics did not apply as stringent criteria for screening or admitting study participants as would be used today, making the low rates of psychosis especially notable.

Though the possibility of chronic neuropsychological effects have never been specifically addressed with respect to psilocybin, earlier studies found changes in personality or neuropsychological function in people reporting frequent or chronic use of LSD, as described in a review by Halpern and Pope (1999). However, later examinations of these studies found that they possessed a number of methodological flaws, including

retrospective study design and failure to account for use of other drugs. Halpern and Pope concluded that long-term changes in personality or psychological function after LSD, if they occurred at all, were liable to be subtle and not clinically significant. Furthermore, when Griffiths and colleagues interviewed, people familiar with participants who took part in study of the ability of approximately 0.43 mg/kg psilocybin to produce spiritual experiences, these individuals stated that two months after psilocybin, the people who received it exhibited several positive life changes, and no negative life changes.

Some people who have used serotonergic hallucinogens, such as LSD or psilocybin, experience persistent, distressing alterations in mostly visual perception that last from weeks to years after use. This condition is now diagnosed as hallucinogen persistent perception disorder (HPPD), and is no longer referred to as "flashbacks," a term now reserved mostly for describing re-experiencing of a traumatic event, such as a "bad trip." HPPD has occurred after use of psilocybin-containing mushrooms (Benjamin 1979; Espiard et al. 2005). To date, there are no reports describing prevalence of HPPD in the general population, but an examination of previous reports and estimates of serotonergic hallucinogen use in the US suggests that HPPD is very rare (Halpern and Pope 2003; Johnston et al. 2003; Johnston et al. 2005). Halpern and Pope note that many to most previous studies of HPPD-like phenomena were affected by selection bias and contained information supporting alternative explanations for the symptoms, such as use of other drugs or diagnosis with another mental illness (Halpern and Pope 2003). Furthermore, at least some reports found that people who stated they had not used hallucinogens nonetheless experienced perceptual disturbances similar to those seen with HPPD. In 2003, between 9% and 17% of individuals adolescents and young adults reported at least some lifetime use of hallucinogens other than LSD, a category including, though not limited to, psilocybin-containing mushrooms (Johnston et al. 2005). If HPPD were a common outcome of using psilocybin-containing mushrooms, then more cases of HPPD would be reported. As well, preliminary data collected by Baggott suggests that only no more than 1% of 1000 hallucinogen users reported HPPD symptoms (Baggott 2006). To date, no cases of HPPD have occurred in volunteers in human psilocybin research studies (see for instance Carter et al. 2004; Carter et al. 2005A; Gouzoulis-Mayfrank et al. 1999A; Griffiths et al. 2006; Hasler et al. 1997; Hasler et al. 2002; Hasler et al. 2004; Umbricht et al. 2002; Vollenweider et al. 1997; Vollenweider et al. 1998; Vollenweider et al. 1999; Wittmann et al. 2006).

As is true of LSD and other serotonergic hallucinogens, people who have taken psilocybin in uncontrolled settings may engage in reckless behavior, such as driving while intoxicated.

Abuse Liability

Psilocybin possesses little or no abuse liability. More details can be found in "Risks" section above and in "Abuse Liability" in the Additional Information section below.

Pharmacokinetics/Toxicokinetics

Absorption, Distribution, Metabolism, Excretion

Psilocybin is detectable in plasma 20 to 40 minutes after oral administration (Hasler 1997) reviewed in (Passie et al. 2002). Psilocybin is metabolized by alkaline phosphatase in the liver, and is chiefly transformed into the active metabolite psilocin, which is detectable in plasma 30 minutes after administration (Hasler 1997; Hasler et al. 1997; Lindenblatt et al. 1998). Psilocin first appeared in plasma 15 to 50 minutes after oral administration of 0.2 mg/kg psilocybin. Psilocin half-life ranges between 2 and 3 hours, and it is detectable 6 hours after oral administration (Hasler 1997; Hasler et al. 1997; Lindenblatt et al. 1998). These two studies reported similar but not identical findings, with peak levels of psilocin appearing between 80 and 105 minutes and psilocin half-life ranging between 2.25 h for 0.2 mg/kg and 2.7 h for 0.22 mg/kg.

Previous investigations indicate that psilocybin is a "pro-drug", with psilocin the major, and possibly sole, active compound. Hasler and colleagues have detected three additional psilocybin metabolites; 4-hydroxy-3-yl-acetaldehyde (4HIA), 4-hydroxy-3-yl-acetic acid (4HIAA), and 4-hydroxytryptophol (4I-IT) (Hasler 1997). See "Pharmacokinetics and biological disposition of the drug" in the Investigator's Brochure (IB) for more details of pharmacokinetics and metabolism.

Previous research in non-human animals found that the phosphoric ester group of psilocybin is cleaved by alkaline phosphatase (Horita and Weber 1961; 1962). While there are currently no studies of psilocin metabolism, psilocin is likely metabolized by deamination and demethylation via liver enzymes such as monoamine oxidase and aldehyde dehydrogenase (Hasler et al. 1997).

Psilocin and psilocybin are eliminated through the kidneys, both as unaltered drug and conjugated with glucuronides (Hasler et al. 2002). People excrete most psilocin and psilocybin three hours after oral administration, with some inter-individual variation in excretion. On the basis of urinary psilocin levels 12 to 24 hours after approximately 0.21 mg/kg psilocybin, it is likely that most or all psilocybin and psilocin are excreted from the body by or within 24 hours after administration (Hasler et al. 2002).

Toxicology

Acute toxicity

As noted in "Safety Pharmacology" above, psilocybin has little or no physical toxicity. LD_{50} values for psilocybin are listed above in "Safety Pharmacology" and exceed doses administered in human psilocybin research.

Reproductive Toxicity

To date, there are no published investigations of the effects of psilocybin in utero. Research using the micronucleus model of mutagenicity did not find any signs of psilocybin being mutagenic (Van Went 1978). These findings suggest that psilocybin is unlikely to damage DNA. There appear to be no case reports of birth defects or

developmental toxicity arising from psilocybin or use of psilocybin-containing mushrooms. Nevertheless, the reproductive risks of psilocybin, though likely minimal, remain unknown.

Previous Human Experience

Researchers conducted many studies of psilocybin in humans forty to fifty years ago in North America and Europe (Nichols 2004; Passie 2005; Passie et al. 2002). Most investigations either examined the psychological, subjective and physiological effects of psilocybin in healthy samples, or they examined the therapeutic potential of psilocybin in psychiatric patients or people in psychotherapy (Passie 2005). At least 19 studies examined the therapeutic potential of psilocybin in approximately 1960 participants (Passie 2005). These studies employed doses ranging from 3 to 30 mg (0.043 to 0.43 mg/kg), with average minimum dose being 8.24 mg (0.118 mg/kg) and average maximum dose being 17.19 mg (0.246 mg/kg). People performing psilocybin-assisted psychotherapy generally followed models first used in combination with LSD. Some therapists performed frequent sessions with low doses in "psycholytic" psychotherapy, and others performed only a few sessions with higher doses in "psychedelic" psychotherapy (Passie 2005). Most people conducting psilocybin-assisted psychotherapy wished to activate unconscious memories and conflicts, while some sought in addition to promote transformative or mystical experiences as a means of producing beneficial change. Nearly from its inception, psychedelic-assisted psychotherapy occurred in structured environment that included comfortable furnishings, use of music and art objects, little direct interaction between therapist and patient, and encouragement to contemplate or follow the experience and to confront emotionally intense material. During this period, researchers in North America and Europe also investigated the effects of psilocybin on visual perception, personality and electroencephalography (EEG) (see for instance (Fischer et al. 1970; Keeler 1965; Malitz et al. 1960; Rinkel et al. 1960). Human trials in the US ceased shortly after the DEA placed psilocybin in schedule 1 in 1970, with the last investigation occurring in 1977. At least one psychotherapist in Germany conducted LSD and psilocybin-assisted psychotherapy until 1986 (Leuner 1993).

Researchers began studying psilocybin in the early 1960s, and a resurgence of interest began in the mid-1990s (Nichols 2004; Passie 2005) . Studies in humans reported that psilocybin chiefly produced changes in perception and emotion, including changes in visual perception and attention, and that it did not produce significant changes in physiological function, as described above (see for instance (Gouzoulis-Mayfrank et al. 1999a; Griffiths et al. 2006; Hasler et al. 2004). Imaging studies found that active doses of psilocybin increased glucose metabolism in frontal areas and anterior cingulate, with possibly greater right than left hemisphere activation (Gouzoulis-Mayfrank et al. 1999a; Vollenweider et al. 1997). Previous human trials of psilocybin, including two studies in people with medical conditions, found that this compound could be safely administered in humans.

Research into the pharmacology, subjective and physiological effects of psilocybin resumed in the 1990s in Switzerland and Germany (Hasler et al. 1997; Spitzer et al. 1996). Recent human trials of psilocybin included investigations of metabolism and pharmacokinetics (Hasler 1997; Hasler et al. 2002; Lindenblatt et al. 1998), physiological and neuroendocrine effects (Gouzoulis-Mayfrank et al. 1999b; Hasler et al. 2004), its effects on brain function (Gouzoulis-Mayfrank et al. 1999a; Vollenweider et al. 1997; Vollenweider et al. 1999), vision, attention, and visual working memory (Carter et al. 2005a; Carter et al. 2004; Carter et al. 2005b; Gouzoulis-Mayfrank et al. 2002), time perception (Wittmann et al. 2006), pre-pulse inhibition (Gouzoulis-Mayfrank et al. 1998a; Vollenweider et al. 2007), auditory evoked response potential (ERP, a form of EEG) (Umbricht et al. 2002)semantic association (Gouzoulis-Mayfrank et al. 1998b; Gouzoulis-Mayfrank et al. 1999a; Spitzer et al. 1996; Umbricht et al. 2003), facilitation of spiritual experiences (Griffiths et al. 2006) and serotonergic and dopaminergic contributions to the subjective effects of psilocybin (Vollenweider et al. 1998; Vollenweider et al. 1999). These studies used doses of psilocybin ranging from about 1.25 to 30 mg psilocybin (0.025 to approximately 0.43 mg/kg), and average dose about 14 mg. In these studies, psilocybin was well tolerated and did not produce any serious adverse events.

Recent, ongoing and planned investigations have studied or plan to study psilocybin as a potential treatment for specific mental and neurological disorders. Moreno and colleagues conducted a randomized, double-blind dose-response study of psilocybin in nine individuals with OCD (Moreno et al. 2006). They reported that up to 300 mcg/kg psilocybin was well-tolerated, and they detected at least transient reductions in OCD symptoms after nearly all doses of psilocybin. However, their finding that even the "active placebo" dose of 25 mcg/kg reduced OCD symptoms raises questions concerning the nature and viability of the "active placebo." Following previous research into LSD-assisted psychotherapy as a means to reduce anxiety in people with advanced stage cancer (Grof et al. 1973; Kurland 1973), Grob and colleagues are conducting an ongoing study of psilocybin-assisted psychotherapy in twelve cancer patients with anxiety and projected life expectancy of less than a year (Grob 2005). They have enrolled ten participants to date. Psilocybin is well-tolerated in this sample and there have been no drug-related serious adverse events. After publishing a case series indicating that both psilocybin and LSD can ameliorate the severe and debilitating condition of cluster headache and that both compounds could reduce frequency and number of cluster "attacks" (Sewell et al. 2006), researchers are planning to study the effects of psilocybin and LSD as a means of reducing headache frequency and cluster headache periods in people with cluster headache. See "Safety and Effectiveness in Humans from Prior Clinical Studies" in the Investigator's Brochure for more details.

Additional Information

Facilities and Setting of Study

Psilocybin-assisted psychotherapy will be conducted in a suite of treatment rooms at thes study site. The site is an accredited facility located on the main campus of the clinic. An emergency room and intensive care unit are also on the premises of the study site. Experimental and open-label psilocybin-assisted psychotherapy sessions will take place in a comfortably furnished private treatment suite that will include a comfortable chair, bed or other furnishing that will allow participants to sit or lie comfortably during any part of the session. There will be a means of presenting musical selections to participants without unduly disturbing others. The treatment room has large windows overlooking [local landscaep]. A private toilet and bathroom are also located inside each treatment suite.

There will be equipment for measuring blood pressure and pulse as needed, and the therapists will offer light snacks if requested to do so later in the session. The site possesses a crash cart and appropriate medication for treating any potential emergencies as needed. The psychotherapy will be performed by a therapy team consisting of one male and one female therapist. There will also be additional medical staff available in the treatment area where the treatment suite is located if necessary.

Drug Dependence and Abuse Potential

Though psilocybin is currently placed in the most restrictive schedules for drugs (Schedule 1), findings in humans and non-human animals indicate that psilocybin has little to no abuse potential. Rhesus monkeys did not consistently self-administer psilocybin when given an opportunity to do so (Fantegrossi et al. 2004). Similarly, rodents and nonhuman primates also do not self-administer significant amounts of LSD (Nichols 2004, see (Hoffmeister 1975). The number of people using psilocybin-containing mushrooms is not measured separately in the annual Monitoring the Future survey, and 2003 figures on adolescent and young adult use of “other” hallucinogens remain low. There are no reports of a psilocybin dependence syndrome. A national survey of drug use in Canada states that hallucinogens, including psilocybin, are rarely used in Canada and are not usually the cause for substance abuse treatment (Poulin et al. 1999). For instance, 1% of all drug abuse treatment cases in Toronto were hallucinogen-related. Taken together, these findings indicate that psilocybin has little to no abuse liability, and it is highly unlikely that participants receiving psilocybin in the context of a psychotherapeutic setting that encourages confronting anxiety and fear of impending death and fostering emotionally intense experiences will develop dependence to psilocybin after exposure.

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Appendix A Asssessments and Measures

Daily Medication Diary: This is a daily log of all anti-anxiety and pain management medication intended as an indirect measure of changes in anxiety and pain. Each form will also remind participants to contact the investigators prior to initiation of any drug or medication not already reviewed during the intake evaluation. This measure is used in a study of MDMA-assisted psychotherapy in people with advanced stage cancer.

Daily Pain Level Diary: This is a daily self-assessment of participant pain. This is a simple measure that consists of a 10-cm line labeled at one end with "no pain" and at the other end with "worst pain possible." Scoring is accomplished by having the participant mark the line to indicate pain intensity, and the line is then measured to the mark on a 0- to 10-point scale. Extensive prior research indicates that visual analog pain scales are reliable and valid as both a sensitive measure of pain and as a measure of change in pain (Ohnhaus and Adler 1975).

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C15: (Groenvold et al. 2006) is the short form of a questionnaire (Aaronson et al. 1993) that currently is one of the most widely accepted measures of quality of life. This instrument has 15 items yielding scores for 5 subscales (physical, role, emotional, social, and cognitive functioning) and 3 symptom subscales (fatigue, pain, and nausea/vomiting). Numbers of items were reduced from all scales save the pain scale.

Functional Assessment of Chronic Illness Therapy- Spiritual Well-Being Scale: (Cella et al. 2002; Cella and Nowinski 2002) has two subscales: one measuring sense of meaning and peace, and the other measuring the role of faith in illness, and total combined score assessing spiritual well-being. It is a psychometrically sound measure of spiritual well-being for individuals with cancer and with other chronic illnesses. Questions do not refer to specific religious beliefs or practices and are not biased for or against any particular religious group. The FACIT-Sp contains 12 items, and participants respond on a five-point scale (0 = not at all, 4 = very much).

Hamilton Anxiety Rating Scale: (Hamilton 1959) This clinician-administered measure is a widely used, accepted and well-validated assessment of anxiety. The HAM-A has 14 items; each is rated on a 5-point scale ranging from 0 (not present) to 4 (severe). A score of 14 or greater is associated with clinically significant symptoms of anxiety.

Hamilton Depression Rating Scale: (Hamilton 1960; 1967) This is a widely used and accepted clinician-administered measure of depression. A score of 10 to 13 indicates mild depression; 14-17= mild to moderate depression; and greater than 17 = moderate to severe depression. We will use the 17-item version of the HAM-D, which, like the HAM-A, is rated on a 5-point scale ranging from 0 (not present) to 4 (severe).

Hospital Anxiety and Depression Scale - (Zigmond and Snaith 1983) was developed to assess anxiety and depression in somatic patients. It is a 14 item self-report instrument. Only participants diagnosed with anxiety via SCID or with HADS anxiety scores of 8 or higher will be considered eligible for study participation. Items are scored on a four-point scale, from 0 (not present) to 3 (considerable). This will be the primary outcome measure in this study.

Karnofsky Performance Rating Scale: (Karnofsky and Burchenal 1949) This is a clinician-rated measure of quality of life, scored from 0 to 100, with 100 indicating normal and no complaints of disease and 0 indicating death.

Mini Mental State Examination: (Folstein et al. 1975) The MMSE is a ten-item clinician-administered instrument for assessing mental status and competency. Scores range from 0 to 30. Scores are age- and education-dependent; generally a score equal to or greater than 27 is considered normal. Participants must have scores of 27 or higher each time MMSE is given to remain enrolled in the study.

Natural Killer (NK) Cell Count: This is a widely-recognized measure of immunological function ("innate" immune function) less liable to be influenced by use of cytokines in cancer treatment. It will be performed using diagnostic flow cytometry.

Reactions to Research Participation Questionnaire: (Newman et al. 2001) This is a measure devised to assess participants' experience of study participation, reasons for participation, and perceived costs and benefits of study participation. It contains 24 items, including open-ended questions, ranking a list of items and responding to items on a 5-point scale (1= strongly disagree, 5= strongly agree).

Self-Expansiveness Level Form: (Friedman 1983) This instrument assesses the construct of "self-expansiveness," or spiritual identity. It consists of 18 self-descriptive statements, and participants indicate how willing they are to identify the self with each item along a 5-point scale. There are three subscales: Personal, Middle, and Transpersonal. Criterion, convergent, discriminant, and factorial validity have been established for this measure.

Spielberger State-Trait Anxiety Inventory: (Spielberger et al. 1970) This measure of anxiety differentiates "state anxiety" (i.e. anxiety dependent on a specific situation or stressor) from "trait anxiety" (long-standing anxious affect or disorder) and is considered the definitive instrument for measuring anxiety in adults. Extensive normative group data exists and the STAI has been administered to advanced-stage cancer patients with anxiety as well. The STAI contains 40 questions and participants respond on a 4-point scale, with 1= "not at all" and 4= "very much so".

States of Consciousness Questionnaire: (Griffiths et al. 2006; Pahnke 1969) This instrument is intended to measure alterations in consciousness, particularly those associated with a mystical, peak or transformative experience, and is based on a measure devised for assessing effects of psychedelic compounds (Pahnke 1969). It contains 100

items scored on a 6-point scale (0 = none at all, 5 = Extreme, more than ever before) and has seven scales; Internal unity, external unity, transcendence of time and space, ineffability and paradoxicality, sense of sacredness, noetic quality, and deeply felt positive mood.

Structured Clinical Interview for DSM-IV: (First et al. 1997) The SCID is a semi-structured clinician-administered interview that permits accurate diagnosis of lifetime and current psychiatric disorders, using DSM-IV criteria.

Appendix B: Case Report Forms

These are sample case report form drafts for the study "Psilocybin-assisted psychotherapy in the management of anxiety associated with stage IV melanoma."

The series of case report forms represents CRFs for the first six visits of the study. The second half of the study, consisting of visits seven through 10, will record identical or nearly identical information as presented in the first six visits.

CONTAINS

SCREENING (Visit #1-#2)
BASELINE EVALUATION (Visit #3)
INTRODUCTORY PSYCHOLOGY SESSIONS (Visits #4-#4.5)
EXPERIMENTAL (PSILOCYBIN-ASSISTED)
PSYCHOTHERAPY SESSIONS (Visit #5)
INTEGRATIVE PSYCHOTHERAPY (Visit #6)
DAILY PAIN ASSESSMENT (Visits #3-#10)
PAIN DIARY (Visits #3-#10)
MEDICATION DIARY (Visits #3-#10)
MEDICATIONS AND ADVERSE EVENTS (Visits #2-#10)

Baseline - Psychiatric Evaluation:

Please write in the score or scores for each outcome measure. All scale scores must be complete.

Baseline Measures: **Date of Administration ___ - ____ - ___**
dd mmm yy

Anxiety, Depression, Hopelessness and Thoughts on Hastened Death

Scale	Score
STAI	
State	
Trait	
Total	
HADS	
Anxiety	
Depression	
Hamilton Anxiety Rating Scale (HAM-A)	
Total	
Hamilton Depression Rating Scale (HAM-D)	
Total	
KPRS	
Total	

Baseline – SCID

Date of Evaluation _____-_____-____

mmm yy dd

DSM-IV Diagnosis	Yes	No	Comment
PTSD			
Major Depression			
Panic Disorder			
Generalized Anxiety Disorder			
Anxiety Disorder 2° to General Medical Condition SPECIFY MEDICAL Condition:			
Bipolar Affective Disorder-1			
Bipolar Affective Disorder-II			
Dissociative Identity Disorder			
Psychosis			
Eating Disorder			
Personality Disorder SPECIFY D/O:			
Substance Abuse or dependence (60 days)			
Other DSM IV diagnosis-1 Specify:			
Other DSM IV diagnosis-2 Specify:			

Any Axis 1 diagnosis? ☐**Yes** ☐**No**

Any Axis 2 diagnosis? ☐**Yes** ☐**No**

Baseline - Measures (continued)

Date of Administration ___ - ____ - ____

dd

mmm, yy

Quality of Life and Everyday Life Functioning

Please fill in the appropriate scale or total scale scores for each scale listed below.

Scale	Score
EORTC-QLQ-30	
Physical	
Role	
Emotional	
Social	
Cognitive	
Fatigue	
Pain	
Nausea/vomiting	
Global	
FACIT-Sp^	
Sense of Meaning and Peace	
Role of Faith	
Total	
Mini-Mental State Exam	
Total	
Self-Expansiveness Level Form	
Personal	
Middle	
Transpersonal	
Total	

Urine Drug Screen

☐ Positive PECIFY:_____
☐ Negative

ARE POSITIVE RESULTS ONLY DUE TO CURRENT MEDICATIONS: ☐ YES ☐NO

Past Substance Use

Previous Alcohol Abuse/dependence ☐ yes ☐ no # of prior treatments_____

In the last 60 days ☐ yes ☐ no

Previous Drug Abuse/dependence ☐ **yes** ☐ **no** **# of prior treatments_____**

In the last 60 days ☐ **yes** ☐ **no**

Baseline - General Well Being

	Visit Date dd-mmm-yy	**Subject Demeanor and State of Mind** enter code	**Notes**
Visit 2			

1= Very stable and calm
2= Stable and calm
3= Slightly stable and calm
4= Slightly distressed
5= Distressed
6= Very distressed

Baseline – Subject Enrollment Decision:

After reviewing all screening and baseline source data, and all inclusion/exclusion criteria does the principal investigator conclude that the subject has met all study criteria?

☐**Yes** ☐**No**

If the answer above is **"No"** please explain:

_____

_____

_____

If "Yes" Date of enrollment _____-_____-_____
dd mmm yy

Assigned Subject Number ____ ____ ____ ____

PI signature _____

Therapy and Evaluation 1:

Please write in the score or scores for each outcome measure. All scale scores must be complete.

Visit 4 **Date of Administration** ___ - ____ - ___
dd mmm yy

Anxiety, Depression, Hopelessness and Thoughts on Hastened Death

Scale	Visit 4	Visit 4.5	Visit 5	Visit 6
STAI				
State				
Trait				
Total				
HADS				
Anxiety				
Depression				
MMSE				
Total				
KPRS				
Total				

Scale	Visit 4	Visit 4.5	Visit 5	Visit 6
EORTC-QLQ-30				
Physical				
Role				
Emotional				
Social				
Cognitive				
Fatigue				
Pain				
Nausea/vomiting				
Global				
FACIT-Sp^				
Sense of Meaning and Peace				
Role of Faith				
Total				
Mini-Mental State Exam				
Total				
Self-Expansiveness Level Form				
Personal				
Middle				
Transpersonal				
Total				

Visit 4-6 - General Well Being:

	Visit Date dd-mmm-yy	**Subject Demeanor and State of Mind** enter code (1 – 6)	**Since last time seen the subject has** enter code (A - C)	**Risk of Suicidality** enter code (X – Z)	**Notes**
Visit 4					
Visit 4.5					
Visit 5					
Visit 6					

1= Very stable and calm
2= Stable and calm
3= Slightly stable and calm
4= Slightly distressed
5= Distressed
6= Very distressed

A= Worsened.

B= Remained pretty much the same.

C= Improved.

X = No risk of suicide
Y = Some risk of suicide
Z = Risk of suicide

Visit 5 - Experimental Session # 1: Inclusion/Exclusion

Review of Inclusion and Exclusion Criteria

Urine Pregnancy Test

☐ Positive
☐ Negative
☐ Not Applicable (Subject is Male, Non-child bearing potential)

Urine Drug Screen

☐ Positive : List positive results: _____ _____ _____
☐ Negative

Liver Function Results	

Are positive results due to participant's medications? ☐**Yes** ☐**No** ☐**N/A**

Does subject continue to **meet all inclusion and no exclusion criteria**? ☐**Yes** ☐**No**

If no, specify: _____

Visit 5 - Experimental Session # 1: Administration

Record time of initial IP administration ____:___ AM / PM

Record Bottle number of Investigational Product _____

Visit 5 - Physiological measures and Body temperature:

Please record maximum and average figures for each measure, and time of measurement for maximum increase. Body temperature should be recorded in degrees Centigrade.

	Average baseline	**Maximum Change in Value**	**Time Max Change Recorded**	**Post-Drug average**
Systolic Blood Pressure (mm/HG)				
Diastolic Blood Pressure (mm/Hg)				
Pulse (BPM)				

Was blood pressure ever above 160/110? ☐**Yes** ☐**No**

If "Yes," for how long was blood pressure higher than 160/110? _____ h _____ min.
If the duration of elevated blood pressure was less than 1 hour, write time in minutes only and write "0" (zero) in "hours."

Visits 5-6 Spontaneously Reported Side-Effects:

Please record the maximum intensity of any spontaneously reported effects up to 24 hours after drug administration.

Visit	Visit 5 Experimental Session #1		Visit 6 24 hrs post
	Duration in hours	Intensity	Intensity
Report Max Intensity for the 24 hour period 0= None Reported 1= Mild 2= Moderate 3= Severe	Report Duration to the nearest hour for the first 24 hours only		
Check None if no symptoms are reported for the 1st 24 hours		☐ None	☐ None
Anxiety			
Chills/feeling cold			
Derealization			
Depersonalization			
Difficulty Concentrating			
Dilated pupils			
Emotional Lability			
Feeling hot			
Impaired cognition			
Impaired gait/balance			
Nausea			
Objects/people different			
Parasthesias			
Perspiration			
Simple visual images			
Somatization			
Repetitive thoughts			
Time perception altered			
Unusual thoughts			
Visual illusions			
Weakness			
Other:			

Visit 6 States of Consciousness Questionnaire

Visit 6 (24 hours post-psilocybin session 1)

Please write in the score or scores for each outcome measure. All scale scores must be complete

Scale	Visit 4	Visit 4.5	Visit 5	Visit 6
SCQ				
Internal unity				
External Unity				
Transcendence of Time and Space				
Ineffability and Paradoxicality				
Sense of Sacredness				
Noetic Quality				
deeply Felt Positive Mood				
Total				
SELF				
Personal				
Middle				
Transpersonal				
Total				

NK cell Count

Please write in the NK cell count recorded at this time _____

VAPS: Month # ______ √ if Last Page

Please fill in each VAPS entry with length of segment preceding the subject's mark upon the line, in millimeters, treating "no pain" as "0" mm. If responses are missing or unclear, please write UNK. Please indicate the date of each response by writing the date in as dd / mmm / yy.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:
_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:
_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:
_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:
_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:

Subject Number __ __ __ __ CRF VAAS Month # ______

S Kumar PhD, Page #_____ of ______

VAPS: Month # ______ √ if Last Page

Please fill in each VAPS entry with length of segment preceding the subject's mark upon the line, in millimeters, treating "no pain" as "0" mm. If responses are missing or unclear, please write UNK. Please indicate the date of each response by writing the date in as dd / mmm / yy.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:
_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:
_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:
_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:
_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:	_____ mm Date:

Subject Number __ __ __ __ CRF VAAS Month # _____

S Kumar PhD, Page #_____ of _____

Daily Diary of Pain and Anxiety

Today's Date _____

Your Initials __ __ __

How Anxious did you Feel Today?

No Anxiety	Much Anxiety

Do you want to say anything else about your anxiety? If you do want to say more, please write any additional thoughts or comments below, including any changes in anxiety, type of anxiety, anxiety triggers or responses to being anxious.

How Much Pain did you Feel Today?

No Pain	Much Pain

Do you want to say anything else about the pain you felt today? Please write in below any additional thoughts or comments about your pain today, including any changes in type or amount of pain, any changes in location of pain, or any changes in your feelings about the pain.

Daily Diary of Medications

Today's Date _____

Initials __ __ __

Pain and Anxiety Medications

Substance	Purpose (Pain or Anxiety)	Dosage	Number of Times Taken Today

Other Medications, vitamins, and nutritional supplements

Substance	Purpose	Dosage	Number of Times Taken Today

Non Psychotropic Concomitant Medications

At Visit 1 record all non psychotropic medications currently being taken and check the prestudy box (include start date if known) Provide diag# (from Med Hx page). Record all new prescription and non-prescription non psychotropic medications taken after visit 1 through termination visit. Provide AE# (from AE page) or other Reason for Treatment. Check the continuing box if continuing at study termination.

☐ **CHECK IF NONE**

Medication	**Route**	**Dose**	**Start Date (dd/mmm/yy)**	**Stop Date (dd/mmm/yy)**	**Reason for Treatment Complete at least one column**		
					Med HX Diag #	AE#	Other
			☐Prestudy	☐continuing			
			☐Prestudy	☐continuing			
			☐Prestudy	☐continuing			
			☐Prestudy	☐continuing			
			☐Prestudy	☐continuing			
			☐Prestudy	☐continuing			
			☐Prestudy	☐continuing			
			☐Prestudy	☐continuing			
			☐Prestudy	☐continuing			
			☐Prestudy	☐continuing			
			☐Prestudy	☐continuing			
			☐Prestudy	☐continuing			

Psychotropic Medication and Tapering

Record psychotropic medications previously used **and** psychotropic medications subject is on at visit1. Check the Prestudy box (include start date if known) and provide Disorder Code. Check Tapered box for medications tapered from V1-V3. Provide route, dose and stop date for all medications. Record **all new psychotropic medications** taken after visit 1 through termination visit. Provide route, dose and start date. Provide AE# (from AE page) and check Rescue box if used as a rescue medication or complete Other Reason for Treatment. Check the Continuing box if continuing at study termination. Do not record each instance of a pain management medication unless it is used only intermittently. ☐ **CHECK IF NONE**

Medication	**Route**	**Dose**	**Start Date (dd/mmm/yy)**	**Stop Date (dd/mmm/yy)**	**Reason for Treatment Complete at least one column**		
					Prestudy Disorder Code#	AE#	Other
			☐Prestudy	☐Tapered		☐ Rescue	
			☐Prestudy	☐ Tapered		☐ Rescue	
			☐Prestudy	☐ Tapered		☐ Rescue	
			☐Prestudy	☐ Tapered		☐ Rescue	
			☐Prestudy	☐ Tapered		☐ Rescue	
			☐Prestudy	☐ Tapered		☐ Rescue	
			☐Prestudy	☐ Tapered		☐ Rescue	
			☐Prestudy	☐ Tapered		☐ Rescue	
			☐Prestudy	☐ Tapered		☐ Rescue	

***Code for prestudy disorders**

1= Depression
2 = Anxiety
3 = Panic Disorder
4 = Pain management (routine)
5 = Pain management (PRN)
6 = Illness-related anxiety
7 = Obsessive-Compulsive Disorder (OCD)
8 = PTSD

Adverse Events

☐ **CHECK IF NONE**

AE #	Adverse event Diagnosis	Serious? a	Onset date (dd/mmm/yy)	Resolution date (dd/mmm/yy)	Severity b	Frequency c	Action taken for Study d	Action taken-treatment e	Action Taken Other Specify	Outcome	Relationship to Drug g

a
Serious?
1 = Serious*
2 = Not serious

* Serious = Fatal, life-threatening, requires prolonged hospitalization, results in persistent or significant disability, or requires medical or surgical intervention to prevent one of the outcomes defined as "serious" listed above.

b
Severity
1= Mild
2 = Moderate
3 = Severe

c
Frequency
1 = Single/Intermittent
2 = Continuous

d
Action Taken: Study
1 = None
2 = Interrupted session
3 = Delayed experimental session
4 = Discontinued experimental session
5 = Removed from study

e
Action Taken: Treatment
1 = None
2 = Procedure or therapy
3 = Blood or Blood products
4 = Withdrawn from study due to AE
5 = Prescription Med
6 = Non Prescription Med
7 = Hospitalization
8 = IV Fluids
9 = Other specify

f
Outcome
1 = Full recovery/return to baseline
2 = Persists, diminishing
3 = Persists, worsening
4 = Persists, the same
5 = Alive with sequelae
6 = Death

g
Relationship to Drug
1 = Not related
2 = Possibly related