Effects of Psilocybin on Anxiety and Psychosocial Distress in Cancer Patients

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Objective:

The primary objective of this double-blind, placebo-controlled pilot study is to assess the efficacy of psilocybin administration (4-phosphoryloxy-N,N-dimethyltryptamine), a serotonergic psychoactive agent, on psychosocial distress, with the specific primary outcome variable being anxiety associated with cancer. Secondary outcome measures will look at the effect of psilocybin on symptoms of pain perception, depression, existential/psychospiritual distress, attitudes toward disease progression, quality of life, and spiritual/mystical states of consciousness. In addition, a secondary objective of the study is to determine the feasibility of administering psilocybin to this patient population, with regards to the following issues: safety, patient recruitment, consent for treatment, and retention. The duration of the proposed investigation will be long enough to administer the drug one time to each of thirty-two patients and to conduct follow-up assessments. This study would be separate but similar to a completed study at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, run by a psychiatrist, Dr. Charles Grob, and an oncologist, Dr. Rowan Chlebowski. Although the outcomes measures would be similar to those used as in the Grob study, the proposed dose of psilocybin would be somewhat higher at 0.3mg/kg and the total number of subjects randomized for the study would be 31 instead of 12 (see below explanation and justification). This study has been approved by the Bellevue Psychiatry Research Committee, the Oncology PRMC Committee, the Food and Drug Administration (FDA) through the issuance of an IND (77,138), the NYU IRB and the NYU-HHC Clinical and Translational Science Institute (CTSI) (previously known as the Bellevue General Clinical Research Center GCRC).

Hypothesis/Potential Mechanism of Action:

It is hypothesized that a one time experience with psilocybin will occasion significant shifts in consciousness and awareness that will lead to short-term (i.e. hours to days) and long-term (up to 5 years in this study following the second experimental session) improvement in anxiety, depression, and pain associated with cancer. The exact mechanism of action is unclear but based on studies conducted with similar serotonergic agents in patients with advanced cancer, improvements in anxiety levels, mood and pain were reported (Grof and Halifax 1977; Kast 1970). However, a treatment model developed by the British psychiatrist, Humphrey Osmond, offers one possibility. In this model, serotonergic hallucinogens' therapeutic mechanism lies in their ability to allow the individual to access novel dimensions of consciousness and their efficacy or lack thereof relies on whether a significant reappraisal or alteration in perception is attained (Osmond 1957). Another possible mechanism relates to what Dobkin de Rios and Grob have described as 'managed altered states of consciousness,' where the power of suggestibility, occurring in a safe setting, allows one to transcend a particular state of consciousness (i.e. anxiety and depression associated with cancer) as a means to facilitate emotional discharge and to manage irreconcilable conflict (Dobkin de Rios, Grob, & Baker 2002).

Rationale and Background:

Despite improvements in the understanding and treatment of cancers within the last several decades that has led to increases in survival rates, addressing the physical and psychological needs of cancer patients remains an inadequately understood and understudied area of focus. In addition to the physical pain associated with cancer, a diagnosis of a potentially life threatening illness often provokes considerable psychological and existential distress for many patients that can involve anxiety, depression, anger, denial and social isolation. These psychological symptoms, in addition to issues such as loss of perceived self-worth, hopelessness, helplessness and loss of independence, have been associated with significant suffering for the patient coping with cancer. Indeed, psychosocial issues, specifically depression and hopelessness rather than pain and discomfort have been found to be the strongest predictors of desire for hastened death in an advanced cancer population (Breitbart et al 2000). The current system of care for patients with advanced cancer is often successful in increasing the amount of time the patient has to live, but very little is customarily done to enhance the quality of intrapsychic and interpersonal experiences during the patient's final months. This led the National Cancer Policy Board of the Institute and the National Research Council to issue a report in 2001 calling for

more research to develop novel therapies aimed at palliative treatment in patients with advanced cancer (Foley & Gelband 2001). The recent and prominent emergence of the discipline of palliative care has emphasized the need for research and clinical therapies to address the severe and debilitating emotional suffering associated with advanced illness cancer patients.

Historically, agents such as psilocybin have been considered and studied as novel therapeutic agents in the treatment of patients with advanced cancer. From the late 1950s to the early 1970s, investigators trained and authorized to administer serotonergic hallucinogens to carefully selected patients with advanced cancers, suffering from significant psychospiritual distress, in highly structured and controlled settings described a number of case reports and clinical research studies with promising treatment outcomes. Experimental work with these agents in patients with advanced illness began with the use of d-lysergic acid diethylamide (LSD) in an attempt to reduce the pain of cancer patients. Eric Kast, a Chicago internist, published a series of reports in the early and mid-1960s reporting on the safety of the use of LSD in patients with advanced cancer and describing superior analgesic effects, relief of depression, improved sleep and lessened fear of death. (Kast, 1966; Kast, 1970; Kast & Collins, 1964). In one study, 100mg of LSD was compared with two short acting opiate mu agonists, hydromorphone and meperidine on 50 patients with cancer and gangrene, who were in severe pain. LSD was more effective at pain relief compared to the opiates in that the pain relief lasted several days as opposed to the opiates where the pain relief was short lived, on the order of several hours. (Kast & Collins 1964). Kast believed that the mechanism of pain management was mediated by "attenuation of anticipation," a diminution of the anxiety associated with perceived loss of control in the process of having a potentially life threatening illness. (Kast 1970). In addition to the analgesic properties of LSD, Kast concluded that the treatment was capable of not only improving the psychological adjustments of patients with advanced illness by making them more responsive to their environments and families, but also of enhancing their ability to appreciate the aesthetic satisfaction associated with the subtleties of everyday life.

In an effort to systematically examine the effects of serotonergic hallucinogens on patients with advanced medical illness, Walter Pahnke and Stanislav Grof of the Maryland Psychiatric Research Institute at Spring Grove State Hospital in Maryland conducted a series of experiments from the mid 60s to the mid 70s. Advanced cancer patients were treated with either LSD or dipropyltryptamine (DPT). It was determined that both agents were safe to use in this patient population across a spectrum of patients with advanced cancer, including those with central nervous system involvement. Regarding overall quality of life measures, 29% of the subjects reported dramatic improvement, and another 41.9% had sustained moderate improvement, with 22.6% essentially unchanged and only 6.4% with an apparent deterioration of status. A reduced need for narcotic analgesia was also observed. (Grof, et al, 1973; Richards et al, 1972, Grof & Halifax, 1977).

One early and prolific hallucinogen investigator, Sidney Cohen of UCLA published a moving account of his views of the potential value of this treatment model in Harper's Magazine entitled "LSD And The Anguish Of Dying." Cohen in the mid-1960s was sufficiently impressed with the medical administration of hallucinogens under highly structured conditions to speculate on the implications of what he had observed:

"Death must become a more human experience. To preserve the dignity of death and prevent the living from abandoning or distancing themselves from the dying is one of the great dilemmas of modern medicine... LSD (and other hallucinogens) may one day provide a technique for altering the experience of dying." (Cohen, 1965).

The first attempt to re-study the safety and efficacy of psilocybin in patients with potentially life threatening cancer began in 2004 in a study that is now completed at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, run by a psychiatrist, Dr. Charles Grob, and an oncologist, Dr. Rowan Chlebowski. It was a double-blind placebo-controlled study that included patients with Stage IV cancer and anxiety. The approved oral dosage given of psilocybin was 0.2mg/kg and a total of 12 patients were studied. There were several medical exclusion criteria including renal disease, abnormal liver function tests, epilepsy, and cardiovascular illness, as well as psychiatric exclusion criteria including the presence of major mental illness and active substance abuse. This study was funded by the Heffter Research Institute and was FDA approved. The study had a prospective follow-up arm that followed patients for up to 6 months post-treatment of psilocybin. The study was recently published in the Archives of General Psychiatry in September

2010 (Grob 2010). The results were as follows: 'Safe physiological and psychological responses were documented during treatment sessions. There were no clinically significant adverse events with psilocybin. The State-Trait Anxiety Inventory train anxiety subscale demonstrated a significant reduction in anxiety at 1 and 3 months after treatment. The Beck Depression Inventory revealed an improvement of mood that reached significance at 6 months; the Profile of Mood States identified mood improvement after treatment with psilocybin that approached but did not reach significance.' This study established the safety and feasibility of administering a moderate dose of psilocybin to patients with advanced cancer and anxiety. Some of the data suggested a treatment effect with reduction in anxiety and depressive symptoms.

In addition to the above study by Dr. Grob, another recent study conducted at Johns Hopkins by Roland Griffiths and colleagues showed that psilocybin can safely be given to normal volunteers without prior experience with serotonergic hallucinogens in a highly supervised setting (Griffiths 2006). The study was a double-blind design where 0.43 mg/kg of oral psilocybin was compared with 0.57mg/kg of oral methylphenidate, where both agents were given to subjects in counterbalanced order. Significantly, 67% of the subjects rated the experience with psilocybin as either the single most meaningful experience of his or her life or among the top five most meaningful experiences of his or her life. Also, sixty-one percent of subjects who received psilocybin met criteria for a 'complete' mystical experience, significantly increased compared to only 11% who received methylphenidate. Prospectively, at the two month follow-up period, compared to the methylphenidate experience, the psilocybin experience was significantly associated with subjective reports of greater improvement in the following domains: positive attitudes about life and oneself, positive mood, altruistic/positive social effects, and positive behavioral changes. These subjective reports were confirmed by community observer ratings of changes in the subjects' behavior and attitudes. In a long-term follow-up to this 2006 study, Griffiths et al. reported in a 2008 published article that at 14 months later subjects reported a persistent and statistically significant sense of well-being and life satisfaction (Griffiths, Richards, Johnson, McCann and Jesse, 2008). As part of future implications for further research with psilocybin, Dr. Griffiths cites two patient populations as potentially benefiting from psilocybin: those with potentially life threatening illness and addicted patients. In fact, Dr. Griffiths is currently conducting a study testing the use of psilocybin in patients with medium to advanced stage cancer (Griffiths Personal Communication 2007, 2010).

PROTOCOL

Objectives and Purpose of the Study:

This is a pilot study of a single treatment designed to preliminarily evaluate the effect of psilocybin in patients with cancer and anxiety. Secondary outcome measures will be pain perception, depression, and existential / psychospiritual distress. Also, issues related to the feasibility of using psilocybin in patients with cancer and anxiety will be described. The study will look at both short-term, immediate effects as well longer-term effects. We plan to collect and analyze data up to 6-months post the second drug administration for all enrolled participants. Participants who complete a psilocybin dosing session and agree to be contacted will be invited to partake in two optional data collection time points, which will look at long-term psychological effects of psilocybin-assisted psychotherapy.. Subjects' participation in these two additional longitudinal timepoints will be optional and will not affect their previous study involvement as research participants. Study participants who opt out or who do not have the option to participate (for example, if they are deceased) will be classified (ie study completers, withdrawn, treatment dropout, etc.) as they were in the main portion of the study. Participants do not need to complete all questionnaires given at previous time points to be eligible to participate in optional time points T13 and T14.

Criteria for patient selection (Inclusion/Exclusion Criteria)

The proposed project will involve up to 47 subjects 18-76 years of age. Subjects will have a current or historical diagnosis of cancer with a projected life expectancy of approximately 6 months or more and a DSM-IV psychiatric diagnosis, as determined by the Structural Clinical Interview for DSM-IV (SCID), of one of the following Anxiety Disorders: Acute Stress Disorder, Generalized Anxiety Disorder, Anxiety Disorder Due to cancer, or Adjustment Disorder with Anxiety. The cancer could be: at any stage of active illness; potentially life

threatening, advanced, or recurrent; or the participant could have a history of a cancer diagnosis and currently be in remission or considered 'cured' as long as they continue to have anxiety related to the historical diagnosis of cancer. Subject's life expectancy of approximately 6 months or more will be verified by the study's oncologist Dr Nierodzik through the review of medical records. However, it is expected that some subjects will not complete the study due to rapid progression of their pre-existing diagnosis of cancer or death due to cancer.

Patients with epilepsy, renal disease, diabetes, abnormal liver function, severe cardiovascular disease (i.e. coronary artery disease, congestive heart failure) and uncontrolled hypertension will be excluded from the study. Subjects with a history of migraine headaches may be excluded based on severity of the migraines per evaluation of the principal investigator.

Cardiovascular screening: There will be at least four blood pressure assessment occasions over at least two separate days. Within a day, assessment occasions will be separated by at least 15 minutes. Each assessment occasion will involve two or more blood pressure readings. To qualify for the study, the mean blood pressure (mm Hg) of the four or more assessment occasions will not exceed 140 systolic and 90 diastolic.

Blood pressure will be measured while subjects are at rest and have been seated or supine for at least 5 minutes. As recommended by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, these assessments will involve the average of 2 or more readings separated by two minutes. If the first 2 readings differ by more than 5 mm Hg, additional readings will be obtained and averaged. On one or more of the blood pressure measurement occasions, the subject will be acclimated to the automated blood pressure monitoring equipment by repeatedly having blood pressure measured (at least 3 readings) with the device. It has been our experience that time-to-time blood pressure readings with the automated equipment can be variable due to measurement artifact, therefore any reading that initially exceeds the protocol's threshold value will be reassessed twice within 4 minutes to assure accuracy.

Psychiatric exclusion criteria are as follows: those with a personal history, as determined by the SCID, or an immediate family history of schizophrenia, bipolar affective disorder, delusional disorder, paranoid disorder, or schizoaffective disorder. Subjects with a current substance abuse disorder will be excluded.

Medication contraindications will include anti-seizure medications, insulin, certain hypertension medications (clonidine, and aldomet specifically), cardiovascular medications and the following psychotropic medications: anti-psychotics (first and second generation agents), anti-depressants and mood stabilizers. Psychotropic medications cannot be taken in the previous two weeks, with prozac (fluoxetine) not being taken within the last 5 weeks prior to receiving any study agents. Subjects may only take prn (as needed) benzodiazepines (i.e. lorazepam) up to three days before the session. If subjects are taking an oral hypoglycemic agent (i.e. metformin as an anti-cancer treatment), then they must have no history of hypoglycemia. In this case, participants will refrain from taking the medication 24 hours prior to the dosing sessions. Subjects will refrain from taking any medications the day of either the experimental or placebo treatment session, except they may take ongoing adjuvant chemotherapy as prescribed, prescribed opiate pain medication or over-the-counter non-narcotic pain medication at any time. It will also be necessary to refrain from alcohol the day before, the day of, and the day after each experimental session.

The effects of psilocybin on an unborn child are not known, and it is not known whether receiving psilocybin can now have effects on unborn children in the future. Therefore, pregnant or lactating (breast-feeding) females or females of childbearing potential, not using an acceptable method of birth control, cannot take part in this study. You must tell the study doctor if you are pregnant or think that you might be pregnant at any time while you are taking part in this study. Acceptable methods of birth control include tubal ligation or removal of the uterus (hysterectomy), the use of oral contraceptives (birth control pills for at least 2 months), an intrauterine device (IUD), hormonal implants (Norplant), hormonal injections (Depo-Provera) and abstaining from sexual intercourse. Women of childbearing potential will have a pregnancy test (urine) during the screening process and before each session of the study to make sure female subjects are not pregnant.

Subjects will be excluded if they have a score of less than 8 on the Hospital Anxiety and Depression (**HAD)** scale administered at baseline (T_0—see below).

Materials and Methods

This pilot investigation is a double-blind, randomized, placebo controlled study of the effects of psilocybin on the anxiety associated with cancer. The study will compare psilocybin and niacin using a crossover design where treatment with single session, one-time administration of the active agent versus placebo will occur 7 (+ 1 week) weeks apart, and the sequence of treatments will be randomized among patients.

Participants: Recruitment and Screening

The study is open to anyone with a history of or current diagnosis of cancer throughout the country. However, it is most likely that the majority of patients will come from New York City or the Tri-State Area. Advertisements in newspapers as well as using contacts in oncology, pain, and palliative care services at local hospitals will be the primary methods used to recruit patients.

In addition to the above-mentioned inclusion and exclusion criteria, Dr. Nierodzik, the Director of the Bellevue Cancer Center and one of the co-PIs, will screen all patients to determine if they have a history of or current diagnosis of cancer with a life expectancy of approximately 6 months or more. Moreover, the other co-PI in the study, Dr. Anthony Bossis will assess patients for pain and issues relating to palliative care. Dr. Bossis will coordinate all activities related to palliative and supportive care services.

Meetings with Monitors Before Treatment Sessions:

Following screening acceptance into the study, subjects will be provided with several brief psychoeducational sessions (at least 3 sessions for a total minimum of 6 hours) over a period of 2-4 weeks prior to the first experimental session to review the purpose and intention of participation in the study, the treatment goals, the structure of the experimental treatment session, the range of effects of the drug, the pre-selected music and personal items to assist in creating a comfortable and familiar setting, and critical issues to be examined during the course of the psilocybin experience. Additional goals of the sessions will be to establish a comfortable level of rapport and trust between the patient and research personnel, and to review significant issues in the patient's life history, and the nature and status of present relationships and concerns. It is expected that the time required to establish such trust will vary among subjects. Establishing and maintaining rapport between the monitors and participant is important to minimize the risk of adverse reactions to psilocybin (Metzner et al. 1965). If sufficient rapport has not been established, as determined by the clinical judgment of Dr. Ross, the subject will be dropped from the study. This procedure could allow for investigator bias in subject selection, but the protection of the psychological wellbeing of the subjects is an overriding factor. The study doctor and the assigned monitors (as a dyad treatment team) will meet each participant on at least 3 sessions for a total minimum of 6 hours prior to the first experimental session.

Meetings with Study Staff and Monitors Following Treatment Sessions:

In the first six weeks following the experimental treatment sessions, several follow-up meetings (at least 3 for a total minimum of 6 hours) in person between the subject, the study staff and the monitors will be arranged to facilitate psychological integration of the psilocybin experience, as well as to administer the research measures. Additional meetings in person or on the telephone will be held at least monthly intervals for further follow-up for six months. The principal investigator will be the primary contact person for the subjects.

Communication with community observers (i.e. family members, friends, co-workers) will be part of follow-up as a way to get an objective measure of patient outcome in addition to self-report.

Drug Conditions

Psilocybin and niacin will be administered in identically appearing opaque, size 0 gelatin capsules with approximately 180ml of water. The dose of psilocybin will be 0.3mg/kg and the niacin dose will be 250mg. Each subject will participate in two experimental treatment sessions. In the study, approximately half of the subjects will be randomized to receive psilocybin (n=15 or 16) or the placebo, niacin (n=15 or 16). Following

the first treatment session of either the active agent or placebo, a cross-over design will be instituted with the alternative drug administered on the second session. Subjects and treatment personnel will be blinded for each experimental drug administration. The time interval between the two experimental treatment sessions will be 7 weeks (+ 1 week).

For both experimental treatment sessions, patients will be weighed as close as possible to the day before the session, and the dose of psilocybin will be mixed and compounded the day prior to the drug administration session at 0.3mg/kg (- 4 day window). Regarding niacin, it too will be mixed and compounded the day before the drug administration session (- 4 day window).

Justification for 0.3mg/kg dose of psilocybin

As mentioned above, one of the possible mechanisms of action of psilocybin relates to the extent to which it is able to produce a shift in consciousness or awareness, often labeled a mystical or spiritual experience that can have transformative properties to alter perception, specifically anxiety, pain, and depression associated with cancer in this instance. According to Dr. Grob, several of the patients in his study at UCLA reported a partial response to the dose of 0.2mg and had hoped for the experience to have been more profound (Grob-personal communication 2007). Given this and data indicating that psilocybin is safe to be given at a dose of 0.3mg/kg (see below in 'Safety Considerations' Section), this study proposes to use 0.3mg/kg of psilocybin. The FDA has approved this dose.

Drug Sessions:

Experimental treatment sessions will take place in a specially prepared room at the NYU Bluestone Center for Clinical Research (BCCR). Subjects will arrive at BCCR at approximately 08:00 a.m. the day of the session. They may eat only a light breakfast of hot cereal or bread/toast on the day of the session. Caffeinated clear liquids or juices will be permitted, but no milk as drug absorption might be affected.

The experimental medicine will be administered between 09:00 and 10:00 hours. Subjects will be asked to remain in the treatment room at the BCCR until both the subject and investigator agree that their perception, cognition, functioning and judgment are no longer impaired by the drug. The procedure will follow the method utilized by Dr. Stanislav Grof in treating advanced cancer patients with LSD (Grof, et al, 1973; Grof, et al, 1977 & Richards, Grof, et al, 1972), as described here:

Subjects will be encouraged to lie comfortably in bed wearing eye shades during the first few hours of the experience and to listen to pre-selected music chosen by the study staff. The treatment team will remain with the subject throughout this time, and be available for any processing of intrapsychic material made manifest by the treatment. In addition, the continued need for conventional medications (e.g. narcotics) to alleviate pain will be monitored in a systematized, ongoing manner. Subjects will be allowed to remain at BCCR for the night, but, based on the clinical judgment of the principal investigator, may have the option of returning home with a responsible adult. Driving will be performed by a family member or friend, but not the subject. Alternatively, a car service can be provided to the subject, as long as a family member or a friend accompanies the subject home.

Immunologic Measures:

The field of psycho-neuro-immunology is predicated on reliable findings that one's psychological state of mind directly affects immune function. One of the hypotheses of this study is that treatment with psilocybin may lead to improvements in psychological well-being. If this were to happen, we would want to include immune measures to correlate this finding. Alternatively, if one's psychological state deteriorates, a similar correlation would provide useful information. The specific immune measures to be included are: Cortisol, ACTH, IL-4, IL-6, IL-10, INF-gamma, TNF-alpha, and Natural Killer (NK) Cell activity. These immune measures would be collected by venipuncture at screening, 1-week (+/- 4 days) post sessions (of both placebo and the active agent), and at 6-month (+/- 4 days) follow-up.

Observations and Measurements to be used to fulfill study objectives (See Table 1):

Measures Assessed 2-4 weeks prior to the First Experimental Session (T_0):

Anxiety and Depression

Treatment efficacy for anxiety and depression will be assessed by the State-Trait Anxiety Inventory **(STAI),** Hospital Anxiety and Depression (**HAD)** scale, Brief Profile of Mood States **(POMS-SR),** Beck Depression Inventory **(BDI),** and Brief Symptom Inventory **(BSI).** The STAI, HAD, POMS-SR, BDI, and BSI will also be re-administered at the following time points: T1, T4-T12. In addition, regarding a broad assessment of affective states, the Positive and Negative Affect Schedule Expanded Form **(PANAS-X),** a 60-item questionnaire, will be administered to assess for positive and negative affect. This scale will be re-administered at the following time points: T6 (2-weeks after drug administration) and T12 (26-weeks after drug administration). The STAI, HAD and BDI will be re-administered at T13 and T14.

Pain

Treatment efficacy for pain perception will be assessed by the Brief Pain Inventory – Short Form **(BPI-SF),** and the Memorial Symptom Assessment Scale **(MSAS)** (only questions relevant to anxiety, depression or pain symptoms) will be administered two weeks prior to the experimental treatment session, the day before, 7-hours after each drug administration session, the day after, two weeks after the session, and then every month for the next six months. In addition, the Memorial Sloan Kettering Pain Card **(MSKCC)** will be self-administered by the subjects every day from two weeks before the treatment session until six weeks after, including just before psilocybin administration and at four and seven hours afterward. Subjects' use of pain medications will be closely monitored throughout the study duration.

Attitudes towards disease progression and death

Attitudes towards disease progression and death will be measured at baseline with the following measures: Death Transcendence Scale **(DTS),** Demoralization Scale **(DEM),** Death Anxiety Scale **(DAS),** and the Hopelessness Assessment and Illness **(HAI)** scale. These measures will also be obtained at the following time points: T6 (2-weeks after drug administration) and T12 (26-weeks after drug administration). The DEM, DAS and HAI will be re-administered at T13 and T14.

Quality of Life/Spirituality:

Quality of Life (QoL) and spirituality assessments will be made with the Functional Assessment of Chronic Illness Therapy **(FACIT),** the Purpose in Life **(PIL)** scale, the World Health Organization Quality of Life scale, Brief Version **(WHO-Bref),** and the World Health Organization Quality of Life, Spiritual, Religious and Personal Beliefs **(WHO-SRPB),** with more questions relating to the spiritual importance to their overall QOL. An additional Forgiveness questionnaire **(FORGIVE),** assessing issues relating to forgiveness and spirituality, will be administered at baseline. These measures will also be obtained at the following time points: T6 (2-weeks after drug administration), and T12 (26-weeks after drug administration). The FACIT and WHO-BREF will be re-administered at T13 and T14.

Spiritual/Mystical States

Regarding the assessment of spiritual/mystical states, The **Mysticism Scale-Lifetime** (Hood et al 2001; Spilka et al. 2005), will be administered, instructing patients to answer questions relating to their total life experience, and the Spiritual Transcendence Scale **(STS)**, a 24-item questionnaire, will be administered to assess an individual's effort to create a sense of personal meaning in his or her life (Piedmont 1999). These scales will also be administered at time points: T6 and T12. The Mysticism Scale-Lifetime will be re-administered at T13 and T14.

*Community observer ratings of changes in subjects' behavior and attitudes **(COM-R):***

After acceptance into the study, each subject will designate 2-3 adults who are expected to have continuing contact with the subject (i.e., spouse or other family members, friends, co-workers) who can observe changes in the subjects' behavior and attitudes over time. The structured interview consists of asking the community rater to rate the subject's behavior and attitudes using a 10-point scale (from 1=not at all to 10=extremely) on 11 dimensions: inner peace, patience, good-natured humor/playfulness, mental flexibility, optimism, anxiety, interpersonal perceptiveness and caring, negative expression of anger, compassion/social

concern, expression of positive emotions, and self-confidence (Griffiths et al. 2006). The COM-R will also be assessed at the following time points: T7, and T12. Due to observers' availability, it is expected that the administration of the COM-R may not occur on the exact scheduled time point. However, every effort will be made to conduct this assessment as close to the required time points as possible.

Measures assessed 1 day before the sessions (T_1):

The STAI, HAD, POMS-SR, BDI, and BSI will be administered to assess for anxiety and depressive symptoms. As mentioned above, regarding pain assessment, the BPI-SF, MSAS, and MSKCC will be administered one day prior to the sessions as well.

Measures assessed just before drug administration (T_2):

The only measure to be administered will be the MSKCC to assess for pain.

Measures assessed throughout the sessions:

Ten minutes before and 30,60,90,120,180,240,300, and 360 minutes after capsule administration, monitor ratings, blood pressure, and heart rate will be obtained.

Blood pressure and heart rate:

Blood pressure (systolic, diastolic, and mean arterial pressure) and heart rate will be monitored.

Monitor rating questionnaire:

At the same points in time in which the above physiological measures will be obtained, the two session monitors will complete the Monitor Rating Questionnaire, which involves rating 20 dimensions of the subject's mood or behavior on a five-point Likert scale from 0 to 4.

Measure assessed 4 hours after drug administration (T_3):

The only measure to be administered will be the MSKCC to assess for pain.

Measures assessed 7 hours after drug administration (T_4):

The STAI, HAD, POMS-SR, BDI, and BSI will be administered to assess for anxiety and depression, and the BPI-SF, MSAS, and MSKCC will be administered to assess for pain.

Changes in state of consciousness will be assessed with the altered states of consciousness rating scale **5D-ASC** (Dittrich 1998; Dittrich, Lamparter et al. 1999), which is a scale suited to depict alterations in waking consciousness — including changes in mood, perception, experience of self and environment, and thought disorders — regardless of the inducing factor(s) (Dittrich 1996; Dittrich 1998). In addition, the Hallucinogen Rating Scale **(HRS)** will be administered, a 100-item scale used to assess altered states of consciousness produced by serotonergic hallucinogens such as psilocybin (Strassman 1994; Riba 2001).

The following measures will be used to assess for mystical/spiritual experiences: **The Mysticism Scale**, a 32-item questionnaire (Hood et al 2001; Spilka et al. 2005), and the Pahnke-Richards Mystical Experience Questionnaire **(PRMEQ)** consisting of 100 questions (Pahnke 1969; Richards 1975).

Assessment of adverse psychiatric symptoms will be made by administration of the Brief Psychiatric Rating Scale **(BPRS)** seven hours after drug administration.

The **Kast questionnaire** assessing the quality of the experience will be administered at 7 hours after study medication administration. This questionnaire will be re-administered at T6 (2-weeks after drug administration).

Subjects will be requested to write or record their experience after the session, for possible further discussion or analysis. This written record can occur at the 7-hour period following drug administration sessions or can be done before the next assessment point (T5) the following day, or during the T5 assessment The Post-Sessions Subjective Experience Questionnaire **(PSEQ)** will include a question asking the subject to describe their subjective experience of the session in general and in particular to describe what were the most

memorable, the most challenging or difficult, and the most spiritually significant aspects of the experience, if there were any.

Measures assessed 1 day after drug administration (T_5):

The STAI, HAD, POMS-SR, BDI, and BSI will be administered to assess for anxiety and depression, and the BPI-SF, MSAS, and MSKCC will be administered to assess for pain.

Measures assessed 2 weeks after drug administration (T_6):

The STAI, HAD, POMS-SR, BDI, and BSI will be administered to assess for anxiety and depression, and the BPI-SF, MSAS, and MSKCC will be administered to assess for pain.

Regarding the assessment of enduring spiritual/mystical states, The **Mysticism Scale-Lifetime** and **STS** will be re-administered.

Regarding the assessment of enduring changes in attitudes and affect, the Persisting Effects Questionnaire **(PEQ)**, an 89-item questionnaire, will be administered to assess changes in attitudes, moods, behavior, and spiritual experience (Pahnke 1969; Richards 1977). The categories of inquiry from this questionnaire include: positive attitudes about life and/or self, negative attitudes about life and/or self, positive mood changes, negative mood changes, altruistic/positive social effects, and antisocial/negative social effects. In addition, regarding a broad assessment of affective states, the Positive and Negative Affect Schedule Expanded Form **(PANAS-X),** a 60-item questionnaire, will be re-administered.

Measures relating to quality of life, spirituality and forgiveness will be re-assessed with the FACIT, PIL, WHO-Bref, WHO-SPRB, and the Forgiveness Questionnaire.

The Kast questionnaire will be re-administered to assess for the quality of the drug administration experience.

The DTS, DEM, DAS, and HAI will be re-administered to assess for attitudes towards disease progression and death.

Measures assessed 6 weeks after drug administration (T_7):

The STAI, HAD, POMS-SR, BDI, and BSI will be administered to assess for anxiety and depression, and the BPI-SF, MSAS, and MSKCC will be administered to assess for pain.

Regarding community observer ratings of changes in subjects' behavior and attitudes, the above-mentioned structured interview (COM-R) will be re-administered.

Measures assessed 10 weeks after drug administration (T_8):

The STAI, HAD, POMS-SR, BDI, and BSI will be administered to assess for anxiety and depression, and the BPI-SF, and MSAS, will be administered to assess for pain.

Measures assessed 14 weeks after drug administration (T_9):

The STAI, HAD, POMS-SR, BDI, and BSI will be administered to assess for anxiety and depression, and the BPI-SF, and MSAS, will be administered to assess for pain.

Measures assessed 18 weeks after drug administration (T_{10}):

The STAI, HAD, POMS-SR, BDI, and BSI will be administered to assess for anxiety and depression, and the BPI-SF, and MSAS, will be administered to assess for pain.

Measures assessed 22 weeks after drug administration (T_{11}):

The STAI, HAD, POMS-SR, BDI, and BSI will be administered to assess for anxiety and depression, and the BPI-SF, and MSAS, will be administered to assess for pain.

Measures assessed 26 weeks after drug administration (T_{12}):

The STAI, HAD, POMS-SR, BDI, and BSI will be administered to assess for anxiety and depression, and the BPI-SF, and MSAS, will be administered to assess for pain.

To re-assess for spiritual/mystical measures, the Mysticism Scale-Lifetime, PRMEQ retrospective scale, and STS will be re-administered.

To re-assess for enduring changes in attitudes, moods, behavior and spiritual experience, the PEQ and PANAS-X will be re-administered.

Measures relating to quality of life, spirituality and forgiveness will be re-assessed with the FACIT, PIL, WHO-Bref, WHO-SPRB, and the Forgiveness Questionnaire.

The DTS, DEM, DAS, and HAI will be re-administered to assess for attitudes towards disease progression and death.

Regarding community observer ratings of changes in subjects' behavior and attitudes, the above-mentioned structured interview (COM-R) will be re-administered.

A Retrospective Subjective Experience Questionnaire **(RSEQ)** will be administered to capture the subjective experience of the subject during the drug-administration session that may have produced or resulted in the most profound changes or alterations in emotional or mental states and/or changes in ordinary consciousness. The questions will inquire about possible changes in emotions, thoughts, states of consciousness, meaningfulness, and spirituality.

Measures assessed at T13 and T14:

The STAI, HADS and BDI will be re-administered to assess for anxiety and depression.

Persisting Effects Questionnaire (PEQ), an 89-item questionnaire, will be re-administered to assess changes in attitudes, moods, behavior, and spiritual experience (Pahnke 1969; Richards 1977).

The Mysticism Scale-Lifetime will be re-administered, instructing patients to answer questions relating to their total life experience. Measures relating to quality of life, spirituality and forgiveness will be re-assessed with the FACIT and the WHO-Bref.

The DEM, DAS, and HAI will be re-administered for this indication.

A short open-ended questionnaire will also be administered to capture the subjective experience of the participant that may be sustained at the T13 and T14 time points.

Optional, Additional Time points

Study participants who completed a psilocybin dosing session and agreed to be contacted in the future (as indicated on their written Informed Consent Document that was signed at the beginning of the primary phase of the study) will be approached by the study team member via phone or email to offer them participation in the optional, additional time points. If the study subjects are interested in participating in these two time points, a designated study-team member will read a telephone consent to the interested volunteer over the phone. The telephone consent discusses the additional study procedures that the volunteer would have to participate in and all risks involved. If the volunteer wants to participate in these optional and additional timepoints, a designated study-team member will send the interested participant a link to openredcap.nyumc.org. This link will include all of the assessments that are to be completed at each additional timepoint. The ability to complete these questionnaires online eliminates the need for the participant to come to an in-person visit at the study site. The T13 and T14 optional time points will occur approximately one year apart. The T13 time point will occur as soon as possible to the time at which verbal telephone reconsent is obtained, and the T14 will occur approximately one year after T13.

Because these timepoints are optional and participants only needed to undergo an active-medication session in order to be eligible, study participants who opt out or who do not have the option to participate (for example, if they are deceased) will be classified (ie study completers, withdrawn, treatment dropout, etc.) as they were in the main portion of the study

For example:

- Participant XYZ completed both medication sessions, active & placebo, as well as all questionnaire timepoints. He has been considered a "study completer" up until this point. If his consent endorses having the study team reach out to him regarding future research, he will be contacted. If he denies

wanting to participant in the optional & additional timepoints, this will not affect his status as a study completer.

- Participant ABC completed both medication sessions & all questionnaire timepoints but is deceased. She will still be considered a study completer even though she obviously cannot be given the choice to participate in T13 & T14.
- Participant LMN completed only 1 medication session but it was her active medication session. She withdrew from the study before her second medication session. However, since the protocol states that in order to be eligible for the optional & additional timepoints, participants must have only completed a psilocybin medication session, she would eligible to participate in these additional and optional timepoints. If her consent endorsed having the study team reach out to her regarding future research, th study team will do so regarding these optional and additional questionnaire timepoints.

For documentation purposes, the study team will keep a log that includes all participants enrolled in the main portion of the trial and note whether or not they are deceased. Any and all information that the study team has regarding the death of a past participant in this trial will be noted.

Statistical Analyses (Including Power Analysis): Done in conjunction with Dr. Chi-Hong Tseng of Biostatistics and Approved on 1/24/07

Descriptive statistics (means, medians, standard deviations, frequency distributions) and graphic displays will be generated for demographics and baseline clinical presentations to characterize study subjects, and to describe the distribution of adverse events, patient dropout, study compliance and all outcome measures.

One of the objectives of this pilot study is to determine the feasibility of giving psilocybin to patients with advanced cancer. Although the safety of giving psilocybin to normal, healthy volunteers has been established within the last decade (Hasler 2004, Griffiths 2006, Moreno 1998), and although the safety of its use in patients with advanced cancer was established in the 1960s, it has not been established in patients with cancer using modern research designs (i.e. double-blind, placebo controlled, prospective methodology). In addition to safety determination considerations, summary statistics will be used to describe the consent and drop out rates as part of patient recruitment and retention. The adverse events associated with study treatments will be tabulated, and percent adverse event and its 95% confidence interval will be calculated.

According to a recent study by Moreno and colleagues, published in 2006, in patients with refractory Obsessive Compulsive Disorder (OCD), an anxiety spectrum disorder, it was found that, with psilocybin, subject's mean YBOCS scores were reduced to 10.67 at 24 hours from 24.11 +/- 6.3 at baseline (Moreno 2006). This represents a reduction of 2 in effect size (assuming a 0.5 correlation between baseline and 24 hours). If we assume placebo has no effect on anxiety, depression and pain, a sample size of 16 subjects in each group (in the first treatment session) will provide 75% power to detect a reduction of 1 effect size, and > 99% power at 2 effect sizes, at the 5% level. This power analysis shows that even if patients dropout before the second cross-over session, the total of 31 patients in the first session will have adequate power for the study endpoints.

Regarding the effect of psilocybin on the outcome variables measuring anxiety, the STAI and HAD scale, analyses will be conducted using a paired t-test to evaluate the effect of treatment over time. The comparisons will be between the following time points: (T0 & T1)-T4, (T0 & T1)-T5, (T0 &T1)-T6, and (T0 & T1)-T7. The comparisons between the active agent and placebo groups will be conducted using an independent sample t-test to look at differences on the STAI and HAD scale measures. Similar analyses will be conducted both within and between groups for the other outcome measures, assessing for depression (POMS-SR, BSI and BDI scales) and pain (BPI-SF, MSAS, and MSKCC scales).

To assess the interaction between drug and time, a series of repeated measures multivariate analyses of variance (MANOVA) will be used to compare the active drug and placebo study arms across time in terms of the major outcome variables during the first and second randomized experimental treatment sessions. Both treatment main effects across time and interactions of treatment with time will be assessed in the repeated measures MANOVA.

Longer-term effects will be measured in two ways looking at the outcome measures of anxiety, depression, and pain. First the effect of time will be assessed with a MANOVA analysis from baseline relative to T7-T12. Also, MANOVA will be used to look at the effect of sequencing of getting the active agent vs. placebo in a sequence x time analysis from baseline relative to T7-T12.

Data Management and Statistics:

A data manager will be recruited and appointed prior to the initiation of the study. The funding for this study from the Heffter Research Institute includes monies to pay for a data manager.

Monitoring for Risk Minimization:

A physical examination will be performed which will include an EKG, urinalysis, and blood chemistry panels (liver and renal function tests and CBCs). An admission urine drug screen will be done for patient safety and protocol compliance. During each experimental treatment session, vital signs, including blood pressure and heart rate, will be taken 10 minutes before and 30,60,90,120,180,240,300, and 360 minutes after drug administration. Body temperature will be measured up to 30 minutes before and at six hours after drug administration. For these measurements, a window of ±10 mins from the allocated time will facilitate the study flow.

Cardiovascular monitoring during a session:

1. Vital Signs are checked ten minutes before and 30,60,90,120,180,240,300, and 360 minutes after capsule administration and monitor ratings (blood pressure and heart rate) will be serially assessed.

2. Monitor Ratings: Blood pressure (systolic, diastolic, and mean arterial pressure) and heart rate will be monitored with an automated blood pressure machine.

3. If Systolic BP is > 160 or Diastolic is > 100 or Heart Rate is >110,vital signs will be checked every 5 minutes until systolic pressure is <160, diastolic pressure <100, and heart rate <110

4. If Systolic BP is > 200 or Diastolic BP is > 110 for three readings (i.e. 15 minutes), the subject will receive sublingual Nitroglycerin 0.4 mg. If blood pressure readings do not decrease below these thresholds after 5 minutes of receiving the first dose of Nitroglycerin, the same dose of Nitroglycerin will be administered. A third dose of nitroglycerin will be given after another 5 minutes, if readings remain elevated above these levels (maximum dose is 0.4mg x 3 doses).

5. If blood pressure remains >200 systolic or >110 diastolic, at the judgment of the treating physician (Dr. Ross), the subject will be immediately transported to the nearby Bellevue Hospital Center Adult Emergency Room (AES) for further evaluation and treatment.

<u>Aversive reactions to sublingual nitroglycerin:</u>

The following effects have occurred in clinical trials: headache, hypotension, cutaneous vasodilation with flushing, dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension. Also possible are nausea, vomiting, restlessness, pallor, perspiration and collapse, drug rash and/or exfoliative dermatitis, paresthesia, rhinitis, peripheral edema, asthenia, and abdominal pain.

PROCEDURE FOR MEDICAL EMERGENCIES:
NEW YORK UNIVERSITY COLLEGE OF DENTISTRY MEDICAL EMERGENCY MANAGEMENT PROTOCOL INCLUDING BLUESTONE CENTER FOR CLINICAL RESEARCH (BCCR):

The Department of Oral and Maxillofacial Surgery (OMS) faculty are trained in managing medical emergencies and will respond to the presentation of medical emergencies at the College of Dentistry.

In a medical emergency security will be called at 89828 and they will dispatch the OMS faculty. Staff members who report the emergency must remain with the subject and administer supportive therapy. Emergency supplies and oxygen is available from the code cart located next to the nurse's station in BCCR.

The OMS team will assess the situation, stabilize the subject, and notify the Emergency Medical Service (EMS), should an ambulance be required to transport the subject to the hospital if this has not been done by BCCR staff. The OMS team will stay with the subject until the emergency has subsided or additional assistance has been obtained.

Other emergency numbers:

- Poison Control: (**800) 222-1222**
- Bellevue Emergency Room: **(212) 562-3015**
- New York University Emergency Room: **(212) 263-5550**

If an excessive rise in BP occurs, SBP >200 and/or DBP >140, it will be reported to the IRB and BCCR within 72 hrs. In addition the number of subjects in whom SBP >150 occurs will be reported as individuals in a special AE Table.

In the event that a subject experiences distressing anxious or psychotic symptoms during the experimental or control session, the clinical personnel in attendance (the principal investigator and treatment team) will initiate verbal communication designed to reorient and reassure the subject. If that does not effectively alleviate the signs of an anxious or psychotic reaction, a benzodiazepine (diazepam 5-10mg given orally or intramuscularly) will be administered to lower anxiety. Only if that is ineffective will an antipsychotic be administered, olanzapine (5-15mg given orally or intramuscularly).

Chemistry, manufacturing, and control information:

After the FDA has approved the content of the protocol, the psilocybin will be manufactured by Organix, Inc., 240 Salem St, Woburn, MA 01801, who will provide this information as a supplement to this IND application.

Safety Considerations

Storage, safeguarding, and regulatory aspects of the drug psilocybin:

Using a 222 DEA form, the psilocybin will be shipped from Organix, Inc. to be stored in a secure are within the NYU Bluestone Center for Clinical Research. To safeguard the psilocybin, a special storage safe will be provided to store only the psilocybin. Designated staff will be the only personnel with access to the psilocybin. Both the active agent and placebo will be prepared by designated study staff by a compounding process. A log of the psilocybin accountability, compounding, and dispensing will be kept by designated study staff in designated NYUSoM space located within Bellevue Hospital Center. This will provide strict safeguarding and accounting of the agent both for internal and external regulatory agencies.

Data Safety & Monitoring Plan (DSMP)

Given the nature of this study, it is important to have individuals who have expertise in general psychiatry, addiction psychiatry, and addiction medicine. In addition, it is important to have individuals who are actively involved in IRB approved research. All regulatory and study-related documents will be kept in accordance with NYUSoM IRB policies and procedures. After this study is closed with the IRB, the study will be closed and archived appropriately according to NYUSoM IRB policies and procedures.

The data safety monitoring board (DSMB) will consist of the following individuals:
1) John Rotrosen MD- chair of the DSMB
Professor of Psychiatry

Director, NYU Langone Center of Excellence on Addiction
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NYU Langone School of Medicine
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4)Donald Goff, MD
Professor of Psychiatry
Vice Chair, Department of Psychiatry
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Phone: 212-263-7419

C. Designation of responsibilities for data and safety monitoring

Tara Malone
Research Coordinator
Division of Alcoholism & Drug Abuse
Department of Psychiatry, NYU School of Medicine
462 First Avenue & 27th Street
New York, NY 10016
E-mail: Tara.Malone@nyumc.org
Phone: (646) 501-4206
Study role: Study Coordinator

1) Responsible for data collection and confidential storage in conjunction with designated staff at the Bluestone Center for Clinical Research (BCCR).

Dr. Stephen Ross MD (Principal Investigator) will be responsible for the following tasks:
1) Responsible for monitoring the data collected
2) Responsible for monitoring all adverse events, serious adverse events, and unanticipated problems
3) Responsible for communication with internal (i.e. IRB) and external regulatory bodies (i.e. FDA, DEA)
4) Responsible for coordinating meeting and review of data and safety monitoring with the DSMB

Dr. John Rotrosen
1) Chair of the DSMB
2) Review of psychiatric and addiction related data

Dr. Jennifer McNeely
1) DSMB member
2) Review of internal medicine related data

Dr. Paul Casadonte
1) DSMB member
2) Review of psychiatric and addiction related data

Dr. Donald Goff
1) DSMB member
2) Review of psychiatric data & protocol adherence

D. Planned DSMB Review
1) Number of subjects screened and enrolled
2) Assessment of dropout rate
3) Assessment of outcomes: An interim analysis will be performed after a cohort of 5 patients has completed the study
    -Efficacy parameters will be analyzed for anxiety and depression
4) Assessment of safety information including vital signs, clinical labs, physical examination, medication history, and adverse events
5) Categorization of adverse events using:
    -The ***General Severity Scale*** to determine the adverse event/serious adverse event grade of severity
    -The General Attribution Scale to determine the relationship of the event with the study drug
6) Determination by DSMB regarding continuation, modification or termination of study
7) Other, per DSMB or PI.

E. Reporting of Adverse Events
a. Anticipated adverse events (AEs) will be reported to the DSMB after every 5 subjects have completed the study or on a quarterly basis, whichever is more frequent, and will be reported to the IRB and BCCR as part of the annual report.

b. Events and Information requiring reporting to the NYU IRB and FDA in clinical trials of drug and biological products conducted under IND regulations (under Title21 of the Code of Federal Regulations {21 CFR} part 56 {Institutional Review Boards}, part 312 {Investigational New Drug Application}:

Unanticipated Problems involving risks to participants or others (UAPS)
UAPS are events (including internal or external events, deaths[1], life-threatening experiences[1], injuries, breaches of confidentiality or other problems) that occur any time during or after the research study, which in the opinion of the DSMB or the PI are:

a)**Unanticipated (unexpected)**- not in the consent form, investigator brochure, protocol, package insert, or label; or unanticipated in its frequency, severity or specificity,

AND

b)**Harmful** –caused harm to participants or others, or placed them at increased risk of harm
AND
c)**Serious-** resulting in death or injury requiring hospitalization (admission)

AND

d)**Related** to the research procedures- caused by, or probably caused by research activity

[1]Unanticipated deaths or life-threatening experiences related to the research will be reported to the NYU IRB, BCCR and the FDA in a written INDS safety report of 'any adverse experience associated with the use of the drug that is both serious and unexpected (§ 312.32(c)(1)(i)(A),(B)) within **24** hours. Otherwise, all other UAPS will be reported to the NYU IRB and FDA within **5** days.

Other reportable events and information
1)A single occurrence, or small number of occurrences of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population
2)Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects
3)An AE that is described or addressed in the investigator's brochure, protocol, or inform consent documents, but occurs at a specificity or severity that is inconsistent with prior observations.
4)New Information indicating a change to the risks of potential benefits of the research, in terms of severity or frequency (i.e. Analysis indicates lower than expected response rate or a more severe or frequent side effect; Other research finds arms of study has no therapeutic value; FDA labeling change or withdrawal from marketing)
5)**Protocol Deviation or Violation.** *Only if:*
- **a.** Intended to eliminate apparent immediate hazard to a research participant, or
- **b.** Harmful (caused harm to participants or others, or placed them at increased risk of harm, or
- **c.** Possible serious or continued noncompliance

6)**Complaint**
- **a.** Unresolved by the research team, or
- **b.** That indicates increased or unexpected risks

7)**Incarceration** when in the opinion of the PI it is in the best interest of the participant to remain on the study

F. Frequency of Review and Rationale for Recommended Frequency
1)At a minimum the DSMB will meet quarterly or after a cohort of 5 patients has completed the study, whichever is more frequent.
2)The DSMB will meet more regularly as necessary to review any AEs, serious AEs, UAPs, or new information that in the opinion of the PI or DSMB may impact risks or study continuation.

Pharmacology and toxicology information:

Please refer to IND No. 56,530, submitted by Dr. Francisco Moreno, M.D. of the University of Arizona.

Previous human experience with the investigational drug (Safety Profile):

Psilocybin is 4-hydroxy-N,N-dimethltryptamine, and occurs in nature in many species of mushrooms, including the genera Psilocybe, Conocybe, Gymnopilus, Panaeolus and Stropharia. As is the case with LSD and mescaline, psilocybin is an extremely potent agonist at 5-HT(2A) and 5-HT(2C) receptors, and their

binding potency to these receptors is directly correlated with their human potency as hallucinogens. (Delgado & Moreno, 1998) Although not provided the extensive degree of investigation received by the prototype hallucinogen, LSD, psilocybin was subjected to a variety of research studies during the 1960s employed to establish its psychopharmacological profile of action. Psilocybin was determined to be active and generally safe in the 100 to 300 μg/Kg range (Moreno, 1998). The experience lasts from 4 to 6 hours.

Research with psilocybin has resumed within the last several years and has been safely given to normal volunteers, regarding physiological parameters, at doses ranging from 0.045mg/kg to 0.43mg/kg (Hasler et al. 2004; Griffiths et al. 2006). It has also been safely administered, again regarding physiological parameters, to patients with OCD at doses ranging from 0.025mg/kg to 0.3mg/kg (Moreno et al. 2006). Moreover, a completed double-blind, placebo-controlled (niacin as the control), Phase I study with a cross-over design at Harbor-UCLA Medical was conducted by Dr. Charles Grob, where patients with advanced cancer and anxiety received a single dose of 0.2mg/kg of psilocybin. In total, 12 out of 12 patients were enrolled and completed the study. As mentioned above, the study established the safety and feasibility of administering a moderate dose of psilocybin to patients with advanced cancer and anxiety. Some of the data suggested a treatment effect with reduction in anxiety and depressive symptoms (Grob 2010).

Regarding the issue of potential adverse psychological effects, these include the relative risks associated with alterations of perception, flashbacks and the low probability of dizziness, nausea, vomiting, headaches, increased pulse, transient moderate to severe elevation in blood pressure, dilated pupils and slightly elevated temperature. Actual reports of psilocybin induced psychosis are very rare. Although psychosis has been associated with the use of hallucinogens, the vast majority of cases are from uncontrolled, recreational use. Sidney Cohen, a distinguished psychiatric researcher at the UCLA School of medicine from the 1950s to 1980s, examined the use of hallucinogens in research settings and estimated the incidence of hallucinogen related psychosis to be about 0.8/1000 experimental subjects (Cohen, 1960). Harvard Medical School psychiatrist Lester Grinspoon has described the risks of hallucinogens within treatment settings: "The main danger in psychedelic drug therapy is the same as the danger of any deep-probing psychotherapy: if the unconscious material that comes can be neither accepted and integrated nor totally repressed, symptoms may become worse, and even psychosis or suicide is possible. But the potential for harm has been exaggerated, for two reasons. First, much irrational fear and hostility is left over from the cultural wars of the sixties. More generally, we tend to misconceive drugs as something utterly different from and almost by definition more dangerous than other ways of changing mental processes; actually the dangers in work with LSD do not seem obviously greater than in comparable forms of therapy aimed at emotional insight" (Grinspoon and Bakalar, 1979). From the 1950s to 1970s an extensive literature emerged from experimentation into the controlled use of hallucinogens in the treatment of psychiatric patients. Lester Grinspoon has described that "between 1950 and the mid-1960s there were more than a thousand clinical papers discussing 40,000 patients, several dozen books and six international conferences on psychedelic drug therapy…many people remember vaguely that LSD and other psychedelic drugs were once used. This was not a quickly rejected and forgotten fad" (Grinspoon and Bakakar, 1979). The model identified as being most efficacious, involving careful attention to developing optimal set (preparation, intention and underlying psychological predisposition) and setting (environmental and interpersonal context), often involved the administration of the active agent on only one occasion. It is important to point out, however, that the one-time hallucinogen facilitated experience occurred within the context of an ongoing psychotherapeutic process. The long-term effects of this single dose experience when utilized in optimal context were often therapeutic.

Potential Side Effects from Placebo agent: Niacin

Side effects from niacin include mild and brief flushing (for example, warmth, redness, itching, and/or tingling). Occasionally, dizziness and increased heart rate and shortness of breath may occur.

Additional information.

Previous INDs

Please refer to IND No. 56,530, submitted by Dr. Francisco Moreno, M.D. of the University of Arizona and IND No. 64,052 submitted by Dr. Charles Grob of UCLA.

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