FINAL CLINICAL STUDY REPORT

Protocol #: LDA-1
IND #: 101,825

August 20, 2013

First Subject First Visit: 28-Mar-2008
Last Subject Last Visit: 8-Aug-2012

Phase 2 Pilot Study:
LSD-assisted psychotherapy in persons suffering from anxiety associated with advanced-stage life threatening diseases.

A randomized, single-center, double-blind, active placebo-controlled, partial crossover Phase 2 pilot study comparing response to psychotherapy assisted by 20µg or 200µg LSD.

A study performed in accordance with the principles of Good Clinical Practice as described in the International Conference for Harmonization guidelines, including the archiving of essential documents.

SPONSOR Multidisciplinary Association for Psychedelic Studies (MAPS)
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1.0 Synopsis

Name of Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)
Name of Investigational Product: d-lysergic acid diethylamide-25 (LSD)
Name of Active Ingredient: d-lysergic acid diethylamide-25 (LSD)
Title of Study: LSD-assisted psychotherapy in persons suffering from anxiety associated with advanced-stage life threatening diseases. A phase-II, double-blind, placebo-controlled dose-response pilot study.
Protocol Number: LDA-1
Investigators: Dr. med. Peter Gasser (Principal Investigator), Barbara Speich BSN (Co-investigator)
Study Center: Hauptbahnhofstrasse 5, 4500 Solothurn, Switzerland
Publication (reference): Gasser P, Holstein D, Michel Y, Doblin R, Yazar-Klosinski B, Passie T., Brenneisen R. (submited for publication) Safety and Efficacy of LSD-assisted Psychotherapy in subjects with Anxiety Associated with Life-threatening Diseases: A Randomized Active Placebo-Controlled Phase 2 Pilot Study.
Study Period: First Subject First Visit: March 28, 2008 Last Subject Last Visit: August 8, 2012 — **Phase of Development:** Phase 2
Objectives: The primary objectives of the study were: 1. To measure if subjects receiving LSD-assisted psychotherapy will experience dose-dependent decreases in anxiety after each experimental session and at two months after the second LSD session, as measured by STAI. Secondary Objectives: 1. To evaluate whether the experimental intervention translates into meaningful improvements in quality of life with the EORTC-QLQ. 2. To compare HADS and SCL-90R scores at baseline, one week after each experimental session, and 2 months after the second experimental session, and SOCQ scores at each experimental session. Safety Objectives: 1. To determine if LSD can be safely administered to subjects with anxiety associated with advanced-stage illnesses, without serious adverse events related to the investigational product.
Methodology: The Phase 2 study followed a randomized, active placebo-controlled, double-blind design, with subjects, psychotherapists, and independent raters blinded to subject condition until the primary end point. The pilot study was conducted in 12 subjects with anxiety from life-threatening illnesses. Subjects received a two month treatment process with nine 60-90 minute drug-free preparatory and integrative psychotherapy sessions supplemented by two day-long LSD- assisted psychotherapy sessions administered two to three weeks apart. Subjects were randomized to one of two blinded dose groups. Eight subjects received 200 µg LSD in each of their two experimental sessions, and 4 subjects received 20 µg LSD with an open-label crossover for the active placebo group.
Number of Subjects (planned and analyzed): 12 subjects planned; 12 subjects enrolled and completed; 11 subjects analyzed

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Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria:

Subjects who met the following criteria would be considered for inclusion in this study:

1. Have a diagnosis of advanced-stage potentially fatal illness or metastatic cancer; this may include autoimmune, neurological, infectious, or rheumatoid diseases. At the moment of qualifying for the study the subject must have a probability of survival of more than six months. The estimated life expectancy in relation to the study must be documented.
2. It must be clear that the subject makes the decision to participate in the study by his or her own will and that there is no inhibition to his or her will or ability of deciding due to the primary disease.
3. Meet DSM-IV criteria for Anxiety Disorder as indicated by the SCID or have a score of at least 40 on each part of the STAI.
4. Have failed to respond adequately or at all to medication or psychotherapy intended to reduce anxiety, or have refused to take anxiolytic medication.
5. May be diagnosed with another affective disorder other than anxiety disorder, except bipolar-I disorder.
6. Are at least 18 years of age.
7. Are willing to commit to medication dosing, experimental sessions, follow-up sessions, and to complete evaluation instruments (although they may withdraw from the study at any time without cause).
8. Are willing to refrain from taking any psychiatric medications during the experimental session period. If they are being treated with antidepressants or are taking anxiolytic medications on a fixed daily regimen at the time they are first evaluated, these potential subjects should independently review their use of these medications with their treatment providers. Such drugs must be discontinued long enough before the first LSD treatment session to avoid the possibility of a drug-drug interaction (the interval will be at least five times the particular drug's half-life).
9. If in ongoing psychotherapy, those recruited into the study may continue to see their outside therapist, provided they sign a release for the investigators to communicate directly with their therapist. Subjects should not change therapists, increase or decrease the frequency of therapy or commence any new type of therapy until after the evaluation session two months after the second LSD treatment session.
10. Subjects must agree that, for one week preceding each LSD treatment session:
    a. Clinical judgment will be used to determine permissible herbal supplements.
    b. They will not initiate any new prescription medications (except with prior approval of the research team).
    c. Clinical judgment will be used to determine permissible nonprescription medications.
11. Subjects must agree to take nothing by mouth except for routine medications, non-alcoholic liquids and light food after 12 A.M. (midnight) the evening before each experimental intervention session. Subjects must also refrain from the use of any psychoactive drug, with the exception of the long-term pain medication or caffeine or nicotine, within 24 hours of each LSD treatment session. They must agree not to use nicotine for at least two hours before and six hours after each dose of LSD. They must agree to not ingest alcohol-containing beverages for at least one day before each LSD

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treatment session. Non-routine PRN medications for treating breakthrough pain taken in the 24 hours preceding the LSD treatment session may result in rescheduling the treatment session to another date, with the decision at the discretion of the investigators after discussion with the subject.

Exclusion Criteria:

Prospective subjects with the following conditions would be excluded from the study:

1. Women who are pregnant or nursing, or of child bearing potential and are not practicing an effective means of birth control.
2. Anyone with past or present diagnosis with a primary psychotic disorder.
3. Meeting DSM-IV criteria for Dissociative Disorder or Bipolar-I Affective Disorder.
4. Meeting DSM-IV criteria for abuse of or dependence on any substance (other than caffeine or nicotine) in the past 60 days.
5. Diagnosed with significant somatic problems, that in the clinical judgment of the investigators poses too great a potential for side effects.
6. No sufficient liver function at the baseline examination or the day before the experimental sessions.
7. Having evidence of CNS affection from the primary disease (e.g. brain metastasis), shown by neurocognitive impairment.
8. Weighing less than 45 kg.
9. Reasonably judged to present a serious suicide risk or who are likely to require psychiatric hospitalization during the course of the study.
10. Unable to fully understand the potential risks and benefits of the study and give informed consent.
11. Requiring ongoing concomitant therapy with a psychotropic drug (other than as needed, anxiety medications, and pain control medications) and are unable or unwilling to comply with the washout period.

Test Product, Dose, Mode of Administration, Lot Number:

200 µg LSD, administered on two occasions during psychotherapy; oral capsules; Lipomed AG Lot # 397-FB, Lot # 397.1810.1

Reference Therapy, Dose, Mode of Administration, Lot Number:

Active placebo dose of 20 µg LSD, administered on two occasions during psychotherapy; oral capsules; Lipomed AG Lot # 397-FB, Lot # 397.1810.1

Duration of Study:

Subjects participating in Stage 1 and the follow-up outcome measures completed the study in approximately 6 months. Subjects participating in Stage 2 completed the study in approximately 11 months.

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Criteria for Evaluation:

Efficacy:

Primary outcome measures involved comparing STAI State and Trait scores and at baseline, one week after each experimental session, and 2 months after the second experimental session. Secondary outcome measures involved comparing EORTC-QLQ, HADS, SCL-90R, scores at baseline, one week after each experimental session, and 2 months after the second experimental session, and SOCQ scores at each experimental session. The sponsor maintained a database containing study data. STAI, HADS, SCL-90, EORTC-QLQ, VAPS (for the study day), and PEP/SOCQ scale scores.

Descriptive statistics were calculated for all outcome measurements, such as those occurring at baseline and two months after the second experimental LSD-assisted psychotherapy session. The STAI scale scores were analyzed to examine trends by condition and visit.

Safety: Blood pressure and pulse were taken pre-drug, four hours and eight hours after drug administration, or as needed. Abnormal lab values were collected after treatments were completed. Adverse events were collected throughout the study and related adverse events were collected during and seven days after each experimental session. General wellbeing was assessed at every face-to-face visit during and after each experimental session. Subjects kept a daily diary to record pain levels.

Statistical Methods:

[Planned] Results of outcome measure assessments were to be analyzed by nonparametric ANOVA using the F1_LD_F1 model. Follow-up and Stage 2 data were to be informally analyzed. No statistical corrections were planned for multiplicity of data, and significance was set at $p < 0.05$.
[Actual] The sponsor conducted an independent T-test comparing STAI scores of active placebo and experimental dose LSD subjects at baseline and the 2-month follow-up. Effect sizes were estimated using Cohen's *d* techniques. Adjustment for multiplicity was applied due to the primary outcome measure consisting of two scales, with $p < 0.025$. Average post-drug values of vital signs between active placebo and experimental dose LSD subjects were not formally compared due to limited sample size.

Summary and Conclusions:

There were no drug-related serious adverse events, nor any adverse physiological or persisting psychological effects. At 2-month follow-up, positive trends were found in reductions in trait anxiety with an effect size of 1.1 and state anxiety was significantly reduced with an effect size of 1.2. Benefits were sustained over time as mean 2-month and 12-month results were virtually identical. Subjects consistently reported beneficial effects from LSD- assisted psychotherapy, which promoted cathartic and insightful experiences.

Efficacy results: STAI State scores indicate a significant reduction in state anxiety in 8 subjects receiving 200µg LSD in comparison to 3 active placebo subjects. STAI Trait scores showed a trend towards decreasing in the 8 subjects receiving 200µg LSD in comparison to 3 receiving active placebo. One subject was excluded from efficacy analysis due to misdiagnosis of life-threatening illness. At 2-month follow-up, average STAI State scores decreased 11.6 points (21.8%) in experimental dose subjects and increased 4.0 points (8.4%) in active placebo subjects. Average STAI Trait scores decreased 8.0 points (18.6%) in experimental dose subjects and

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increased 5.7 points (13.2%) in active placebo subjects. STAI scores remained virtually the same over time in the follow-up period.

Efficacy conclusions: LSD-assisted psychotherapy with 200µg LSD generated a clinically significant response in this small subject sample. Even after adjustment for multiplicity, results demonstrate statistical significance in state anxiety and a trend toward significant reductions in trait anxiety. Future studies with larger sample size are warranted.

Safety results: There were no drug-related Serious Adverse Events. All subjects completed the planned treatments. One subject exhibited elevation in systolic blood pressure above the predetermined cutoff of 140/90 mm Hg during one experimental session that lasted for an hour. No interventions were needed and this event was not clinically significant. Related adverse events occurred but generally resolved by the day after each experimental session, and 102 possibly or probably related adverse events were collected. Subjects that received 200 µg LSD reported a greater number of expected reactions to the study drug than subjects receiving active placebo. Illusions (percpetual distortions and pseudohallucinations), feeling abnormal and feeling cold were most frequently reported. None of the unexpected adverse events were related to administration of the study drug.

Safety conclusions: LSD-assisted psychotherapy did not cause any drug-related Serious Adverse Events. Cardiovascular effects and related adverse events were similar to those reported in the literature, were self-limiting and did not require intervention. Data suggest that LSD-assisted psychotherapy does not cause undue harm in this subject population.

Date of Final Report: August 20, 2013

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2.0 List of Abbreviations and Definition of Terms

5-HT	5-hydroxytryptamine or serotonin
5-HT_{2A}	Serotonin 2A receptor
AE(s)	Adverse Event(s)
ALT/SGPT	Alanine aminotransferase
AST/SGOT	Aspartate aminotransferase
BAG	Swiss Federal Office for Public Health
BDI	Beck Depression Inventory
C	Celsius
CRA	Clinical Research Associate
CRF(s)	Case Report Form(s)
DEA	Drug Enforcement Administration
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - IV
ECG/EKG	Electrocardiogram
EORTC-QLQ	European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire
F	Fahrenheit
FDA	Food and Drug Administration
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HADS	Hospital Anxiety and Depression Inventory
HCl	Hydrochloric acid
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
LSD	d-lysergic acid diethylamide
MAPS	Multidisciplinary Association for Psychedelic Studies
MDMA	3,4-methylenedioxymethamphetamine
QC	Quality Control
SAE(s)	Serious Adverse Event(s)
SCID	Structured Clinical Interview for Diagnoses
SOP(s)	Standard Operating Procedure(s)
SSRI	Selective Serotonin Reuptake Inhibitor
STAI	State-Trait Anxiety Inventory
SUD	Subjective Units of Distress
U.S.	United States of America
VAPS	Visual Analog Pain Scale

3.0 Ethics

The study and any amendments were reviewed and approved by the following Institutional Review Board (IRB): Kantonale Ethikkomission, Department Gesundheit und Soziales [Health and Social Science], Bachstrasse 15, 5001 Aarau, Kanton Aargau, Switzerland. See Appendix 14.1.3 Ethics Committee Approvals and Information for Subjects.

This study was conducted in accordance with the ethical principles of Good Clinical Practice (GCP) and U.S. FDA regulations that have their origins in the Declaration of Helsinki.

The informed consent forms (ICF) were reviewed and approved by the IEC. After a brief interview with the investigator conducted over the telephone or in person, prospective subjects met with investigator to discuss the study and to give written informed consent to take part in the study if they chose to participate. Only after subjects gave their informed consent were initial psychiatric evaluations conducted. These activities were completed prior to enrollment. See representative ICFs for the study attached as Appendix 14.1.3.

4.0 Investigators and Study Administrative Structure

Dr. med. Peter Gasser was the Principal Investigator (PI) for this study. Dr. med. Gasser worked with co- investigator Barbara Speich, B.S.N. Both conducted psychotherapy and Dr. med. Gasser administered study drug during experimental sessions. The study took place at the offices of Dr. med. Gasser in Solothurn, Switzerland. The study was developed by Dr. med. Gasser and the sponsor. Administration of screening and outcome measures was performed by Dr. Phil. Marcela Jegerlehner. The study was monitored by the sponsor.

PI: Dr. Med. Peter Gasser
Co-Investigator: Barbara Speich, B.S.N.
Independent Rater: Marcela Jegerlehner, Ph.D.
Randomization Monitor: Rudolf Brenneisen, Ph.D.
Medical Monitor: Michael Mithoefer, M.D.
Biostatisticians: Lisa Jerome, Ph.D., Yvonne Michel, Ph.D., Dominique Holstein, Ph.D.

Please see Appendix 14.1.5 for signatures of the PI and sponsor's Medical Monitor and Appendix 14.1.4 for CVs of investigators.

5.0 Introduction

This report describes a pilot study of d-lysergic acid diethylamide (LSD)-assisted psychotherapy in twelve subjects with anxiety related to advanced-stage illness leading to shortened life expectancy. This study was sponsored by MAPS, a non-profit organization focused on clinical research and public education. The protocol was developed based on early phase research studies conducted 40 years ago in the U.S. and Europe.

LSD is an ergoline compound first synthesized in 1938 by the Swiss chemist Albert Hofmann. LSD's highly specific actions on the brain and human consciousness were discovered by chance by Hofmann in 1943 [1]. The first psychotherapeutic study was conducted in 1946 [2, 3]. A structured setting for LSD-assisted psychotherapy was developed approximately 10 years later by psychotherapeutically-focused psychiatrists such as Stanislav Grof [4], Hanscarl Leuner [5] and others.

After a period of rich scientific activity in the 1950s and 1960s investigating the therapeutic potential of LSD, [14, 17, 21], this research came to a halt, chiefly as a result of political concerns and in response to large-scale use and abuse in subcultures at that time. Though research reported some promising results, it did not follow optimal designs, and there had not been any prospective, double-blind, placebo-controlled investigations of LSD-assisted psychotherapy since the early 1970s [14].

LSD-assisted psychotherapy was permitted in Switzerland from 1988 to 1993. During this period, 170 patients with a wide range of clinical conditions were treated and the results of the treatments were summarized in a follow-up case series study [22]. However, patients were not compared with a control group and the researchers did not document the investigation or the process itself, because the treatments were understood as therapeutic and not part of a controlled study. The follow-up study suggested that the treatment may have been safe and efficacious, as more than 80% of patients who responded to the follow-up were satisfied with the result of the treatment, and there were no reported occurrence of severe persisting adverse effects.

This study was a part of the sponsor's clinical development plan evaluating the safety and efficacy of LSD as an adjunct to psychotherapy for anxiety associated with end of life. The investigators in this study, LDA-1, conducted a randomized, active-placebo controlled investigation in order to redevelop a treatment method of LSD-assisted therapy and to gather preliminary evidence on the safety and efficacy of this treatment in this population using current scientific standards. Eight of 12 subjects were assigned to the experimental dose condition (experimental dose, 200 μ g LSD) and four were assigned to the low dose condition (active placebo dose, 20 μ g LSD). Subjects enrolled in the study received two blinded experimental sessions of LSD-assisted psychotherapy separated by a two to four week interval. These experimental sessions were embedded within a course of six to eight individual non-drug psychotherapy sessions that prepared subjects for LSD-assisted therapy and then helped subjects integrate material from the LSD-assisted sessions.

An independent rater assessed anxiety levels and quality of life throughout the study and up to two months after the second experimental session. This rater was a clinically trained psychologist who is familiar with diagnostic tools such as the SCID and with the assessments, STAI, EORTC-QLQ-C30, and all other questionnaires used for this study. This rater was blinded. The use of anxiety and pain medications were assessed throughout the study via diaries kept by subjects.

This pilot study was a part of the sponsor's clinical development plan to reevaluate the therapeutic potential of LSD-assisted psychotherapy and to develop LSD as a prescription treatment administered by licensed psychiatrists and psychotherapists in specially regulated clinics [23]. Similar studies with patients suffering from anxiety related to advanced-stage cancer were conducted in the U.S [24] using psilocybin, a compound with similar effects. These studies were conducted to assess the potential of these compounds as a treatment for anxiety arising from facing a life-threatening illness.

6.0 Study Objectives

The following main questions were explored in this study:

- Can LSD-assisted psychotherapy be safely administered to individuals with a severe prognosis and shorted life expectancy who suffer from anxiety related to their diagnosis and the severity of their disease and condition?
- Will this therapy produce improvements in symptoms of anxiety?

The primary objectives of the study were:

1. To measure if subjects receiving LSD-assisted psychotherapy will experience dose dependent decreases in anxiety after each experimental session and at two months after the second LSD session, as measured by STAI.

Secondary Objectives:

1. To evaluate whether the experimental intervention translates into meaningful improvements in quality of life with the EORTC-QLQ.

2. To compare HADS and SCL-90R, scores at baseline, one week after each experimental session, and 2 months after the second experimental session, and SOCQ scores at each experimental session.

The safety objectives presented in the protocol are grouped under the main first objective of the study and have been formulated as individual objectives below:

1. Assessments of treatment safety included changes in physiological function (blood pressure and heart rate)
2. Extent or intensity of experienced pain and resultant use of pain-relieving medications, and related adverse events during and one week after each experimental session. Physiological measures, self-reported pain and medication, and adverse events were collected and compared in active placebo and experimental dose subjects.

The altered state during the experimental session will be measured by the States of Consciousness Questionnaire (SOCQ), a process measure that was previously called the Peak Experience Profile (PEP), on the day after experimental sessions to explore the subjective effects of active placebo and full-dose LSD.

7.0 Investigational Plan

7.1 Overall Study Design and Plan

This study followed a randomized, active-placebo controlled, double-blind design, with subjects, psychotherapists, and independent raters blinded to condition assignment. After screening conducted by the PI and independent rater at Visit 3, four of 12 subjects were randomly assigned to the active placebo condition, and eight of 12 were assigned to the experimental dose condition. Subjects in the active placebo condition received 20µg LSD and subjects in the experimental dose condition received 200µg LSD on each of two experimental sessions. The study included eight conventional (non-drug assisted) psychotherapy sessions with the PI, and at least two that involved the co-therapist. These sessions lasted for one hour. There were two drug-assisted experimental sessions with the PI and the co-therapist that lasted eight hours, and four administrations of outcome measures by the independent rater, immediately before treatment (Visit 6), one week after each experimental session (Visit 9 and 12) and at 2-month follow-up (Visit 14). After unblinding, active placebo subjects had the opportunity to take part in an open-label continuation of the study, referred to as Stage 2. Data gathered 2 months after the second experimental session was treated as the baseline for Stage 2, and outcome measures were administered one weeks after each experimental session and at 2-month follow-up. Completion of the active treatment phase of the study occurred approximately four months after screening.

7.2 Discussion of Study Design Including Control Groups

Subjects in this study received one of two treatments: a low, or active placebo, or an experimental dose of the study drug. Because of the known psychoactive nature of the study drug, the study used an active placebo to maintain the study blind for the investigators conducting psychotherapy. A low dose of LSD was chosen as a credible placebo that would not possess the therapeutic effects of the experimental dose. See 7.4.4 Selection of Doses in Study. Use of an inactive placebo permits a clear determination of effects due to the study drug at the cost of difficulty maintaining the blind. There is not yet enough information to establish what dose or material will make the best active placebo. This study was the sponsor's first attempt to assess the study blind with this study drug in this manner.

The study followed a between-group partial crossover design. All subjects were assigned to either active placebo or experimental dose LSD in a blinded manner, meaning subjects, the investigators performing psychotherapy, and the independent rater were unaware of condition assignment, with dropouts replaced until twelve subjects had completed the study. The study was designed to enroll 8 subjects in the experimental dose condition and four in the active placebo condition, with randomization designed accordingly to maintain this ratio while also maintaining the study blind. After completing the study, all active placebo subjects had the option of enrolling in Stage 2, an open-label crossover arm of the study. The goal of this arm was to investigate how subjects respond to experimental dose LSD-assisted psychotherapy when compared to active placebo as a within-subject control group. Long-term follow-up evaluation was conducted as a separate extension study in subjects who received experimental dose LSD in either Stage 1 or Stage 2, twelve months after the final experimental session. Use of the partial crossover meant that the investigators were unable to compare subjects who received active placebo to those who received experimental dose LSD at the time of the long-term follow up, which was the reason for excluding subjects who elected not to continue to Stage 2 in the follow-up analysis. However, the follow-up data was useful for an exploratory observation of changes in anxiety symptoms over 12 months since experimental dose LSD treatment.

7.3 Selection of Study Population

Twelve subjects who met all inclusion criteria without meeting any exclusion criteria were admitted to the study. Subjects were recruited for the study by call for referral from specialized institutions such as counseling centers, as well as psychiatrists and psychotherapists in private practice.

7.3.1 Inclusion Criteria

Compliance with inclusion criteria was continually evaluated throughout the course of the study. Individuals were included as potential subjects if they meet the following criteria:

1. Have a diagnosis of advanced-stage potentially fatal illness or metastatic cancer; this may include autoimmune, neurological, infectious, or rheumatoid diseases. At the moment of qualifying for the study the subject must have a probability of survival of more than six months. The estimated life expectancy in relation to the study must be documented.
2. It must be clear that the subject makes the decision to participate in the study by his or her own will and that there is no inhibition to his or her will or ability of deciding due to the primary disease.
3. Meet DSM-IV criteria for Anxiety Disorder as indicated by the SCID or have a score of at least 40 on each part of the STAI.

4. Have failed to respond adequately or at all to medication or psychotherapy intended to reduce anxiety, or have refused to take anxiolytic medication.
5. May be diagnosed with another affective disorder other than anxiety disorder, except bipolar-I disorder.
6. Are at least 18 years of age.
7. Are willing to commit to medication dosing, experimental sessions, follow-up sessions, and to complete evaluation instruments (although they may withdraw from the study at any time without cause).
8. Are willing to refrain from taking any psychiatric medications during the experimental session period. If they are being treated with antidepressants or are taking anxiolytic medications on a fixed daily regimen at the time they are first evaluated, these potential subjects should independently review their use of these medications with their treatment providers. Such drugs must be discontinued long enough before the first LSD treatment session to avoid the possibility of a drug-drug interaction (the interval will be at least five times the particular drug's half-life).
9. If in ongoing psychotherapy, those recruited into the study may continue to see their outside therapist, provided they sign a release for the investigators to communicate directly with their therapist. Subjects should not change therapists, increase or decrease the frequency of therapy or commence any new type of therapy until after the evaluation session two months after the second LSD treatment session.
10. Subjects must agree that, for one week preceding each LSD treatment session:
    a. Clinical judgment will be used to determine permissible herbal supplements.
    b. They will not initiate any new prescription medications (except with prior approval of the research team).
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11. Subjects must agree to take nothing by mouth except for routine medications, non-alcoholic liquids and light food after 12 A.M. (midnight) the evening before each experimental intervention session. Subjects must also refrain from the use of any psychoactive drug, with the exception of the long-term pain medication or caffeine or nicotine, within 24 hours of each LSD treatment session. They must agree not to use nicotine for at least two hours before and six hours after each dose of LSD. They must agree to not ingest alcohol-containing beverages for at least one day before each LSD treatment session. Non-routine PRN medications for treating breakthrough pain taken in the 24 hours preceding the LSD treatment session may result in rescheduling the treatment session to another date, with the decision at the discretion of the investigators after discussion with the subject.

7.3.2 Exclusion Criteria

Compliance with exclusion criteria were continually evaluated throughout the course of the study. Individuals were excluded from study participation if they are/have:

1. Women who are pregnant or nursing, or of child bearing potential and are not practicing an effective means of birth control.
2. Anyone with past or present diagnosis with a primary psychotic disorder.
3. Meeting DSM-IV criteria for Dissociative Disorder or Bipolar-I Affective Disorder.
4. Meeting DSM-IV criteria for abuse of or dependence on any substance (other than caffeine or nicotine) in the past 60 days.
5. Diagnosed with significant somatic problems, that in the clinical judgment of the investigators poses too great a potential for side effects.

6. No sufficient liver function at the baseline examination or the day before the experimental sessions.
7. Having evidence of CNS affection from the primary disease (e.g. brain metastasis), shown by neurocognitive impairment.
8. Weighing less than 45 kg.
9. Reasonably judged to present a serious suicide risk or who are likely to require psychiatric hospitalization during the course of the study.
10. Unable to fully understand the potential risks and benefits of the study and give informed consent.
11. Requiring ongoing concomitant therapy with a psychotropic drug (other than as needed, anxiety medications, and pain control medications) and are unable or unwilling to comply with the washout period.

7.3.3 Removal of Subjects from Therapy or Assessment

The subject, or where applicable, the subject's legally acceptable representative(s), could withdraw consent for participation in the study at any time without prejudice. The investigator could 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.

Subjects were clinically monitored after withdrawal, reasons for withdrawal are recorded on the "Study Termination" CRF and, where appropriate, on the subject's medical records. If withdrawal of a subject resulted from an adverse event, this was documented in accordance with the protocol. Whenever possible, the tests and evaluations listed for the termination and outcome visits were carried out.

7.4 Treatments

7.4.1 Treatments Administered

7.4.1.1 Psychotherapy

All subjects took part in two introductory psychotherapy sessions prior to the first experimental session, where they reviewed their disease-related anxiety and discussed what was to occur during the experimental session. Non-drug assisted psychotherapy occurred with both investigators one day after each experimental session, and with just the PI 5-10 days after each experimental session. The final psychotherapy session occurred 5-10 days after the second experimental session. Subjects were assessed prior to and after receiving LSD-assisted psychotherapy. Measures and schedule of assessments is described in more detail in Section 7.5, "Efficacy and Safety Variables."

During the introductory psychotherapy sessions, the investigators and the subject reviewed and discussed anxiety and any other issues or goals for the initial experimental session. Subjects learned more about the effects of LSD and the procedures occurring during and after each experimental session.

Psychotherapy follow-up sessions were conducted in the morning on the day after the experimental sessions, where the investigators and subject reviewed the events of the experimental session and integrated thoughts, feelings or experiences. Psychotherapy occurring after the first experimental session also involved preparation for the second experimental session. Approximately one week after an experimental session, the subject and the investigators continued

to integrate material from the experimental session. Psychotherapy continued to focus on reducing anxiety, but also addressed other issues that arose during or after the experimental sessions. The subject could request additional psychotherapy sessions during the course of the study if needed.

7.4.1.2 Psychotherapy During Experimental Session

The two LSD treatment sessions scheduled two to eight weeks apart were supervised and facilitated by the PI, psychiatrist Dr. Peter Gasser, accompanied by an experienced female co-investigator/co-therapist, B. Speich. Both investigators were present throughout the experimental sessions. The sessions followed the principles developed by Grof for LSD psychotherapy [4] and adapted by the Swiss Society for Psycholytic Therapy[25]. At the beginning of the session, the investigators discussed the subject's goals and intentions for the session, including intentions regarding working with psychological issues related to their episodes of anxiety. During the experimental sessions, the investigators engaged with the subject, supporting and encouraging emotional processing and resolution of whatever psychological material emerged. If the subject did not speak spontaneously within the first hour, the investigators checked in with the subject. The investigators also encouraged periods of silent introspection to support and increase the psychological insights mediated by the LSD treatment. Non-alcoholic, non-caffeinated beverages were freely available throughout the session, and food was available during the latter part of the session. The site was equipped with medical emergency equipment, i.e. appropriate medications, defibrillation kit to address medical emergencies, and the site was within a three-minute ride via car or ambulance to a hospital with an intensive care unit.

The experimental session concluded after approximately six to ten hours, if all medical and psychological parameters were acceptable and the subject was alert, ambulatory, and emotionally stable. Subjects spent the night in a comfortably furnished space at the same location as the LSD-assisted psychotherapy. A relative or significant other was permitted to accompany the subject during his or her stay to assist him or her and to offer support, and if the subject did not locate someone to offer support, a nurse was available to accompany the subject. Subjects were able to contact at least one of the investigators throughout the night through telephone to answer questions or concerns. If necessary, the investigators could return to the practice to assess or treat the subject.

7.4.1.3 Open Label Continuation for Active Placebo Subjects

Two months after the second LSD-assisted session, after completing outcome measures, subjects met with the PI and the study blind was broken. If a subject had received the active placebo dose during the course of the study, she or he was offered an opportunity to enroll in the open label study continuation, "Stage 2." He or she could give written informed consent to take part in this second stage of the study independently of consenting to taking part in the first stage. In open label Stage 2, the subject received the experimental dose of LSD (200 µg) during two experimental sessions scheduled two to eight weeks apart. Experimental sessions occurred after a single introductory session scheduled no later than two weeks after breaking the blind for Stage 1. Subjects received non-drug psychotherapy, experimental sessions, and follow-up sessions the day after and 5-10 days after each LSD-assisted psychotherapy session.

7.4.2 Identity and Handling of Investigational Product

The investigational product is d-lysergic acid diethylamide (LSD, lysergamide, Delysid, $C_{20}H_{25}N_3O$,), an indole alkaloid with the molecular weight of 323.4 Daltons, first synthesized in 1938 by Albert Hofmann at Sandoz Laboratories. This study used the hydrate form, which is an

off-white powder. The drug was administered orally as a capsule. Lipomed AG, Fabrikmattenweg 4, 4144 Arlesheim manufactured the LSD for this study. Product reference and batch number are LSD-397-FB and 397.1B10.1. Identity was confirmed by IR, UV, and melting point vs. reference (quality certification QA-F-20.1, 15.9.2003). Quality control of the drug was performed at the University of Bern, DKF by Prof. Dr. R. Brenneisen to check identity by GC/MS and purity by HPLC on February 21, 2008 this confirmed the material as LSD >99% pure.

The formulation of 200 µg (experimental dose) and 20 µg (Active Placebo) tablets (weight of hydrate) was performed by the Grosse Apotheke Dr. G. Bichsel, Bahnhofstr. 5a, 3800 Interlaken. Dextrose tablets were impregnated by an ethanolic solution of LSD using an appropriate technique and under GMP conditions. Full and Active Placebo did not differ in appearance (weight, color, size etc.) or taste. The quality control of the tablets, performed by the DKF, included checking identity (GC/MS, HPLC), and content (HPLC). The QC data is included in Appendix 14.1.10 of the final report and has been sent to Swissmedic. The LSD capsules were stored in a locked safe and only the investigator had access to the study drug. Supply, handling, formulation, and the clinical use of LSD followed the regulations of the Swiss Narcotics Law. A general narcotics permit of the Federal Office for Public Health (BAG), was issued to Prof. Dr. R. Brenneisen, (AB-8/5-BetmG-/06.004679), for supply and handling of the LSD scheduled according to Art. 4 Bst. d ("Illicit Substances"). A special production permit for Bichsel and an LSD trial permit for Dr. P. Gasser (PI) were obtained, respectively.

7.4.3 Method of Assigning Subjects to Treatment Groups

At least 24 hours before the first experimental session, each subject was randomly assigned to one of two conditions, either active placebo (20 µg) or experimental intervention (200 µg). Four of twelve subjects were assigned to receive active placebo and eight were be assigned the experimental dose. Professor R. Brenneisen, Ph.D., University of Bern, Department of Clinical Research, Laboratory for Phytopharmacology, Bioanalytics and Pharmacokinetics, Murtenstrasse 35, CH-3010 Bern, generated and maintained the randomization code and procedure.

7.4.4 Selection of Doses in Study

The lowest dose contained in one capsule was 20 µg, was the active placebo dose. The highest dose contained in one capsule was 200 µg, was the experimental intervention dose.

Table 1. Doses

Treatment Condition	Dose
Active Placebo Dose	20 µg LSD
Experimental Dose	200 µg LSD

The dose of LSD (20 µg) chosen for the active placebo dose condition was selected on the basis of its ability to produce minimal but detectable subjective effects [29]. On the basis of previous research in healthy volunteers [29] and in the treatment of cancer [17, 19], the LSD dose of the experimental condition (200 µg) is expected to produce most of the expected effects of LSD. Psychiatrists employing LSD-assisted psychotherapy in people with advanced stage cancer administered doses of 200 µg or higher to produce powerful alterations in consciousness and experiences of transcendence [17, 19].

7.4.5 Blinding

Condition assignments were maintained through Stage 1 of the study. The blind was broken after completing Stage 1, and subjects in the active placebo condition were permitted to continue with an open-label arm of the study, called Stage 2. The blind could have been broken for an individual subject on the occurrence an adverse event or other emergency requiring knowledge of the subject's condition assignment, as when pharmacological intervention was necessary.

7.4.6 Prior and Concomitant Therapy

All prescription concomitant medications were recorded at baseline. During the study subjects kept a daily log of medications taken while actively enrolled in the study. Only changes to anxiolytic and pain management baseline medications were recorded on the CRF.

7.4.7 Treatment Compliance

The PI was responsible for adequate and accurate accounting of investigational product usage. The PI administered all investigational product only to subjects included in the study following the procedures set out in the study protocol, within the context of an LSD-assisted psychotherapy session. Subjects did not receive take-home doses. The date, dosage and time of dosing were recorded. The PI tracked capsules received and used and retained all unused capsules and containers thereof in locked storage, until the sponsor was satisfied that the drug accountability records were correct. At the end of the study, all but one capsule of unused investigational product was returned to the randomization monitor and destroyed. The PI obtained special permission from BAG to administer one capsule of investigational product under a Compassionate Use Application approved during the study.

Information on concomitant medications was collected throughout the study to ensure treatment compliance. Urinary drug screens were performed once at baseline, and prior to each LSD administration. These tests demonstrated that all the subjects remained compliant and did not use controlled substances prior to experimental sessions. (See Appendix 14.2.5.1)

7.5 Efficacy and Safety Variables

7.5.1 Efficacy and Safety Measurements Assessed and Flow Charts

Outcome measures were administered to subjects by the independent rater on four occasions (visits V6, 9, 12 & 14) during Stage 1; as well as once during screening prior to enrollment. Baseline was assessed at the visit immediately before the first experimental session. Outcomes were assessed prior to each psychotherapy session scheduled at 5-10 days after an experimental session, and two months after the second experimental session. The independent rater remained blind to condition assignment and was not present during experimental or non-drug psychotherapy sessions. Only the daily anxiety and pain diaries and the SOCQ, a process measure, were administered within 24 hours after each experimental session. Outcome measures gathered two months after the second experimental session served as Stage 2 baseline measures. Subjects enrolled in the open-label Stage 2 completed outcome measures on a similar schedule to that of Stage 1, with outcome measures administered at 2-month follow-up in Stage 1 serving as Stage 2 baseline. Subjects completed outcome assessments at equivalent time points in Stage 2.

Table 2. Study Measures Assessed

Type of Measure	Name of Measure	Administered by
Screening	Structured Clinical Interview for Diagnoses according to DSM-IV criteria (SCID-IV)	Independent Rater
Medical Screening	Medical history and physical examination	Physician other than PI
Medical Screening	Electrocardiogram (ECG)	Physician other than PI
Screening, Safety	Urine tests: drugs, pregnancy (if applicable)	Investigators
Screening, Safety	Liver panel, serum electrolytes, thyroid hormones in blood	Clinical lab
Screening, Efficacy	STAI	Independent Rater
Efficacy	EORTC-QLQ	Self-report
Efficacy	HADS-A; HADS-D	Self-report
Efficacy	SCL-90-R	Self-report
Safety	Visual analog pain scale	Self-report
Safety	Vital signs	Investigators
Safety	Adverse events	Investigators
Safety	General well-being	Investigators
Process	SOCQ	Self-report
Process	Belief of Condition Assignment	Investigators

7.5.2 Appropriateness of Measurements

7.5.2.1 Diagnostic Measures

Screening measures conducted prior to enrollment constitute a standard battery of tests designed to thoroughly examine the potential subject for any medical issues. Psychological assessments consisted of the Structured Clinical Interview for Diagnoses according to DSM-IV criteria (SCID-IV) to determine whether an individual satisfied eligibility criteria. The SCID is a semi-structured interview that permits accurate diagnosis of lifetime and current psychiatric disorders.

At baseline, medical history, a standard physical examination, electrocardiogram (ECG), metabolic profile, assessment of blood levels of thyroid hormones, serum electrolytes, , and urinary drug and pregnancy tests (when appropriate) were conducted to establish medical eligibility for the study.

7.5.2.2 Efficacy Measures

Efficacy measures were established measures of anxiety known to be reliable and valid.
All outcome measures were given to subjects by an independent rater who also provided an objective evaluation of clinical outcome, but primary outcome assessment relied on the STAI, a self-report measure. The independent rater was blind to subject condition and was not present during psychotherapy sessions.

Spielberger State-Trait Anxiety Inventory (STAI) differentiates "state anxiety" (i.e. anxiety dependent on a specific situation or stressor) from "trait anxiety" (longstanding anxious affect or disorder) and is considered the definitive instrument for measuring anxiety in adults [33-35]. Extensive normative group data exists and the STAI has been administered to advanced-stage cancer patients with anxiety. The STAI has 40 questions with four possible answers each. A score of 40 or greater in each of the two sub-scales is associated with clinically significant symptoms of anxiety. This was the primary outcome variable for anxiety.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [30] has satisfactory psychometric properties and currently is one of the most widely accepted measures of quality of life. This instrument has 30 items yielding scores for five subscales (physical, role, emotional, social, and cognitive functioning) and 3 symptom subscales (fatigue, pain, and nausea/vomiting). This will be the primary outcome variable for quality of life.

Hospital Anxiety and Depression Scale[31] was developed to assess anxiety and depression in somatic patients. It is a 14-item self-report instrument widely used in clinical trials.

Symptom Checklist 90-[R]. This is a standardized instrument used to measure subjective, feeling states [32]. Reliability, validity, and utility have been demonstrated across close to 1000 studies and normative data values have been published. The SCL90 has subscales along 9 primary symptom dimensions (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism) and 3 global indices (global severity index, positive symptom distress index, and positive symptom total). The SCL90 has 90 questions with a 5-point rating scale.

7.5.2.3 Safety Measures

Visual Analog Pain Scale. This is a simple and efficient tool that consists of a drawn 10-cm line labeled at one end "no pain" and at the other end with "worst pain possible." Scoring is accomplished by having the subject 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 the VAPS is reliable and valid as both a sensitive measure of pain and as a measure of change in pain (Ohnhaus and Adler 1975). The current format for the daily analog pain scale was developed for a study of MDMA-assisted psychotherapy.

Daily Diary. Subjects kept a daily log of medications taken while actively enrolled in the study protocol. Only changes to pain and psychoactive baseline medications were recorded on the CRF. The forms provided to subjects reminded them to contact the investigators prior to initiation of any drug or medication not already reviewed during the intake evaluation. Subjects also completed the VAPS (see Visual Analog Pain Scale below) daily. The VAPS was originally developed for use in a study of MDMA-assisted psychotherapy in subjects with anxiety arising from a diagnosis of advanced stage cancer.

Vital Signs Monitoring:
Blood pressure and pulse were measured at the beginning, middle, and end of each experimental session. The investigators could take additional readings on the basis of clinical judgment as to the severity of elevated blood pressure. If necessary, the investigator could reduce elevated blood pressure via antihypertensive medication, and if antihypertensives failed to significantly reduce blood pressure, then the investigator could have the subject transported to the hospital.

Adverse Events:
An adverse event (AE) : any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily 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 the 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: an adverse event 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 were monitored until resolution or, if the AE became chronic, a cause identified. If an AE was unresolved at the conclusion of the study, a clinical assessment was made by the investigator and Medical Monitor as to whether continued follow-up of the AE was warranted.

The severity of events reported on the "Adverse Events" CRF were 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 was 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 was 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.

A severe adverse event need not be serious in nature and a serious adverse event need not, by definition, be severe.

A pre-existing event or condition resulting in hospitalization were recorded as medical history. The hospitalization was not 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.

Adverse Event Collection:
All SAEs were collected for the duration of the study. All SAEs that occurred during the course of the trial, whether considered to be associated with the study IP or not, were expected 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	+1-843-849-6899
Study Monitor:	Berra Yazar-Klosinski; berra@maps.org;	+1-831-429-6362
Ethics Committee:	Ethikkommission Aargau	+41-062 835 29 10

Adverse events collected for the duration of the study were:

- 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 during and for seven days after each experimental session

- Spontaneously reported related expected AEs

7.5.2.4 Process Measures

The SOCQ served as a process measure of alteration of consciousness. It was administered on the day after each experimental session in regards to the experimental session completed on the day prior. The SOCQ was developed from the Peak Experience Profile, a measure designed in the 1960s by Pahnke and colleagues for the description of psychedelic experiences [37]. It was subsequently revised and used in healthy subjects given psilocybin [38, 39]. The SOCQ is a 100-item questionnaire. Subjects respond to the SOCQ using a six-point Likert-type scale anchored at 0=none at all and 5=extreme (more than ever before in my life). It has seven subscale scores; internal unity, external unity, transcendence of time and space, ineffability and paradoxicality (claim of difficulty in describing the experience in words), sense of sacredness, noetic quality, and deeply felt positive mood. The measure was self-report taking 20 to 30 minutes to complete. The study used a revised version of 100 items, translated into German.

7.5.3 Primary Efficacy Variable

The primary efficacy variable for this study was the STAI. Change in State and Trait scores from baseline to 2-month follow-up was used by the sponsor to judge efficacy of treatment within the subject group enrolled in the study. For the purpose of this pilot study, response was considered significant based on hypothesis testing, with the understanding that this was conducted to contextualize effect size estimates from this small pilot study. Hence, larger populations and similar studies will be necessary to draw more definitive conclusions about efficacy.

7.6 Data Quality Assurance

7.6.1 Clinical Procedures

MAPS personnel visited the study site prior to initiation of the study to review information about the investigational product, protocol requirements, randomization procedures, CRFs, monitoring requirements, and reporting of AEs and SAEs with the investigators.

7.6.2 Monitoring

At visits during and after the study, the site was monitored by a study monitor for compliance, including accurate and complete recording of data on CRFs, source documents and drug accountability records. The sponsor monitored the study at a rate that was appropriate for enrollment to ensure the study was conducted according to the principles of GCP.

7.6.3 Data Handling

Data management was conducted according to sponsor SOPs. Data recorded on CRFs were verified by checking the CRF entries against source documents in order to ensure data completeness and accuracy. The PI ensured that CRFs and source documents of subjects enrolled in the study were available for inspection by MAPS representatives at the time of each monitoring visit.

Medical records, score sheets of study measures, and source documents were the primary source of data. The PI completed source documents upon consultation with the subjects and after reviewing medical records and score sheets. Study monitors reviewed the source documents in the presence of the PI to validate the recorded data in terms of correctness, completeness, legibility and accuracy. In case of obvious mistakes, those were discussed with the PI and corrected, initialed and dated by the PI accordingly. Entries to source and CRFs were made by the investigators only. If needed, the PI provided additional information by adding it to the subject's source documents. The validated CRFs were then collected from the study site.

Data entry personnel of the sponsor entered data from CRFs into an Excel database. Sponsor staff then reviewed the data and generated queries to the study site concerning any potential errors, omissions, or unlikely values in the data. After query resolution, the data was reviewed by sponsor staff and the PI. Once it was determined that the data had met quality assurance standards, a series of locked Excel files were generated and sent to the biostatistician. The biostatistician transferred data directly from Excel to SPSS Version 20.0 and additional restructuring was performed when necessary through SPSS. AEs were coded using MedDRA Version 15.

7.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

7.7.1 Statistical and Analytical Plans

The STAI and EORTC QLQC-C30 scale scores were to be analyzed by nonparametric methods for longitudinal data. The nonparametric framework was chosen for two reasons, that of the sample size being too small to assess the assumptions that underlie a parametric model, and because the primary outcome measures was thought to use an ordinal scale at the time the original protocol was written. The first step of the analysis consisted of descriptively summarizing the data by graphing the time course of STAI and EORTC QLQC-C30 scores on average. The second step consisted of comparing the time courses of the control group and the treatment group. An F1_LD_F1 was planned with experimental intervention condition (LSD versus active placebo) serving as a between-group factor and time of measurement serving as a within-subjects factor. The data was planned to be tested for an interaction between experimental intervention condition and time. Statistical significance was set at 0.05 with no adjustment for multiplicity because the STAI was the primary outcome measure. SOCQ scale scores assessed 24 hours after an experimental session were planned to be computed and correlated with STAI and EORTC-QLQ scale scores assessed 5-10 days after each experimental session.

All data processing and statistical evaluation was to be performed by the team of Prof. F. X. Vollenweider, Vice-director, University of Zurich, Clinic of Affective Disorders and General Psychiatry. Data entry was performed in the practice of the PI, and only the fully anonymized data was sent to the institute or to the study monitor.

The sponsor maintained a database containing study data. STAI, HADS, SCL-90, EORTC-QLQ, VAPS, SOCQ scale scores and pain ratings for the study day were compared with baseline and final evaluation scores attained two months after the second experimental or open-label session. The data were also planned to be analyzed by a statistician working with the sponsor.

7.7.2 Determination of Sample Size

The sample size for this study was dictated by its exploratory nature. This small pilot study was conducted to test different variables in study design in preparation for large-scale studies in the future. There was no effect size available for calculation at the time the protocol was written, as this was the first sponsor- supported study of LSD-assisted psychotherapy conducted with modern research design. The investigation was a pilot study designed to obtain estimates of effect size. Since prior investigations did not use randomized, active placebo-controlled methods, they could not be used as the basis for sample size selection. In order to increase the likelihood of receiving the active treatment and to learn more about the effects of LSD in people with life-threatening illnesses, the study design assigned a greater number to receive the experimental dose versus the active placebo dose of LSD.

7.8 Changes in the Conduct of the Study or Planned Analyses

Changes to the conduct of the study were made in four amendments to the protocol and two amendments to the consent form, and based on current practices of the Ethics Committee the changes to the study were numbered cumulatively. Due to the exploratory nature of this pilot study, changes to the protocol were not considered to effect how the data would be analyzed. For a comprehensive list of changes to the protocol, see Appendix 14.1.1. Below is a brief summary of changes:
Protocol Amendment 1, dated January 23, 2008: Addition of the SCL-90R and rescheduling of study measures to the day after drug administration to reduce subject fatigue.

Amendment 2, dated May 15, 2009: Submission of the certified translation of the Informed Consent, 30-Oct-07, Version 2, which was certified by Luz, Inc.

Protocol Amendment 3, dated May 15, 2009: Addition of a long-term follow-up visit, 12 months after the experimental sessions. The visit consisted of a semi-structured interview and the study measures (STAI and EORTC-QLQ-30) to be administered by Katharina Kirchner, M.S.

Amendment 4, dated May 3, 2010: Addition of audio/video recording in subjects who agreed to it, with the corresponding revision of the translated and certified informed consent.

Protocol Amendment 5, dated May 3, 2010: Addition of data analysis to be conducted from the Sponsor's database, and the adjustment of visit windows to avoid deviations.

Protocol Amendment 6, dated February 28, 2011: Change of statistics analysis group.

The sponsor maintained a locked database for this study. The sponsor chose to conduct a parametric analysis in order to ensure that the nonparametric statistical model was not leading to over-interpretation of the data. In order to obtain estimates of effect size in line with the original intent of the study protocol, a parametric analysis was required to calculate means and standard deviations without transforming the data. The initial assumption that the primary outcome measure, the STAI, was an ordinal scale was found to be incorrect. As a result, the non-parametric analysis proposed in the study protocol was no longer appropriate. The sponsor retained the initial plan of estimating effect size using Cohen's techniques as well as conducting a trend analysis using repeated measures analysis of variance (ANOVA).

An examination of the data at all intervals indicated that two subjects had not completed the outcome assessment occurring after the second experimental session due to intervening cancer treatments. In order to avoid substantially reducing the sample size due to missing data, the sponsor statistician performed an analysis using available data including baseline, once after the first experimental session, and two months after the second experimental session. To avoid selection bias inherent with ANOVA, where subjects with missing data are excluded from the entire analysis, the sponsor chose to exclude the outcome assessment one week after the second experimental session for all subjects. In addition, one active placebo subject did not satisfy inclusion criteria for the study after receiving treatment due to a correction in the diagnosis of the qualifying life-threatening illness (cancer). As inclusion/exclusion was continually evaluated throughout the study, exclusion of this subject from analysis was found to be justified per protocol. Although no adjustment for multiplicity was planned, the STAI was known to consist of two scale scores measuring different types of anxiety. Due to reductions in sample size described above, the sponsor chose to adjust for multiplicity to minimize the potential for over-interpretation of the data. A revised data analysis plan was prepared to describe the main efficacy and safety analyses, as well as additional and subsidiary analyses. See Appendix 14.1.9 for the analysis plan. All statistics performed by the sponsor used SPSS Version 20.0 with data from the sponsor's locked database.

8.0 Study Subjects

8.1 Disposition Of Subjects

The investigators screened 70 subjects for participation and enrolled 12 subjects. All subjects completed the main study, and ten subjects completed the long-term follow up. Three of four eligible subjects took part in Stage 2, the open label arm of the study.

Figure 1. CONSORT LSD/Anxiety Flow Diagram

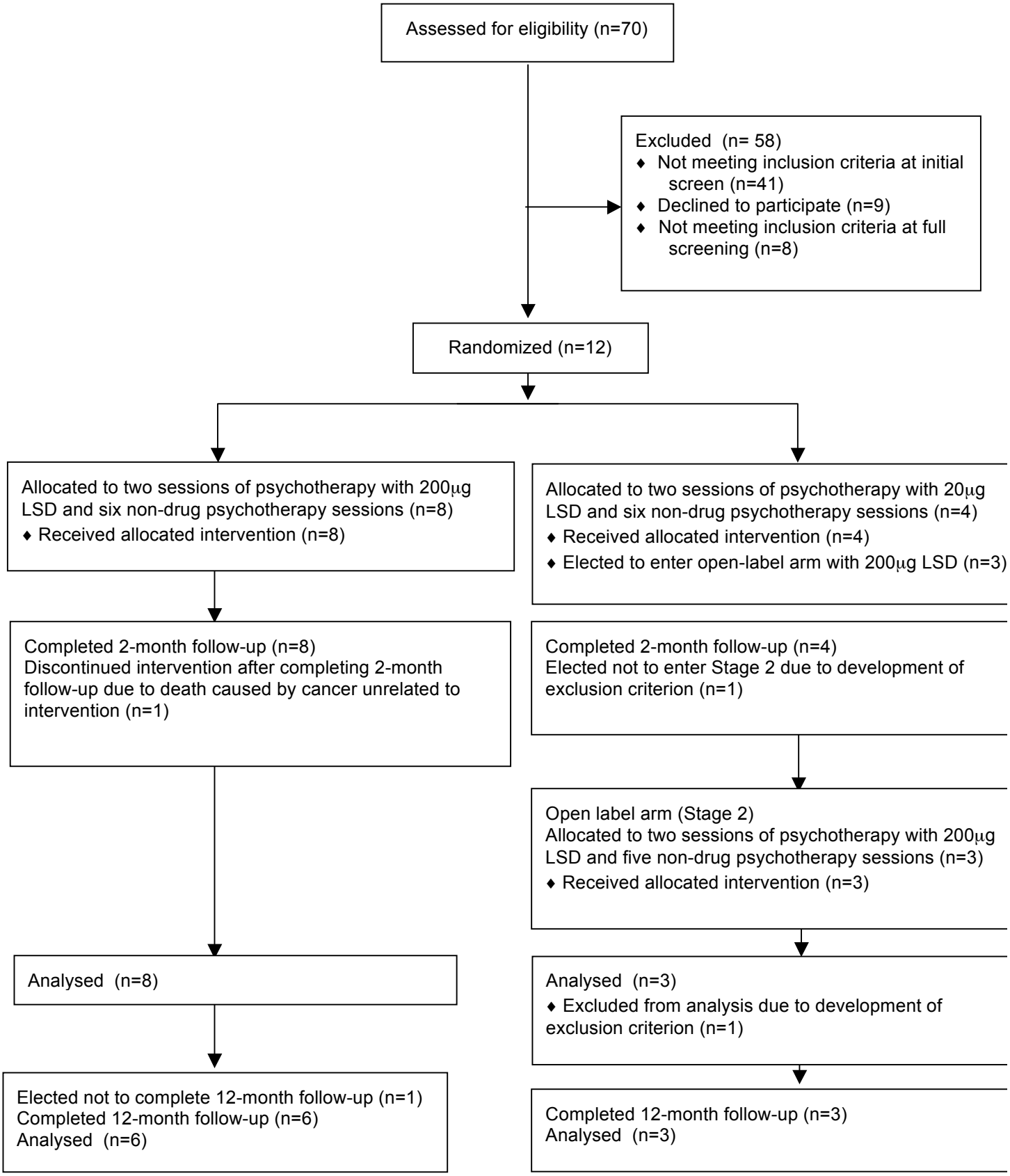
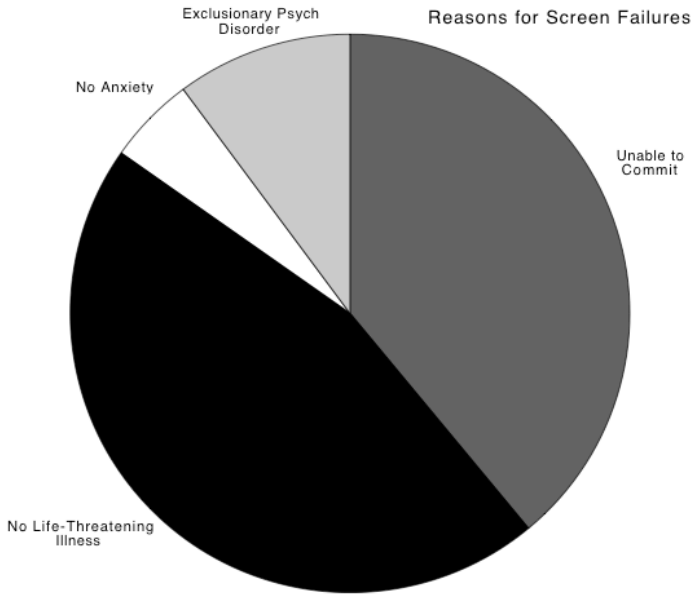


Figure 2. Reasons for Screen Failures



8.2 Protocol Deviations

All protocol deviations are included as a categorized listing in Appendix 14.2.2.1. There were a total of seventy-two deviations nearly split evenly amongst the two groups. Deviations from the protocol are summarized by category in Table 3. There were no systematic deviations. Four subjects were enrolled who did not meet criteria.

Subject 102 (active placebo) was enrolled with metastatic cancer, however during the course of the trial it was discovered the subject was misdiagnosed and experienced a dramatic change in prognosis. Subject 103 (active placebo) was enrolled based on migraine illness that were so severe that the subject had been suicidal in the past. After consultation with the Ethics Committee, the PI and Medical Monitor agreed to enroll the subject with the understanding that the subject was not suicidal at the time of enrollment but had experienced shortened life expectancy.

Subject 105 (active placebo) entered the study with a STAI Trait score of 32, below the cut off of 40 on each STAI scale. Subject 108 (experimental dose) entered the study with a STAI State score of 33, below the cut off of 40 on each STAI scale. Both subjects had scores above 40 on the alternate STAI scale. State and Trait anxiety are different manifestations of anxiety that are inter-related. Upon further examination of normative values of the STAI, it was determined that a score above 40 on either scale indicates acceptable levels of anxiety and future studies should use inclusion criteria revised as such.

The most common deviations were visits performed outside of the window specified in the protocol. There were forty-five visits out of window none of which created a safety risk and no data was excluded from analyses due to the window deviation. Seventeen of these were non-drug therapy sessions, nine were outcome measures, fourteen were experimental sessions, four were screening and enrollment visits and one was an enrollment in Stage 2 that was out of window.

There were ten incidents of informed consent procedures not performed per protocol. Most of the deviations were protocol procedures performed prior to the ICF being signed by the subject. Most of these procedures were psychological and medical screenings performed before a signature was

obtained since medical screenings had to be completed by the subject's primary care provider. All subjects did sign the informed consent prior to any experimental session and some deviations were related to new versions of informed consents not being signed by all subjects. Multiple versions of the informed consent were created during the study to ensure use of certified translations.

There were seven protocol procedures not performed per protocol. Two subjects did not complete outcome measures and one subject missed two non-drug psychotherapy visits and completed outcome assessments by mail due to adverse events. Three subjects did not complete the VAPS.

Table 3. Number of Subjects with Protocol Deviations

	Total (N=12)	Experimental Dose (N=8)	Active Placebo (N=4)
Number of Protocol Deviations	72	39	33
Entered study but did not meet entry criteria	4	1	3
Developed withdrawal criteria during study but not withdrawn	0	0	0
Protocol procedure not performed per protocol	7	4	3
Protocol Procedure Performed out of Range	51	30	21
Informed consent performed not per protocol	10	4	6

Source: Appendix 14.2.2.1

9.0 Efficacy Evaluation

9.1 Data Sets Analyzed

All subjects who completed Stage 1 were included in main efficacy analyses with the exception of subject 102. Completion of Stage 1 was defined as completion of two blinded experimental sessions with associated integrative sessions. Criteria for inclusion in analyses were developed prior to the start of the study.

9.2 Demographic and Other Baseline Characteristics

Table 4. Listing of Demographic Characteristics

Subject ID	Condition Assignment	Date Enrolled	Date of Birth	Age	Religion	Observant?
101	200 µg LSD	23-APR-08	14-DEC-64	43	N/A	No
102	20 µg LSD	22-AUG-08	25-MAY-65	43	N/A	No
103	20 µg LSD	07-AUG-08	15-JUL-62	46	Protestant	No
104	200 µg LSD	12-DEC-08	26-MAY-52	57	Protestant	No
105	20 µg LSD	29-MAY-09	05-FEB-47	62	N/A	No
106	200 µg LSD	19-OCT-09	02-MAY-63	46	N/A	No
107	200 µg LSD	16-FEB-11	20-APR-49	62	N/A	No
108	200 µg LSD	30-JUL-10	13-JUN-71	39	N/A	No
109	20 µg LSD	06-APR-10	20-APR-46	64	Roman Catholic	No
110	200 µg LSD	29-OCT-10	13-APR-51	60	Buddhist	Yes
111	200 µg LSD	25-AUG-10	10-JUL-67	43	N/A	No
112	200 µg LSD	05-JAN-11	28-APR-64	47	N/A	No

Table 5. Subject Demographic Summary

Characteristic	Categories	200 µg *n*=8	20 µg *n*=3	Total *n*=11
Gender	Female	3 (37.5%)	1 (33.3%)	4 (36.4%)
	Male	5 (62.5%)	2 (66.7%)	7 (63.6%)
Mean Age (SD)	Range 39-64 years	49.6 (8.5)	57.4 (9.9)	51.7 (9.1)
Marital Status	Single	1 (12.5%)	1 (33.3%)	2 (18.2%)
	Married/Living with Partner	4 (50%)	2 (66.7%)	6 (54.5%)
	Divorced/Separated	3 (37.5%)	0 (0%)	3 (27.3%)
Work Status	On Disability	1 (12.5%)	0(0%)	1(9.1%)
	Fit for Limited Employment	2 (25%)	2 (66.7%)	4 (36.4%)
	Working full time	4 (50%)	0 (0%)	4 (36.4%)
	Retired	1 (12.5%)	1 (33.3%)	2 (18.2%)
Spiritual Orientation	Protestant	1 (12.5%)	1 (33.3%)	2 (18.2%)
	Roman Catholic	0 (0%)	1 (33.3%)	1 (9.1%)
	Buddhist	1 (12.5%)	0 (0%)	1 (9.1%)
	Not Religious	6 (75%)	1 (33.3%)	7 (63.6%)
History of Substance Abuse/Dependency	Alcohol	0 (0%)	0 (0%)	0 (0%)
	Illegal Drugs	0 (0%)	0 (0%)	0 (0%)
History of Suicidal Tendencies	None	8 (100%)	1 (33.3%)	9 (81.8%)
	Mild	0 (0%)	2 (66.7%)	2 (18.2%)
Life-threatening Disease	Metastatic Breast Carcinoma	3 (37.5%)	1 (33.3%)	4 (36.4%)
	Metastatic Gastric Carcinoma	2 (25%)	0 (0%)	2 (18.2%)
	Plasmocytoma	1 (12.5%)	0 (0%)	1 (9.1%)
	Non Hodgkin Lymphoma	0 (0%)	1 (33.3%)	1 (9.1%)
	Celiac Disease	0 (0%)	1 (33.3%)	1 (9.1%)
	Parkinson's Disease	1 (12.5%)	0 (0%)	1 (9.1%)
	Bechterew's Disease	1 (12.5%)	0 (0%)	1 (9.1%)
Co-morbid Disorder	Generalized Anxiety Disorder	5 (62.5%)	1 (33.3%)	6 (54.5%)
	Major Depression	6 (75%)	1 (33.3%)	7 (63.6%)
	Reactive Depression	0 (0%)	1 (33.3%)	1 (9.1%)
	Dysthymia	1 (12.5%)	1 (33.3%)	2 (18.2%)
	PTSD	1 (12.5%)	0 (0%)	1 (8.3%)
	Panic Disorder	2 (25%)	1 (33.3%)	3 (27.3%)
	Social Phobia	1 (12.5%)	0 (0%)	1 (8.3%)
Pre-study Medications	Antidepressant	3 (37.5%)	1 (33.3%)	4 (36.4%)
	Anti-anxiety	1 (12.5%)	2 (66.7%)	3 (27.3%)
	Pain Relief	3 (37.5%)	2 (66.7%)	5 (45.4%)
	None	3 (37.5%)	1 (33.3%)	4 (36.4%)

Source: Appendix 14.2.4.1, 14.2.4.2, 14.2.4.3, 14.2.4.4, 14.2.4.5, 14.2.4.6, 14.2.4.7, 14.2.4.8

Subject 102 was a non-religious 43-year old Caucasian [European] male with a SCID diagnosis of major depression and panic disorder as well as reactive anxiety due to renal cancer diagnosis. The subject was not suicidal and had no previous diagnosis of substance use. The subject was not religious.

The sample enrolled consisted of seven men and five women, average age 51 (range 39-64 years), the majority (8 of 12) with a diagnosis of cancer, but also including diagnoses of Parkinson's disease and Bechterew's disease (ankylosing spondylitis). Eight of 12 subjects did not list an affiliation with an organized religion, and the four listing a religious affiliation included two Protestants, a Roman Catholic and a Buddhist. None of the subjects had a history of substance abuse. Ten of twelve did not appear to be suicidal at the time of enrollment, and two appeared to be mildly suicidal. None of the subjects withdrew from the study during the treatment period.

9.3 Measurements of Treatment Compliance

The study drug was always administered under the supervision of the PI and the co-therapist during the experimental sessions. The PI was responsible for recording dosing on the source records and CRF and completing accountability logs.

9.4 Efficacy Results and Tabulations of Individual Subject Results

9.4.1 Analysis of Treatment Efficacy

All subjects experienced anxiety at study baseline, and more than half of the subjects had a diagnosis of Generalized Anxiety Disorder. Effect sizes comparing baseline to 2-month follow-up were estimated with and without Subject 102, who no longer satisfied inclusion criteria during the course of the study. The effect sizes of the investigational treatment were 1.1 (mean difference: -13.67, pooled SD: 12.5) on STAI Trait and 1.2 (mean difference: -15.62, pooled SD: 13.0) on STAI State anxiety (N=11). When Subject 102 was included, the effect size estimates dropped to 0.77 (mean difference: -9.25, pooled SD: 12.0) on STAI Trait and 0.38 (mean difference: -5.38, pooled SD: 14.0) on STAI State anxiety (N=12). At 12-month follow-up both the State and Trait values remained stable, with a mean difference of 1.0 or less, comparing the pooled average of Stage 1 and Stage 2 2-month follow-ups to the 12-month follow-up.

In the trend analysis, STAI Trait scores were compared prior to experimental sessions, after the first experimental session and at two-month follow up. The interaction between condition (full versus active placebo dose) and time of administration on the 11 subjects with continued illness was found to have a p value of 0.033 ($F(1, 9) = 4.15$), with subjects given an experimental dose of LSD exhibiting lower scores after experimental sessions than subjects that received an active placebo dose of LSD. Despite this finding, only two out of eight subjects in the experimental dose condition experienced a drop in anxiety below the diagnostic cut-off of 40 for study eligibility.

Trend analyses of the 11 subjects with sustained illness examined STAI State scores prior to the first experimental session, one week after the first experimental session, and at 2 month follow up yielded a significant interaction after adjustment of alpha cutoff for multiplicity between condition and time of administration. The analysis detected a significant interaction ($p < 0.025$) between Condition (experimental dose versus active placebo dose condition) and time of administration, with $p = 0.021$. Receiving the 200 μg dose of LSD led to a greater drop in STAI State scores than receiving 20 μg LSD, and less anxiety was experienced two months after two sessions of psychotherapy with the experimental dose of LSD.

Table 6. Condition Assignment vs. STAI State Scores; Higher scores indicate greater anxiety

Condition Assignment		Baseline STAI State Score	Post Stage 1 Session 1 STAI State Score	Post Stage 1 Session 2 STAI State Score	Stage 1 2-month Follow-up STAI State Score	Post Stage 2 Session 1 STAI State Score	Post Stage 2 Session 2 STAI State Score	Stage 2 2-month Follow-up STAI State Score	Long-term Follow-up STAI State Score
20 µg LSD	N	4	3	3	4				
	Mean	54.25	43.33	53.67	48.00				
	(SD)	(17.02)	(15.04)	(9.87)	(9.35)				
	Min-Max	36-74	29	47	37				
200 µg LSD	N	8	8	7	8	3	3	3	9
	Mean	53.125	46.50	48.57	41.5	48.33	41.00	36.00	36.11
	(SD)	(13.51)	(12.32)	(12.15)	(9.71)	(69.00)	(13.11)	(12.49)	(8.28)
	Min-Max	27-71	27-63	27-63	26-56	39-60	29-55	26-50	23-50
Total	N	12	11	10	12				
	Mean	53.5	45.64	50.1	43.67				
	(SD)	(13.98)	(12.40)	(11.23)	(9.70)				
	Min-Max	27-74	27-63	27-65	26-58				

Figure 3. Mean STAI State and Trait Anxiety by Condition and Study Visits

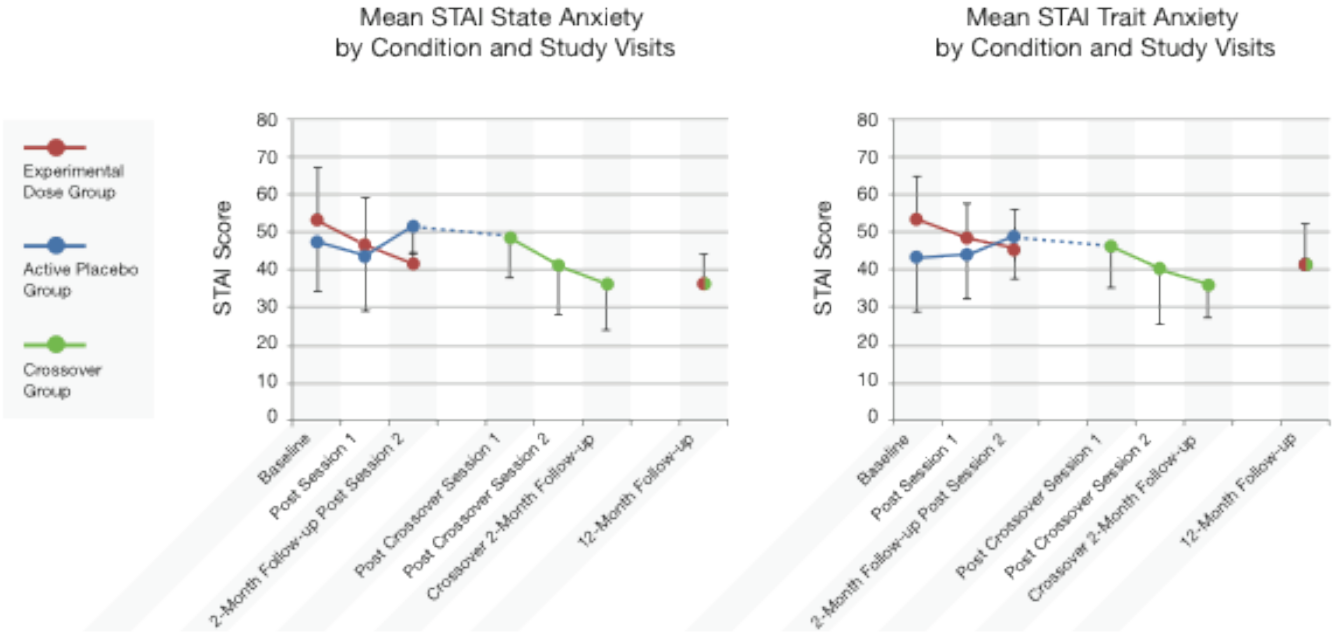


Table 7. Condition Assignment vs. STAI Trait Scores

Condition Assignment		Baseline STAI Trait Score	Post Stage 1 Session 1 STAI Trait Score	Post Stage 1 Session 2 STAI Trait Score	Stage 1 2-month Follow-up STAI Trait Score	Post Stage 2 Session 1 STAI Trait Score	Post Stage 2 Session 2 STAI Trait Score	Stage 2 2-month Follow-up STAI Trait Score	Long-term Follow-up STAI Trait Score
20 µg LSD	N	4	3	3	4				
	Mean	44.00	44.00	47.00	45.25				
	(SD)	(29)	(12)	(9.85)	(11.93)				
	Min-Max	29-59	32-56	39-58	34-62				
200 µg LSD	N	8	8	7	8	3	3	3	9
	Mean	53.25	48.38	48.29	45.25	46.00	40.67	36.00	41.11
	(SD)	(11.26)	(8.85)	(9.78)	(10.31)	(10.82)	(19.48)	(8.54)	(10.81)
	Min-Max	31-70	33-60	34-61	32-59	37-58	24-53	27-44	23-53
Total	N	12	11	10	12				
	Mean	50.17	47.18	47.9	45.25				
	(SD)	(11.96)	(9.37)	(9.26)	(10.31)				
	Min-Max	29-70	32-60	34-61	32-62				

Table 8. Condition Assignment vs. HADS Anxiety (A) Score

Condition Assignment		Baseline HADS A Score	Post Stage 1 Session 1 HADS A Score	Post Stage 1 Session 2 HADS A Score	Stage 1 2-month Follow-up HADS A Score	Post Stage 2 Session 1 HADS A Score	Post Stage 2 Session 2 HADS A Score	Stage 2 2-month Follow-up HADS A Score	Long-term Follow-up HADS A Score
20 µg LSD	N	4	3	3	4				
	Mean	12.25	8.67	9.33	9.75				
	(SD)	(2.50)	(1.15)	(2.52)	(3.10)				
	Min-Max	9-15	8-10	7-12	7-14				
200 µg LSD	N	8	8	7	8	3	3	3	9
	Mean	11.75	8.63	8.86	8.13	9.67	9.00	7 .00	7.63
	(SD)	(3.45)	(3.34)	(2.41)	(3.23)	(0.57)	(5.57)	(2.65)	(4.53)
	Min-Max	6-16	3-13	6-10	4-12	9-10	3-14	4-9	2-14
Total	N	12	11	10	12				
	Mean	11.92	8.64	9.00	8.67				
	(SD)	(3.06)	(2.84)	(2.31)	(3.14)				
	Min-Max	6-16	3-13	6-12	4-14				

Due to the small sample size, hypothesis testing was not conducted on secondary outcome measures for this pilot study. Descriptive statistics are presented for all available HADS anxiety scores above, with higher scores indicative of greater levels of anxiety. Informal comparison of baseline to 2-month follow-up data suggests dose dependent reduction in anxiety in both groups, with a greater reduction in the 200 µg LSD group. This result is supported by further reductions experienced by the partial crossover group when they received the 200 µg LSD treatment in Stage 2 after receiving the 20 µg LSD treatment in Stage 1.

Table 9. Condition Assignment vs. HADS Depression (D) Score

Condition Assignment		Baseline HADS D Score	Post Stage 1 Session 1 HADS D Score	Post Stage 1 Session 2 HADS D Score	Stage 1 2-month Follow-up HADS D Score	Post Stage 2 Session 1 HADS D Score	Post Stage 2 Session 2 HADS D Score	Stage 2 2-month Follow-up HADS D Score	Long-term Follow-up HADS D Score
20 µg LSD	N	4	3	3	4				
	Mean	9.00	7.00	9.00	7.5				
	(SD)	(3.46)	(3.00)	(5.29)	(3.32)				
	Min-Max	6-14	4-10	5-15	4-12				
200 µg LSD	N	8	8	7	8	3	3	3	9
	Mean	10	8.50	8.00	7.50	8.33	7.00	4.67	7.56
	(SD)	(4.47)	(3.34)	(4.93)	(3.34)	(3.21)	(2.40)	(4.04)	(4.67)
	Min-Max	1-16	3-14	0-13	3-13	6-12	0-12	0-7	0-13
Total	N	12	11	10	12				
	Mean	9.67	8.09	8.3	7.50				
	(SD)	(4.03)	(3.18)	(4.76)	(3.18)				
	Min-Max	1-16	3-14	0-15	3-13				

Due to the small sample size, hypothesis testing was not conducted on secondary outcome measures for this pilot study. Descriptive statistics are presented for all available HADS depression scores above, with higher scores indicative of greater levels of depression. Informal comparison of baseline to 2-month follow-up data suggests dose dependent reduction in depression in both groups, with a greater reduction in the 200 µg LSD group. However, data from the partial crossover group was not further reduced beyond the effect of the treatment with 20 µg LSD, suggesting that depression may not be the main target of the investigational treatment, and that trends observed in these scores may be unrelated to the treatment.

Table 10. Condition Assignment vs. EORTC Global Health Scores

Condition Assignment		Baseline Global Health EORTC Score	Post Stage 1 Session 1 Global Health EORTC Score	Post Stage 1 Session 2 Global Health EORTC Score	Stage 1 2-month Follow-up Global Health EORTC Score	Post Stage 2 Session 1 Global Health EORTC Score	Post Stage 2 Session 2 Global Health EORTC Score	Stage 2 2-month Follow-up Global Health EORTC Score	Long-term Follow-up Global Health EORTC Score
20 µg LSD	N	4	3	3	4				
	Mean	41.50	50.00	36.00	45.75				
	(SD)	(11.79)	(17.00)	(24.25)	(22.11)				
	Min-Max	33-58	33-67	8-50	25-75				
200 µg LSD	N	8	8	7	8	3	3	3	9
	Mean	37.42	35.38	48.67	50.00	55.33	58.33	52.67	54.44
	(SD)	(9.96)	(13.80)	(19.03)	(14.91)	(4.62)	(16.50)	(21.13)	(18.17)
	Min-Max	25-58	17-58	33-75	33-75	50-58	42-75	33-75	25-83
Total	N	12	11	10	12				
	Mean	38.78	39.36	44.87	48.58				
	(SD)	(10.25)	(15.42)	(20.24)	(16.71)				

Due to the small sample size, hypothesis testing was not conducted on secondary outcome measures for this pilot study. Descriptive statistics are presented for all available EORTC Global Health Scores above, with higher scores indicative of greater quality of life. Informal comparison of baseline to 2-month follow-up data suggests dose dependent increases in functioning in both groups, with a greater increase in the 200 µg LSD group. However, data from the partial crossover group decreased in Stage 2, suggesting that either the measure itself was not well suited to the study population, or that improvements in overall quality of life may not be the main target of the investigational treatment, and that trends observed in these scores may be unrelated to the treatment.

Table 11. Condition Assignment vs. SCL90R GSI Scores

Condition Assignment		Baseline SCL90R GSI Score	Post Stage 1 Session 1 SCL90R GSI Score	Post Stage 1 Session 2 SCL90R GSI Score	Stage 1 2-month Follow-up SCL90R GSI Score	Post Stage 2 Session 1 SCL90R GSI Score	Post Stage 2 Session 2 SCL90R GSI Score	Stage 2 2-month Follow-up SCL90R GSI Score
20 µg LSD	N	4	3	3	4			
	Mean	63.50	61.00	64.00	64.50			
	(SD)	(13.30)	(10.54)	(14.00)	(10.47)			
200 µg LSD	N	8	8	7	8	2	3	3
	Mean	69.63	64.13	64.29	60.25	65.50	59.67	57.33
	(SD)	(6.70)	(5.91)	(7.43)	(7.19)	(9.19)	(12.10)	(15.01)
Total	N	12	11	10	12			
	Mean	67.58	63.27	64.20	61.67			
	(SD)	(9.27)	(6.99)	(8.97)	(8.19)			

Due to the small sample size, hypothesis testing was not conducted on secondary outcome measures for this pilot study. Descriptive statistics are presented for all available SCL-90-R Global Severity scores above, with higher scores indicative of greater psychological distress. Informal comparison of baseline to 2-month follow-up data supports dose dependent reduction in psychological distress in the 200 µg LSD group, in contrast to a slight increase in the 20 µg LSD group. This result is supported by further reductions in psychological distress experienced by the partial crossover group when they received the 200 µg LSD treatment in Stage 2 after receiving the 20 µg LSD treatment in Stage 1.

Table 12. Condition Assignment vs. SCL90R PSDI Scores

Condition Assignment		Baseline SCL90R PSDI Score	Post Stage 1 Session 1 SCL90R PSDI Score	Post Stage 1 Session 2 SCL90R PSDI Score	Stage 1 2-month Follow-up SCL90R PSDI Score	Post Stage 2 Session 1 SCL90R PSDI Score	Post Stage 2 Session 2 SCL90R PSDI Score	Stage 2 2-month Follow-up SCL90R PSDI Score
20 µg LSD	N	4	3	3	4			
	Mean	56.25	57.00	54.67	59.00			
	(SD)	(52.32)	(6.56)	(8.08)	(49.00)			
200 µg LSD	N	8	8	7	8	2	3	3
	Mean	62.13	57.38	56.14	53.38	55.50	58.67	54.67
	(SD)	(5.46)	(7.60)	(48.00)	(39.00)	(4.95)	(10.97)	(14.69)
Total	N	12	11	10	12			
	Mean	60.17	57.27	55.70	55.25			
	(SD)	(5.92)	(6.93)	(5.17)	(8.13)			

Due to the small sample size, hypothesis testing was not conducted on secondary outcome measures for this pilot study. Descriptive statistics are presented for all available SCL-90-R symptom intensity scores above, with higher scores indicative of greater intensity of symptoms. Informal comparison of baseline to 2-month follow-up data supports dose dependent reduction in intensity of symptoms in the 200 µg LSD group, in contrast to an increase in the 20 µg LSD group. However, this result is followed by only a slight decrease in symptom intensity experienced by the partial crossover group when they received the 200 µg LSD treatment in Stage 2 after receiving the 20 µg LSD treatment in Stage 1. These data suggest that general psychological symptoms may not be the direct target of the investigational treatment, or that the measure was not well suited to measure treatment effects.

Table 13. Condition Assignment vs. SCL90R PST Scores

Condition Assignment		Baseline SCL90R PST Score	Preparatory Session 2 SCL90R PST Score	Post Stage 1 Session 1 SCL90R PST Score	Post Stage 1 Session 2 SCL90R PST Score	Stage 1 2-month Follow-up SCL90R PST Score	Post Stage 2 Session 1 SCL90R PST Score	Post Stage 2 Session 2 SCL90R PST Score	Stage 2 2-month Follow-up SCL90R PST Score
20 µg LSD	N	4	4	3	3	4			
	Mean	63.75	62.25	61.67	63.67	64.00			
	(SD)	(10.90)	(11.53)	(13.50)	(10.26)	(11.40)			
200 µg LSD	N	8	8	8	7	8	2	3	3
	Mean	68.13	67.88	63.63	64.43	61.25	68.00	58.00	56.67
	(SD)	(8.79)	(6.75)	(8.18)	(8.12)	(8.00)	(9.90)	(12.53)	(14.84)
Total	N	12	12	11	10	12			
	Mean	66.67	66.00	63.09	64.20	62.17			
	(SD)	(9.29)	(8.54)	(9.17)	(8.22)	(8.83)			

Due to the small sample size, hypothesis testing was not conducted on secondary outcome measures for this pilot study. Descriptive statistics are presented for all available SCL-90-R symptom frequency scores above, with higher scores indicative of greater number of self-reported symptoms. Informal comparison of baseline to 2-month follow-up data supports dose dependent reduction in number of symptoms reported in the 200 µg LSD group, in contrast to a slight increase in the 20 µg LSD group. This result is followed by a substantial decrease in number of symptoms reported by the partial crossover group when they received the 200 µg LSD treatment in Stage 2 after receiving the 20 µg LSD treatment in Stage 1. These data suggest that the number of psychological symptoms may be influenced by the investigational treatment, and may be related to the effects on the SCL-90-R Global Severity score.

Table 14. Condition Assignment vs. Mean Total SOCQ Score

Condition Assignment		Average Stage 1 Total SOCQ Score	Average Stage 2 Total SOCQ Score
20 µg LSD	N Mean (SD)	4 0.137 (0.039)	
200 µg LSD	N Mean (SD)	8 0.506 (0.196)	3 0.391 (0.082)
Total	N Mean (SD)	12 0.383 (0.239)	

Due to the small sample size, hypothesis testing was not conducted on process measures for this pilot study. Descriptive statistics are presented for all available SOCQ mean total scores above, with higher scores indicative of more mystical or spiritual elements experienced during the altered state produced by the investigational treatment. Informal comparison of data from the two dose groups supports dose dependent mystical effects, with greater effects reported in the 200 µg LSD group, compared to the 20 µg LSD group. These data are consistent with scientific literature and support that the experimental dose of 200 µg LSD was a moderate dose and not a high dose. As this study was primarily a safety study, the dose selected for the treatment was appropriate, as it was intended to produce a controlled altered state of consciousness.

9.4.2 Statistical/Analytical Issues

The general statistical approach planned for this trial has been described in Section 7.7. This section is to address statistical issues specifically as they relate to data from this clinical study. These issues will be discussed briefly here and the reader is referred to the statistical Appendix 14.1.9 for further details. Any departures from preplanned analyses were noted in Section 7.8. Since the study is a small pilot study, variation in the sample by chance is to be expected.

A subject who enrolled in the study with a diagnosis of metastatic renal cancer experienced a significantly improved prognosis during the study when the subject learned that the qualifying diagnosis of metastatic cancer was incorrect. This subject completed all psychotherapy and assessments. Effect size estimates with and without data from this subject have been conducted to deal with potential variation arising from the effects of improved prognosis upon this subject.

There were no study drop-outs from the main study, and one subject drop-out from the long-term follow up extension.

One full dose subject and one active placebo subject did not complete outcome measures after their second experimental session. Owing to the absence of data for the assessment approximately a week after the second experimental session, analyses of outcome measures have omitted this time point. Not assessing outcome measures after the second experimental session allows for assessing nearly the entire sample during repeated measures analyses.

All subjects indicated that they were Caucasian Europeans, and so no effects of race/ethnicity were expected in a sample of this size. There was no variation between mean age of subjects in the active placebo and the experimental dose condition, as indicated by a one-way ANOVA ($F(1, 10) = 0.513$, $p > 0.05$. Chi-square tests performed on gender and religion in both conditions also failed to detect significant differences. (Gender, Pearson's chi-square (df 1, 12) = 0.188, p. = 0.665; religion chi-square (3, 12) = 3.0, p. = 0.39.) No analyses accounted for variations in subject demographics.

When appropriate, statistical significance was assessed with Bonferroni correction for the use of multiple tests for the STAI State and Trait scales.

The Sponsor and investigators agreed to work with a sponsor statistician and a site statistician during the study, but the final statistical approach for the purposes of publication and this report were based on the sponsor statistician.

9.4.3 Tabulation of Individual Response Data

Individual responses to the primary and secondary outcome measures are provided in Appendix 14.6.2. These include individual STAI, EORTC, SCL-90R, HADS-A and HADS-D scores.

9.4.4 Drug Dose, Drug Concentration, and Relationships to Response

See cumulative exposure Table 15 in Section 10.1. Measures of LSD or metabolites in plasma were not collected. All subjects either received a single dose of either 20 or 200 µg during each of two blinded experimental sessions, and subjects enrolled in Stage 2 received two doses of 200 µg LSD in two open label experimental sessions. Doses were not adjusted by weight and no supplemental doses were available. The results of the study enabled a comparison of two doses,

and results support a dose dependent relationship to response on the primary outcome measure and some secondary outcome measures.

9.4.5 Drug-Drug and Drug-Disease Interactions

No drug-drug interactions were reported for this study. The study drug has a half-life of 175 minutes and was administered on two to four occasions during the study. Subjects were required to taper off of medications that might interact with the same targets as LSD, such as other serotonergic drugs, for at least five half-lives prior to each experimental session.

In this small subject sample, based on the safety profile of the drug discussed in Section 10.0, drug-disease interactions were not observed.

9.4.6 Efficacy Conclusions

Overall, while encouraging, the results of this small exploratory pilot study have demonstrated clinically significant improvements in anxiety but are not sufficient to demonstrate statistically significant treatment efficacy. Taking a conservative approach in hypothesis testing with Bonferroni corrections, the sponsor observed trends in reductions of Trait anxiety (also known as anxiety proneness) suggesting two experimental psychotherapy sessions assisted by 200 µg LSD may lead to some subjects feeling less prone to anxiety than subjects given 20 µg LSD. In the absence of Bonferroni correction this result would have been significant in this small sample. The sponsor also found a significant reduction in State anxiety, suggesting that the same treatment can cause some subjects to experience less anxiety symptoms. This result survived the Bonferroni correction, which is promising and supports the need for future studies of LSD-assisted psychotherapy in larger samples. Reduction in State and Trait anxiety persisted in subjects who had received 200µg LSD during blinded or open label sessions assessed at 12 month follow-up. Effect size estimates suggest a large effect was observed in this sample.

Mean global EORTC scores appeared to rise in both groups, from 36.25 to 50 in subjects in the 200 µg condition and from 41.75 to 45.75 two months after two sessions of LSD-assisted psychotherapy. HADS-A scores declined from 13 to 9.75 in subjects in the active placebo condition and from 11.75 to 8.13 in the experimental dose condition.

10.0 Safety Evaluations

10.1 Extent of Exposure

Table 15. Cumulative Exposure to Study Drug by Subject

Subject ID	Condition Assignment	Sex	Age	Cumulative Exposure to Study Drug
101	200 µg LSD	Male	43	400 µg LSD
102	20 µg LSD	Male	43	40 µg LSD
103	20 µg LSD	Male	46	440 µg LSD
104	200 µg LSD	Male	57	400 µg LSD
105	20 µg LSD	Female	62	440 µg LSD
106	200 µg LSD	Male	46	400 µg LSD
107	200 µg LSD	Female	62	400 µg LSD
108	200 µg LSD	Female	39	400 µg LSD
109	20 µg LSD	Male	64	440 µg LSD
110	200 µg LSD	Male	60	400 µg LSD
111	200 µg LSD	Female	43	400 µg LSD
112	200 µg LSD	Male	47	400 µg LSD

10.2 Adverse Events

10.2.1 Brief Summary of Adverse Events

The investigators collected unexpected and expected adverse events during the study. None of the unexpected adverse events were related to the study drug. Seven of 13 arose directly or indirectly from the potentially life-threatening diagnosis that produced the subject's anxiety. The greater number of unexpected AEs in subjects receiving 200 µg LSD is likely the result of their greater numbers, with eight subjects receiving the experimental dose during Stage 1 and three of four active placebo subjects enrolling in Stage 2. There were two SAEs, both unrelated to the study drug; tumor metastasis and infection of the renal basin. A variety of related adverse events were collected on the day of each experimental session and on the day after each session. No related adverse events persisted beyond the day after the experimental session. Sixteen of 102 related adverse events occurring on the day of the experimental session were rated as severe, with all save one severe rating occurring after 200 µg LSD. The rest of these reactions, and the six reactions reported on the following day, were rated as moderate or mild. The most frequently reported reaction was experiencing one or more types of illusion, including sensory distortions and visual images, with likelihood of experiencing this effect much greater in people given the experimental dose of LSD. Feeling abnormal, feeling cold, and emotional distress were also frequently reported reactions. Subjects tolerated the administration of LSD, and there were no psychological or medical emergencies stemming from LSD administration.

10.2.1.1 Related Adverse Events

Related AEs were collected for a total of seven days after each experimental session. AEs that continued beyond this window were recorded as unexpected AEs for the full duration. All subjects enrolled and treated experienced at least one reaction on the day of the experimental

session. Only three of eight subjects receiving 200 µg LSD experienced related AEs (emotional distress, feeling abnormal, feeling cold, illusion) on the day after the experimental session, and none persisted beyond that day. None of the subjects receiving 20 µg LSD experienced related AEs on the day after the experimental session.

10.2.1.2 Unexpected Adverse Events

Thirteen unexpected unrelated AEs occurred during the course of study, two of which were serious. Adverse events were reported in seven of 12 subjects: four subjects in the experimental dose condition and two subjects in the active placebo condition. However, only a single unexpected AE, a skin lesion, occurred after 20 µg LSD, while the other AEs in people in the active placebo condition occurred during enrollment in Stage 2 and after 200 µg LSD. Three of the AEs occurred prior to drug administration, and ten occurred after drug administration. Five subjects (three in the experimental dose condition and two in the active placebo condition) did not report any adverse events. Both of the SAEs were unrelated to drug administration.

Table 16. Unexpected Adverse Events

Dose Administered	AE Before Dose	20 µg LSD	200 µg LSD	Total (N)
Any AEs	3	1	9	13
Subjects	3	1	6	7
At Least Possibly Related AEs	0	0	0	0
Serious AEs	1	0	1*	2
At Least Possibly Related SAEs	0	0	0	0

*Occurred during Stage 2 in individual initially assigned to 20 µg LSD.

10.2.2 Display of Adverse Events

An overview of subjects experiencing unexpected adverse events is presented in Table 16. Summaries of related adverse events on the day of and one day after drug administration are presented in Appendices 14.2.7.6 and 14.2.7.7.

A detailed summary of severe adverse events is presented in Appendix 14.7.2.3. Nine of the thirteen treatment-emergent AEs (69%) occurred after the subjects received experimental dose LSD either in Stage 1 or Stage 2. Detailed listings for unexpected severe adverse events are presented in Appendix 14.2.7.3. One severe event occurred prior to drug administration, one occurred after 20 µg LSD administration, and three occurred after 200 µg LSD administration. There was one death, unrelated to drug administration, from metastasis of esophageal cancer, which was the outcome of one of the SAEs in Appendix 14.2.7.4. Another subject died prior to taking part in the long-term follow-up, but after completing two experimental sessions and the 2-month follow-up.

10.2.3 Analysis of Adverse Events

10.2.3.1 Related adverse events

Table 17. Related adverse events
Items in italics fall under the MedDRA Preferred Term listed above and are given verbatim

Dose Condition	**20 μ g LSD**	**200 μ g LSD**	**Total**
Number of Subjects	4	11	15
Number of Experimental Sessions	8	22	30
Eye Disorders			
Mydriasis (dilated pupils)	0	4	4
Psychiatric			
Anxiety	3	5	8
Anger	2	1	3
Affect Lability (emotional lability)	0	3	3
Bradyphrenia (**slow** thoughts)			
Depersonalization*			
Derealization (reality withdrawal, derealization)	0	2	2
Emotional Intensity	2	8	10
Illusion	1	29	30
Body Image Altered	0	1	1
*Time Perception Altered**	0	9	9
Illusions	0	4	4
Melting/Merging	0	3	3
Objects Moving	0	1	1
Objects, Shapes, Colors Different	1	5	6
People Look Different	0	2	2
Music Perception Altered^*	0	1	1
Visual Illusions (visual perception altered)	0	3	3
Hallucination	0	1	1
Perseveration	0	1	1
Tachyphrenia (fast thoughts)	1	0	1
Thinking Abnormal	2	2	4
*Unusual Ideas**	1	0	1
Impaired Cognition	0	1	1
*Fascination with Specific Idea**	1	1	2
Nervous System			
Disturbance in Attention (attention altered)	1	0	1
General			
Asthenia^	0	1	1
Feeling Abnormal	2	10	12
Aware of Altered Cognition	2	5	7
Light/Floating Feeling	0	4	4
Somatization	0	1	1
Feeling Cold	0	10	10
Feeling of Relaxation^	0	1	1
Impaired Gait (unsteadiness, impaired gait)	0	5	5
Skin and Subcutaneous Tissue Disorders			
Perspiration (perspiration, sweating)	0	3	3
Total	**14**	**88**	**102**

***** = Uncodable in MedDRA V15 ; ^ = Only asked during Stage 2 sessions

Table 18. Frequency and Mean Severity of Related Adverse Events by Preferred Term

	Day of Session	**Day of Session**	**Day after Session**	**Day after Session**
	200 µg LSD	20 µg LSD	200 µg LSD	20 µg LSD
	Sessions: 22	Sessions: 8	Sessions: 22	Sessions: 8
Related Adverse Events	***n* (%) (Mean Severity)**	***n* (%) (Mean Severity)**	***n* (%) (Mean Severity)**	***n* (%) (Mean Severity)**
Affect Lability	3 (3.4%) (1.3)	0	0	0
Anger	1 (1.1%) (2.0)	2 (14%) (1.5)	0	0
Anxiety	5 (5.7%) (2.2)	3 (21%) (2.3)	0	0
Bradyphrenia	1 (1.1%) (1.0)	0	0	0
Depersonalization*	1 (1.1%) (1.0)	0	0	0
Derealization	2 (2.3%) (2.0)	0	0	0
Disturbance in Attention*	0	1 (7.1%) (1)	0	0
Emotional Distress	8 (14%) (2.0)	2 (14%) (1.5)	2 (33%) (1.0)	0
Feeling of Relaxation*	1 (1.1%) (2.0)	0	0	0
Feeling Abnormal	10 (11%) (2.1)	2 (14%) (1.0)	1 (17%) (1.0)	0
Feeling Cold	10 (11%) (2.0)	0	2 (33%) (1.5)	0
Gait Disturbance	5 (5.7%) (1.3)	0	0	0
Hallucination	1 (1.1%) (1.0)	0	0	0
Hyperhidrosis	3 (3.4%) (1.3)	0	0	0
Illusion	29 (33%) (1.9)	1 (7.1%) (1.0)	1 (17%) (1.0)	0
Mydriasis	4 (4.6%) (1.5)	0	0	0
Perseveration	1 (1.1%) (2.0)	0	0	0
Tachyphrenia	0	1 (7.1%) (1.0)	0	0
Thinking Abnormally	2 (2.3%) (1.5)	2 (7.1%) (1.5)	0	0
Asthenia*	1 (1.1%) (1.0)	0	0	0
Total AEs Listed	**88**	**14**	**6**	**0**

n: Number of spontaneous reports * = Preferred Term encompasses several LLTs and/or items that could not be coded via MedDRA (such as altered time or music perception).
(%): *n* in percentage of sessions
Severity: 1 = mild, 2 = moderate, 3 = severe

10.2.3.2 Unexpected Adverse Events

Adverse events were reported in seven of 12 subjects: four subjects in the experimental dose condition and two subjects in the active placebo condition, with the majority of the AEs occurring in active placebo subjects occurring during Stage 2. Five subjects (three in the experimental dose condition and two in the active placebo condition) did not report any adverse events. The larger number of unexpected AEs after experimental dose results both from the larger number of subjects assigned to this condition and enrolling active placebo subjects in an open-label arm that occurred after the blinded arm. Illness progression likely increased the occurrence of AEs in this sample.

Table 19. Unexpected Adverse Events by Relatedness

Dose Administered	AE Before Dose	20 µg LSD	200 µg LSD	Total (N)
Any AEs	3	1	9	13
Subjects	3	1	6	7
At Least Possibly Related AEs	0	0	0	0
Serious AEs	1	0	1*	2
At Least Possibly Related SAEs	0	0	0	0

*Occurred during Stage 2 in individual initially assigned to 20 µg LSD. Note that the number of AEs listed under 200 µg LSD exceeds the number of subjects assigned to that condition because the AEs occurred when active placebo subjects were enrolled in Stage 2.

Table 20. AEs Listed by MedDRA System Organ Class

System Organ Class	Pre Dose	20 µg LSD	200 µg LSD	Total
Blood and Lymphatic System Disorders			1 (7%)	1
Infections and Infestations			1 (7%)	1
Injury, Poisoning, and Procedural Complications	1 (7%) (200 µg LSD)			1
Investigations			1 (7%)	1
Neoplasms: Benign, Malignant, and Unspecified	1 (7%) (200 µg LSD)		1 (7%)	2 (15%)
Nervous System Disorders			1 (7%)	1
Renal and Urinary Disorders			1 (7%)	1
Reproductive System and Breast Disorders			1 (7%)	1
Skin and Subcutaneous Tissue Disorders	1 (7%) (20 µg LSD	1 (7%)	2 (15%)	4 (31%)
Total AEs	**3 (23%)**	**1 (7%)**	**9 (69%)**	**13**

Seven of 12 subjects experienced at least one unexpected adverse event (AE) during the course of the study. Thirteen AEs occurred during the study, including two serious adverse events (SAEs). All AEs were deemed to be unrelated to the study drug. Two subjects assigned to 20 µg LSD reported five AEs, with only one of them occurring after administration of 20 µg LSD, and six subjects assigned to receive 200 µg LSD reported eight AEs. Two subjects initially assigned to receive 20 µg LSD reported two AEs during the open label arm of the study (Stage 2). Four of five AEs reported in subjects in the active placebo condition occurred during enrollment in Stage 2. Five study subjects (two assigned to receive 20 µg LSD and three assigned to receive 200 µg LSD) did not experience any AEs during the course of the study.

Nine of the thirteen AEs reported occurred after administration of 200 µg LSD; three occurred after study enrollment but prior to drug administration, and one occurred after the administration of 20 µg LSD. One of the three AEs reported prior to drug administration occurred during the same month as study enrollment. Skin conditions and subcutaneous tissue disorders made up over a third of all reported AEs (4 of 13, or 31%), and included itching, skin lesions, and palmar-plantar dysaesthesia ("hand and foot syndrome"), a response to chemotherapy. Cancer progression (as metastasis or progression) made up 15% of AEs reported (2 of 13). Other unexpected adverse events included pneumonia, headache, inflammation of the renal basin (pyelonephritis), broken femur, excessive menstrual bleeding, anemia, and increased blood cholesterol. At least three of the AEs are directly related to the illnesses that qualified subjects for study participation, either directly or arising from treatment for the illness.

Two SAEs were reported during the course of the study. Subject 104 experienced a metastasis of esophageal cancer. This subject had enrolled in the study because of the cancer. The metastasis led to the subject's death on October 26, 2009. Subject 105 was diagnosed with an infection of the renal basin on February 26, 2010 after recurring urinary tract infections caused by blockage of the ureter by enlarged lymph nodes. The subject was hospitalized two months after administration of low dose LSD in December 2009 and diagnosed with infection of the left renal pelvis. The subject was placed on the cancer medications Avastin and Femara and was discharged from the hospital in December 2009. The condition was reported as persisting but diminishing. A broken femur, listed in at least one previous annual report as serious, occurred upon the same month as study enrollment and nearly three months prior to the first administration of the study drug. Though the AE resulted in hospitalization, it was rated as moderate and the subject fully recovered.

There were five severe unexpected AEs reported by four subjects, including the two SAEs described above. Other severe AEs included pneumonia (subject 104), skin lesion (subject 109) and cancer progression (subject 111). The skin lesion and cancer progression were listed as persisting and worsening. The subject with pneumonia recovered fully from the infection despite tumor metastasis.

Subjects recovered fully from a little over half of the AEs reported (7 of 13 AES, or 54%, reported by five subjects). There were five persisting AEs, two of them diminishing at the time of reporting and two worsening, and one remaining the same over the course of the study. As described above, tumor metastasis was a cause of death for the subject with the metastases. A majority of the AEs (9 of 13) were continuous, while a minority (4 of 13) were single or intermittent events. Three AEs led to a delay in scheduling an experimental session. These included a broken femur, a skin lesion in the ear canal and tumor progression. Treatment of AEs could consist of procedures or therapies, prescription or non-prescription drugs, blood or blood products, hospitalization, IV fluids and "other" treatments, with other treatment specified, or no treatment listed. More than one action could be taken per AE. No treatment (4 instances), a

procedure or therapy (3 instances) and medication (prescription or non-prescription, four cases) were the most commonly occurring actions to treat AEs.

In summary, most unexpected AEs reported were unrelated to the study drug, continuous and rated moderate or severe. Full recovery was more common than persistence, but a significant minority of AEs either persisted with improvement or persisted and worsened. The AEs reflect to some degree the health status of the sample, since study enrollment required diagnosis with one or more potentially life-threatening illness. The higher proportion of events occurring after administration of 200 µg LSD when compared with 20 µg is a likely result of twice as many people enrolled in the experimental dose condition and enrollment in the open label arm by three of the four subjects who originally received 20 µg LSD.

Table 21. Frequency of Unexpected Adverse Events by Relatedness

Relatedness	Pre Dose	20 µg LSD	200 µg LSD	Total
Unrelated	3 (23%)	1 (7%)	9 (69%)	13 (100%)
Possibly Related	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Probably Related	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Percentage of total is given in terms of the entire set of 13 AEs. Percentage within each dosage column is by number of AEs reported by dosage.

Table 22. Frequency of Unexpected Adverse Events by Severity

Severity	Pre Dose	20 µg LSD	200 µg LSD	Total
Mild	0	0	2	2 (15%)
Moderate	2	0	4	6 (46%)
Severe	1	1	3	5 (38%)
Totals	**3**	**1**	**9**	**13**

Table 23. Frequency of Unexpected Adverse Events by Outcome

Outcome	Pre Dose	20 µg LSD	200 µg LSD	Total
Full Recovery	1	0	6	7 (54%)
Persists, Diminishing	1	0	1	2 (15%)
Persists, the Same	0	0	1	1 (7%)
Persists, Worsening	0	1	1	2 (15%)
Death	1*	0	0	1 (7%)
Totals	**3**	**1**	**9**	**13**

*Metastasis began prior to drug administration; subject completed the main study.

Table 24. Frequency of Unexpected Adverse Events by Treatment

Treatment	Pre Dose	20 µg LSD	200 µg LSD	Total
None	2	1	1	4
Procedure	0	0	3	3
Medication	0	0	4	4
Hospitalization	1	0	1	2
Other (blood product, IV fluids)	0	0	3	3

10.2.3.3 Expected Adverse Events

There were 102 instances of related adverse events collected from subjects in the blinded and open label arms of the study. Reactions were initially coded and listed on the basis of effects reported in the literature on the acute effects of LSD. The investigators collected subject reports on the day of each experimental session and on the day following the session. Reactions were categorized via MedDRA into system organ class (SOC) and preferred term (PT) categories using MedDRA V15.0. Reactions fell into the following SOCs; Eye Disorders (1), General Disorders and Administration Site Conditions (5), Neurological Disorders (1), Psychiatric Disorders (12) and Skin and Subcutaneous Tissue Disorders (1). A greater number of reactions occurred in people given 200 µg LSD (88 of 102 or 86%) than events occurring in people given 20 µg LSD (14 of 102, or 14%). Most reactions consisted of acute alterations of perception and cognition or mood and emotion. Perceptual or cognitive alterations included distorted perception of time or vision, being aware of one's own altered consciousness, and bradyphrenia or tachyphrenia (slow or quick thoughts). Mood or emotional alterations included anxiety and labile affect (fluctuation in emotions). Subjects reported 30 such events, with 29 occurring after 200 µg LSD and one (alterations in objects or shapes) occurring after 20 µg LSD.

Reactions were rated mild (1), moderate (2) or severe (3), and duration in hours was collected on the day of the experimental session. Average severity ranged from 1.0 to 2.2. Anxiety and feeling abnormal obtained the highest average ratings of severity, and feeling weak (asthenia), bradyphrenia and pseudohallucination (coded as hallucination) attained the lowest average severity ratings. Most related adverse events subsided on the day after the session, with only 6% (16 of 102) reactions continuing on to the next day. Emotional distress, chills or feeling cold, an illusion (body image alterations) and feeling abnormal (somatization) were amongst the reactions still experienced on the next day, with five of six instances rated mild and one rated as moderate on the day following an experimental session.

Sixteen expected adverse events (16% of all reports) were rated as severe. The most commonly rated reactions were anxiety (3), chills or feeling cold (3), and illusions, which included changes in time perception (2) and feelings of melting or merging with one's surroundings (2). Other reactions rated severe included feeling abnormal or abnormal cognition, including awareness of altered cognition, withdrawal from reality, a light or floating feeling, and emotional intensity. Fifteen of sixteen severe reactions were reported in subjects given 200 µg LSD either during Stage 1 or Stage 2, while one reaction, anxiety, was reported in an individual given 20 µg LSD. All reactions were transient; 13 of 16 lasting no longer than the day of the experimental session, and the three reactions that continued to the next day declined in severity, from moderate (feeling cold) to mild (feeling cold, feeling abnormal).

10.2.4 Listing of Adverse Events by Subject

Adverse events are listed by subject in Appendix 14.4.17.

10.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

10.3.1 Listing of Death, other Serious Adverse Events, and other Significant Adverse Events

10.3.1.1 Deaths

Table 25. Deaths

Subject Number	Dose	Adverse Event Diagnosis	Serious	Date of Last LSD Administration	Onset Date	Resolution Date	Severity	Frequency	Action Taken for Study	Action Taken for Treatment	Outcome	Relationship to Drug
104	200 µg	Metastatic Esophageal Cancer	Yes	29-Jan-09	Before Dosing	26-Oct-09	Severe	Continuous	None	None	Death	None

10.3.1.2 Other Serious Adverse Events

Table 26. Serious Adverse Events

Subject Number	Dose	se Event Diagnosis	te of Last LSD Administration	Onset Date	Resolution Date	Severity	Frequency	Action Taken for Study	Action Taken for Treatment	Action Taken Other	Outcome	Relationship to Drug
104	200 µg	Metastatic Esophageal Cancer	29-Jan-09	Before Dosing	26-Oct-09	Severe	Continuous	None	None	Hospitalization	Death	None
105	20 µg	Inflammation of Renal Basin	01-Oct-09	26-Feb-10	Ongoing	Severe	Continuous	None	Prescription Medication	Hospitalization	Persists, Diminishing	None

10.3.1.3 Other Significant Adverse Events

Table 27. Severe Adverse Events

Subject Number	Dose	Stage	Adverse Event Diagnosis	Date Last Drug Administration	Onset Date	Date Stopped Being Severe	Resolution Date	Serious	Frequency	Action Taken for Study	Action Taken for Treatment	Outcome
102	20 µg	1	Anxiety	18-Sep-08	18-Sep-08	18-Sep-08	18-Sep-08	N	Continuous	None	None	Return to Baseline
104	200 µg	1	Illusion	8-Jan-09	8-Jan-09	8-Jan-09	8-Jan-09	N	Continuous	None	None	Return to Baseline
106	200 µg	1	Anxiety	12-Mar-10	12-Mar-10	12-Mar-10	12-Mar-10	N	Continuous	None	None	Return to Baseline
106	200 µg	1	Derealization	12-Mar-10	12-Mar-10	12-Mar-10	12-Mar-10	N	Continuous	None	None	Return to Baseline
108	200 µg	1	Mydriasis	16-Sep-10	16-Sep-10	16-Sep-10	16-Sep-10	N	Continuous	None	None	Return to Baseline
110	200 µg	1	Feeling Abnormal	9-Dec-10	9-Dec-10	9-Dec-10	9-Dec-10	N	Continuous	None	None	Return to Baseline
104	200 µg	1	Illusion	29-Jan-09	29-Jan-09	29-Jan-09	29-Jan-09	N	Continuous	None	None	Return to Baseline
106	200 µg	1	Anxiety	26-Mar-10	26-Mar-10	26-Mar-10	26-Mar-10	N	Continuous	None	None	Return to Baseline
106	200 µg	1	Illusion	26-Mar-10	26-Mar-10	26-Mar-10	26-Mar-10	N	Continuous	None	None	Return to Baseline
106	200 µg	1	Feeling Abnormal	26-Mar-10	26-Mar-10	26-Mar-10	26-Mar-10	N	Continuous	None	None	Return to Baseline
108	200 µg	1	Affect Liability	23-Dec-10	23-Dec-10	23-Dec-10	23-Dec-10	N	Continuous	None	None	Return to Baseline
112	200 µg	1	Feeling Cold	17-Feb-11	17-Feb-11	18-Feb-11	18-Feb-11	N	Continuous	None	None	Return to Baseline
103	200 µg	2	Feeling Abnormal	18-Dec-08	18-Dec-08	19-Dec-08	19-Dec-08	N	Continuous	None	None	Return to Baseline
103	200 µg	2	Illusion	18-Dec-08	18-Dec-08	18-Dec-08	18-Dec-08	N	Continuous	None	None	Return to Baseline
105	200 µg	2	Feeling Cold	18-Feb-10	18-Feb-10	19-Feb-10	19-Feb-10	N	Continuous	None	None	Return to Baseline
105	200 µg	2	Feeling Cold	18-Mar-10	18-Mar-10	18-Mar-10	18-Mar-10	N	Continuous	None	None	Return to Baseline

10.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

One death occurred in Subject 104, a Caucasian man aged 57 upon enrollment. The subject died on October 26, 2009 due to metastatic esophageal cancer. This subject was diagnosed with esophageal cancer prior to drug administration in May 2008. The subject enrolled in the study in December 12, 2008. In November 2008, the subject was diagnosed with metastasis during a routine check with his oncologist. This subject received 200µg LSD on January 8, 2009 and on January 29, 2009. This was followed by chemotherapy sessions for the metastatic cancer. The subject lived in Germany and was unable to complete visits after chemotherapy and died due to progression of the metastatic cancer.

10.3.3. Analysis of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Diagnosis with a potentially life-threatening illness was one of the key criteria for study enrollment. Severe or debilitating illnesses and death were an expected outcome of diagnosis with a life-threatening illness such as cancer. There is no indication from previous reports that any of the unexpected AEs could have arisen as a result of administration of LSD.

10.4 Clinical Laboratory Evaluation

10.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

10.5.1 Listing of Vital Signs, Physical Findings, and Other Observations Related to Safety by Subject

Table 28. Listing of SBP and DBP During First Experimental Session

Subject ID	Condition Assignment	SBP mmHg Beginning	SBP mmHg Middle	SBP mmHg End	DBP mmHg Beginning	DBP mmHg Middle	DBP mmHg End
101	200 µg LSD	150	170	145	90	100	90
102	20 µg LSD	128	122	116	82	78	76
103	20 µg LSD	130	120	135	90	90	90
104	200 µg LSD	110	100	120	70	60	70
105	20 µg LSD	135	130	135	85	85	80
106	200 µg LSD	120	125	120	70	80	75
107	200 µg LSD	135	130	130	90	85	85
108	200 µg LSD	140	130	130	90	90	90
109	20 µg LSD	150	150	145	95	95	90
110	200 µg LSD	160	150	135	80	80	80
111	200 µg LSD	130	125	130	80	80	85
112	200 µg LSD	125	125	125	75	75	75

10.5.2 Evaluation of Vital Signs, Physical Findings, and Other Observations Related to Safety

Blood pressure and heart rate were recorded at the start of each experimental session, during the approximate midpoint and at the end of each session for all subjects. Values were averaged across

the two Stage 1 sessions and the resulting averages were compared across condition using repeated measures ANOVA with time of administration (beginning, midpoint and end) as a between-subjects variable and condition (20 or 200 µg LSD) as a between-subjects factors. There were no significant main effects of time or condition on HR, SBP or DBP, and no significant interaction between time and condition. In all cases for main effects and interactions, the value of the F statistic was below 1.0, with p. > 0.05. These findings suggest that an experimental dose of 200 µg LSD does not produce any consistent changes in blood pressure or heart rate. There is no indication of maximum (peak) blood pressure or heart rate being significantly greater than values recorded at baseline or at session end across all subjects or between the active placebo (20 µg) and experimental dose conditions.

Blood pressure rose to 170/100 in Subject 101, a 43 year-old, 79-kg Caucasian man diagnosed with gastric carcinoma. The elevation occurred approximately 3.5 hours after the administration of 200 µg LSD, at the session midpoint. Blood pressure had returned to values equal to or lower than the peak approximately 5 hours later (8.75 hours after drug administration). It is notable that 101 had the second-highest baseline SBP of all subjects. There was no need for medical intervention to treat any changes in blood pressure or heart rate.

Table 29. Average Stage 1 Vital Signs

Condition Assignment		Average Starting HR Across Stage 1 Experimental Sessions	Average Middle HR Across Stage 1 Experimental Sessions	Average Endpoint HR Across Stage 1 Experimental Sessions	Average Starting SBP Across Stage 1 Experimental Sessions	Average Middle SBP Across Stage 1 Experimental Sessions	Average Endpoint SBP Across Stage 1 Experimental Sessions	Average Starting DBP Across Stage 1 Experimental Sessions	Average Middle DBP Across Stage 1 Experimental Sessions	Average Endpoint DBP Across Stage 1 Experimental Sessions
20 µg LSD	N	4	4	4	4	4	4	4	4	4
	Mean	79.00	74.00	77.00	132.25	130.00	131.38	108.38	108.25	107.00
	(SD)	(16.69)	(18.40)	(13.90)	(10.22)	(15.05)	(13.70)	(8.50)	(11.62)	(10.26)
	Max	62.00	56.00	58.00	119.00	116.00	113.00	96.00	94.00	93.00
	Min	100.00	96.00	90.00	142.50	147.50	145.00	115.00	120.00	117.50
200 µg LSD	N	8	8	8	8	8	8	8	8	8
	Mean	74.75	73.00	73.25	130.31	129.06	126.25	103.75	103.75	102.19
	(SD)	(9.38)	(9.80)	(11.51)	(11.61)	(14.57)	(7.44)	(7.91)	(10.86)	(7.61)
	Max	62.00	62.00	62.00	107.50	100.00	115.00	87.50	80.00	90.00
	Min	88.00	90.00	94.00	145.00	152.50	140.00	110.00	117.50	112.50
Total	N	12	12	12	12	12	12	12	12	12
	Mean	76.167	73.33	74.50	130.96	129.38	127.96	105.29	105.25	103.79
	(SD)	(11.68)	(12.40)	(11.85)	(10.73)	(14.041)	(9.63)	(8.04)	(10.80)	(8.44)
	Max	62.00	56.00	58.00	107.50	100.00	113.00	87.50	80.00	90.00
	Min	100.00	96.00	94.00	145.00	152.50	145.00	115.00	120.00	117.50

Table 30. Average Stage 2 Vital Signs

Condition Assignment		Average Starting HR Across Stage 2 Experimental Sessions	Average Middle HR Across Stage 2 Experimental Sessions	Average Endpoint HR Across Stage 2 Experimental Sessions	Average Starting SBP Across Stage 2 Experimental Sessions	Average Middle SBP Across Stage 2 Experimental Sessions	Average Endpoint SBP Across Stage 2 Experimental Sessions	Average Starting DBP Across Stage 2 Experimental Sessions	Average Middle DBP Across Stage 2 Experimental Sessions	Average Endpoint DBP Across Stage 2 Experimental Sessions
	N	3	3	3	3	3	3	3	3	3
	Mean	78.67	70.67	72.67	138.33	135.00	130.00	87.50	85.00	85.33
	(SD)	(16.29)	(9.02)	(9.02)	(18.43)	(13.92)	(15.21)	(10.00)	(6.61)	(5.20)
	Max	60.00	62.00	64.00	117.50	120.00	112.50	77.50	77.50	77.50
			80.00	82.00	152.50	147.50	140.00	97.50	90.00	87.50

Table 31. Condition Assignment vs. Stage 1 Average HR

Condition Assignment		Stage 1 Experimental Sessions Average Starting HR	Stage 1 Experimental Sessions Average Middle HR	Stage 1 Experimental Sessions Average Endpoint HR	Stage 2 Experimental Sessions Average Starting HR	Stage 2 Experimental Sessions Average Middle HR	Stage 2 Experimental Sessions Average Endpoint HR
20 µg LSD	N	4	4	4			
	Mean	79.00	74.00	77.00			
	(SD)	(16.69)	(18.40)	(13.90)			
	Min-Max	62.00-100.00	56.00-96.00	58.00-90.00			
200 µg LSD	N	8	8	8	3	3	3
	Mean	74.75	73.00	73.25	78.67	70.67	72.67
	(SD)	(9.38)	(9.80)	(11.51)	(16.29)	(9.02)	(9.02)
	Min-Max	62.00-88.00	62.00-90.00	62.00-94.00	60.00-90.00	62.00-80.00	64.00-82.00
Total	N	12	12	12			
	Mean	76.17	73.33	74.50			
	(SD)	(11.68)	(12.40)	(11.85)			
	Min-Max	62.00-100.00	56.00-96.00	58.00-94.00			

Table 32. Condition Assignment vs. Stage 1 Average SBP

Condition Assignment		Stage 1 Experimental Sessions Average Starting SBP	Stage 1 Experimental Sessions Average Middle SBP	Stage 1 Experimental Sessions Average Endpoint SBP	Stage 2 Experimental Sessions Average Starting SBP	Stage 2 Experimental Sessions Average Middle SBP	Stage 2 Experimental Sessions Average Endpoint SBP
20 µg LSD	N	4	4	4			
	Mean	132.25	130.00	131.38			
	(SD)	(10.22)	(15.05)	(13.70)			
	Min-Max	119.00-142.50	116.00-147.50	113.00-145.00			
200 µg LSD	N	8	8	8	3	3	3
	Mean	130.31	129.06	126.25	138.33	135.00	130.00
	(SD)	(11.61)	(14.57)	(7.44)	(18.43)	(13.92)	(15.21)
	Min-Max	107.50-145.00	100.00-152.50	115.00-140.00	117.50-152.50	120.00-147.50	112.50-140.00
Total	N	12	12	12			
	Mean	130.96	129.38	127.96			
	(SD)	(10.73)	(14.04)	(9.63)			
	Min-Max	107.50-145.00	100.00-152.50	113.00-145.00			

Table 33. Condition Assignment vs. Stage 1 Average DBP

Condition Assignment		Stage 1 Experimental Sessions Average Starting DBP	Stage 1 Experimental Sessions Average Middle DBP	Stage 1 Experimental Sessions Average Endpoint DBP	Stage 2 Experimental Sessions Average Starting DBP	Stage 2 Experimental Sessions Average Middle DBP	Stage 2 Experimental Sessions Average Endpoint DBP
20 µg LSD	N	4	4	4			
	Mean	108.38	108.25	107.00			
	(SD)	(8.50)	(11.62)	(10.26)			
	Min-Max	96.00-115.00	94.00-120.00	93.00-117.50			
200 µg LSD	N	8	8	8	3	3	3
	Mean	103.75	103.75	102.19	87.50	85.00	83.33
	(SD)	(7.91)	(10.86)	(7.61)	(10.00)	(6.61)	(5.20)
	Min-Max	87.50-110.00	80.00-117.50	90.00-112.50	77.50-97.50	77.50-90.00	77.50-87.50
Total	N	12	12	12			
	Mean	105.29	105.25	103.79			
	(SD)	(8.04)	(10.80)	(8.44)			
	Min-Max	87.50-115.00	80.00-120.00	90.00-117.50			

10.5.6 Evaluation of Visual Analog Pain Scale

Table 34. Visual Analog Pain Scale Ratings on Study Day

Subject ID	Condition assignment	Average Pre LSD	Average Post Exp. 1	Average Post Exp. 2	Pain rating at long-term follow up
101.00	200 µg LSD	31.67	19.67	21.00	28
102.00	20 µg LSD	0.00	0.00	0.00	
103.00	20 µg LSD	8.33	16.00	31.00	
104.00	200 µg LSD	16.67	0.00		
105.00	20 µg LSD	3.67	1.33	0.00	7
106.00	200 µg LSD				4
107.00	200 µg LSD	14.00	11.00	11.00	1
108.00	200 µg LSD	9.00	10.50	9.50	6
109.00	20 µg LSD	0.00	3.00	0.00	0
110.00	200 µg LSD				
111.00	200 µg LSD	21.33	68.67	61.25	0
112.00	200 µg LSD	15.33	17.00	18.50	2

Ratings were collected at or near each point identified via visit log and database. None of the subjects completed the measure up through two-month follow up.
109 did not complete measure during stage; responses reflect stage 2 open label 200 µg session

The VAPS was intended to capture overall changes in overall pain experienced by study subjects to see whether LSD administration improved or intensified existing overall pain. Ratings represent the length, in millimeters, of a line drawn from the beginning of a subject's mark on the line, with a mark placed farther to the right of the start describing a greater amount of pain. Subjects were instructed to rate pain on a daily basis with the VAPS after they began preparatory sessions and up until the 2-month follow up. Subjects 106 and 110, both assigned to the experimental dose condition, failed to complete the VAPS throughout the course of the study. Subject 110 was enrolled with a diagnosis of Parkinson's disease and may not have experienced disease-related pain. It is unclear why Subject 106, who had a diagnosis of gastric cancer, did not complete the measure. Subject 109 did not complete the VAPS during the time this subject received 20 µg LSD, but began completing the measure during Stage 2. Hence scores from this subject are considered to have occurred after 200 µg LSD. Five of 12 subjects rated their pain on a regular basis up until the two-month follow up. Six of 12 did not rate pain up to the point of the two-month follow-up. However, all subjects save 104, 106 and 110 rated their pain at a point after the second experimental session.

VAPS ratings were collected on or near the day of as many study visits as available, and at 2-month and 12-month follow-up, if available. If no ratings were given on or close to a given study visit, then the subject's ratings were considered absent. In order to deal with variability in data, VAPS ratings were further summarized by averaging all VAPS ratings made on study visits prior to drug administration, all VAPS ratings taken on study visits after the first administration of LSD, all ratings occurring on visits after the second administration of LSD, and at 12-month follow-up.

A repeated measures ANOVA failed to find a difference in pain scores rated prior to receiving LSD, after the first experimental session and after the second experimental session, ($F(2, 16) = 0.85$, $p. > 0.05$). Analyses of variance comparing pre-drug VAPS scores in active placebo versus

full-dose LSD was significant ((F (1,8) = 12.32, p < 0.05), with subjects assigned to receive experimental dose reporting greater pain prior to study drug administration than subjects in the active placebo condition (mean (SD) = 18 (7.79) versus 3 (3.95). An analysis of covariance with pre-drug values serving as a covariate that compared time of administration (post-experimental session 1, post experimental session 2) and the active placebo and high dose condition failed to find a main effect for dose (F (1, 1) = 0.001, p. < 0.05, and there was no interaction between dose and time (F (1, 6) = 2.44, p. > 0.05 (0.169). The administration of either dose of LSD does not alter average self-reported pain, and 200 µg LSD did not have any greater effects on average pain ratings than 20 µg LSD.

10.6 Safety Conclusions

Administering 200 µg LSD in combination with psychotherapy conducted in a supportive setting appears to be safe for people experiencing anxiety as a result of confronting a life-threatening illness. The study drug has few physiological effects and was not associated with any of the unexpected AEs collected during the study. The reactions to LSD reported during this study are similar to those reported in healthy controls, the most frequently reported effects being alterations in perception, cognition or emotion. These effects rarely lasted more than a day, with rated severity declining over time. The SAE that led to a study death arose as a result of progression of a life-threatening illness. Experiencing a severe expected AE was greater for subjects given the experimental dose when compared with those given the active placebo. However, anxiety during the course of the experimental session occurred at nearly the same rate in both conditions (5 instances in subjects given 200 µg LSD; 3 instances in subjects given 20 µg LSD). Future studies treating anxiety arising from facing a life-threatening illness could use the doses of LSD administered in this study. Neither dose of LSD significantly affected heart rate or pulse, and there were no significant differences in blood pressure or heart rate produced by LSD. Average self-reported pain did not increased after LSD administration, and there was no significant difference in average pain ratings provided by people after the active placebo versus the high dose of LSD. Taken together, it appears that the administration of 200 µg LSD does not increase risk of harm, adverse events or undesirable changes in cardiovascular function or pain in subjects experiencing anxiety arising from diagnosis with a potentially life-threatening illness.

11.0 Discussion and Overall Conclusions

This is the first study to investigate the safety and efficacy of LSD along with psychotherapy as a treatment for anxiety in the face of life-threatening illnesses to take place in 40 years. Findings from this study suggest that it may be possible to treat anxiety in people with life-threatening conditions via LSD-assisted psychotherapy. When compared with an active placebo dose of LSD, subjects receiving 200 µg LSD and psychotherapy experienced a reduction in state anxiety and a trend toward reduced trait anxiety as well. Unlike early investigations of LSD-assisted psychotherapy, the current study employed a randomized, blinded active placebo controlled design. There were no adverse events often attributed to LSD like prolonged anxiety (“bad trip”), and lasting psychotic or perceptional disorders, and the few somatic effects of LSD were mild and of no clinical significance. Anxiety remained at reduced levels when it was assessed again at 12-month follow-up, implying durability of effects for LSD-assisted psychotherapy. The results of this small pilot study are promising, and should be pursued in larger samples.

A possible mechanism of action for reduced anxiety after receiving classic psychedelics within a structured, supportive setting is the increased likelihood of mystical experiences [38-39]. This may especially be the case when people have an opportunity to contemplate these experiences and communicate about them to others.

This treatment may serve as an important option in palliative care for individuals who find living with dread of their death or increasing deterioration unbearable. It is notable that research is now underway investigating the therapeutic potential of other psychedelic compounds, such as psilocybin, in combination with psychotherapy as a means of reducing anxiety in people with advanced stage cancer [24].

LSD and compounds with similar pharmacological profiles may have an important role to play in palliative care.

12.0 Tables Figures and Graphs Referred to But Not Included In Text

None provided.

12.1 Demographic Data

See Section 9.2.

12.2 Efficacy Data

Summary figures and tables

12.3 Safety Data

Summary figures and tables

12.3.1 Display of Adverse Events

See Section 10.2.

12.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

See Section 10.3.

12.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

12.3.4 Abnormal Laboratory Value Listings (Each Subject)

13.0 Reference List

1. Hofmann, A., *How LSD originated.* J Psychedelic Drugs, 1979. **11**(1-2): p. 53-60.
2. Stoll, W., *Lysergsäure-diäthyl-amid, ein Phantastikum aus der Mutterkorngruppe.* Schweiz. Arch. Neur, 1947. **60**(279): p. 1-2.
3. Stoll, W., *Ein neues, in sehr kleinen Mengen wirksames Phantastikum.* Schweiz Arch Neurol, 1949. **64**: p. 483-484.
4. Grof, S., *LSD Psychotherapy: 4th Edition*. 2001, Ben Lomond, CA: Multidisciplinary Association for Psychedelic Studies.
5. Leuner, H., *Hallucinogens*. 1981, Bern, Switzerland: Hans Huber Verlag.
6. Grinspoon, L. and J.B. Bakalar, *Psychedelic drugs reconsidered*. 1979, New York, NY: Basic Books.
7. Jensen, S.E., *A treatment program for alcoholics in a mental hospital.* Q J Stud Alcohol, 1962. **23**: p. 315-20.
8. Kast, E., *Attenuation of anticipation: a therapeutic use of lysergic acid diethylamide.* Psychiatr Q, 1967. **41**(4): p. 646-57.
9. Kurland, A., et al., *LSD in the treatment of alcoholics.* Pharmakopsychiat, 1971. **4**: p. 83-94.
10. Ling, T.M. and J. Buckman, *The Treatment of Anxiety with Lysergic Acid and Methyl Phenidate.* Practitioner, 1963. **191**: p. 201-4.
11. Mangini, M., *Treatment of alcoholism using psychedelic drugs: a review of the program of research.* J Psychoactive Drugs, 1998. **30**(4): p. 381-418.
12. Krebs, T.S. and P.O. Johansen, *Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials.* J Psychopharmacol, 2012. **26**(7): p. 994-1002.
13. Martin, A.J., *LSD (lysergic acid diethylamide) treatment of chronic psychoneurotic patients under day-hospital conditions.* Internat. J. Social Psychiatr., 1957. **3**(3): p. 188-196.
14. Nichols, D.E., *Hallucinogens.* Pharmacol Ther, 2004. **101**(2): p. 131-81.
15. Strassman, R.J., *Hallucinogenic drugs in psychiatric research and treatment. Perspectives and prospects.* J Nerv Ment Dis, 1995. **183**(3): p. 127-38.
16. Pahnke, W.N., et al., *The experimental use of psychedelic (LSD) psychotherapy.* Jama, 1970. **212**(11): p. 1856-63.
17. Grof, S., et al., *LSD-assisted psychotherapy in patients with terminal cancer.* Int Pharmacopsychiatry, 1973. **8**(3): p. 129-44.
18. Kast, E. and V. Collins, *Study of Lysergic Acid Diethylamide as an Analgesic Agent.* Anesth Analg, 1964. **43**: p. 285-91.
19. Kurland, A.A., Grof, S., Pahnke, W. N., Goodman, L.E., *Psychedelic Drug Assisted Psychotherapy. In Patients With Terminal Cancer*, in *Psychotheramacological Agents for the Terminally Ill and Bereaved 1973,*, I.K. Goldberger, S. Malitz, and A.H. Kutscher, Editors. 1973, Columbia University Press: New York, NY. p. 86-133.
20. Pahnke, W.N., et al., *LSD-assisted psychotherapy with terminal cancer patients.* Curr Psychiatr Ther, 1969. **9**: p. 144-52.
21. Grinspoon, L. and J.B. Bakalar, *Can drugs be used to enhance the psychotherapeutic process?* Am J Psychother, 1986. **40**(3): p. 393-404.

22. Gasser, P., *Die Psycholytische Therapie in der Schweiz von 1988 - 1993.* . Schweiz. Arch. Neurol. Psych., 1996. **147**(2): p. 59-65.
23. Doblin, R., *Doblin R (2001) The regulation of the medical use of psychedelics and marijuana; available at http://www.maps.org.* , in *Kennedy School of Government*. 2001, Harvard University: Cambridge, MA.
24. Grob, C.S., et al., *Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer.* Arch Gen Psychiatry, 2011. **68**(1): p. 71-8.
25. Benz, E., *Halluzinogen – unterstützte Psychotherapie. Dissertation*. 1989: Zurich.
26. Bonny, H.L. and L.M. Savary, *Music and your Mind*. 1990, Tarrytown NY: Station Hill.
27. Grof, S., *The Psychology of the Future*. 2000, Albany, NY: SUNY Press.
28. Unkefer, R.F., *Music Therapy in the Treatment of Adults with Mental Disorders: Theoretical Bases and Clinical Interventions.* . 1990, New York, NY: Schirmer Books.
29. Abramson, H., et al., *Lysergic acid diethylamide (LSD-25): I. Physiological and perceptual responses.* Journal of Psychology, 1955. **39**(3).
30. Aaronson, N.K., et al., *The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology.* J Natl Cancer Inst, 1993. **85**(5): p. 365-76.
31. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale.* Acta Psychiatr Scand, 1983. **67**(6): p. 361-70.
32. Derogatis, L.R., *Symptom Checklist-90 (Revised edition).* . 1994, Minneapolis, MN: Pearson Assessments. .
33. Saavedra, J.M., *[Clinical use of psychotoxic drugs].* Prensa Med Argent, 1970. **57**(5): p. 246-9.
34. Spielberger, C.D., et al., *Manual for the State-Trait Anxiety Inventory.* 1983, Palo Alto, CA.: Consulting Psychologists Press.
35. Spielberger, C.S., R.L. Gorsuch, and R.E. Lushene, *Manual for the State Trait Anxiety Inventory.* . 1970, Palo Alto, CA: Consulting Psychologists Press.
36. First, M.B., et al., *Structured Clinical Interview for DSM-IV Axis I Disorders - Patient Edition (SCID-I/P, Version 2.0, 4/97 Revision).* , ed. V. 2. 1997, New York: Biometrics Research Department, New York State Psychiatric Institute.
37. Pahnke, W.N., *Psychedelic drugs and mystical experience.* Int Psychiatry Clin, 1969. **5**(4): p. 149-62.
38. Griffiths, R., et al., *Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later.* J Psychopharmacol, 2008. **22**(6): p. 621-32.
39. Griffiths, R.R., et al., *Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance.* Psychopharmacology (Berl), 2006. **187**(3): p. 268-83; discussion 284-92.
40. Brunner, E., S. Dormhof, and F. Langer, *Nonparametric Analysis of Longitudinal Data in Factorial Experiments.* . 2002, New York: Wiley.
41. Brunner, E. and F. Langer, *Nichtparametrische Analyse longitudinaler Daten. R. München Wien*. 1999, Munich, Germany: Oldenbourg Verlag,.