July 30, 2012

University of Arizona Institutional Review Board
Human Subjects Protection Program
The University of Arizona
1618 E. Helen St.
PO Box 245137
Tucson, AZ, 85724

Dear University of Arizona IRB Chair and Personnel

We are submitting for your review the attached FDA-approved (cleared) protocol IND# 110513, "Placebo-Controlled, Triple-Blind, Randomized Crossover Pilot Study of the Safety and Efficacy of Five Different Potencies of Smoked or Vaporized Marijuana in 50 Veterans with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)." Dr. Sue Sisley is the Principal Investigator, with co-investigators Lauren Lee MD and E. Deborah Gilman MD. Medical Monitors are Michael Mithoefer, MD and Julie Holland MD, with statistical consultant Yvonne Michal, Ph.D.

To supplement the protocol, we're submitting this cover letter which provides a rationale for elements of study design, some of which were discussed in a teleconference with FDA and weren't elaborated in the protocol itself. Both the design and procedures by which this study will be conducted are based on drug development principles, which can differ from academic, basic science research.

This study is sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS), an IRS-approved non-profit organization developing off-patent Schedule 1 drugs such as marijuana and MDMA into FDA-approved prescription medicines. MAPS operates for public benefit, with the protocol and all the data generated placed in the public domain, with no claims of proprietary or intellectual property rights. MAPS' clinical team, led by Amy Emerson and Berra Yazar-Klosinski, Ph.D., will monitor the study per GEP and FDA/EMEA standards to ensure it will pass FDA audit, which we anticipate will occur.

The sponsor and Principal Investigator designed this protocol to serve as the first exploratory pilot study in a drug development program for smoked and/or vaporized marijuana (cannabis) as a treatment for veterans suffering from chronic, treatment-resistant PTSD. The goals of this pilot study are to gather preliminary data in this patient population evaluating marijuana potency, cannabinoid content and drug delivery method on safety and on reducing PTSD symptoms. In addition, this study will gather evidence to address the key scientific methodological challenge of designing a successful double-blind study with a psychoactive drug. This study is exploratory in nature and is not designed with the goal of obtaining statistically significant evidence of safety or efficacy or information about mechanisms of action about how marijuana might work to treat subjects with chronic, treatment-resistant PTSD.

MAPS is currently sponsoring an international series of Phase 2 pilot studies investigating the use of MDMA-assisted psychotherapy in subjects with chronic, treatment-resistant PTSD. Our

current US MDMA/PTSD study has enrolled the 10th of 24 veterans, fire-fighters and police officers with chronic, treatment-resistant PTSD. We have previously obtained data suggesting that MDMA-assisted psychotherapy offers the potential to cure PTSD in a substantial percentage of patients. In contrast, we consider marijuana primarily to offer the opportunity for symptom reduction, requiring chronic dosing though with a relatively inexpensive medication that, if it works, may take effect within days and be a preferred medicine for some patients.

INCLUSION/EXCLUSION CRITERIA: PTSD AND COMORBID DEPRESSION

Up to 40% of people with PTSD are also diagnosed with another affective disorder, such as depression or another anxiety disorder. Rather than exclude participants with any other psychiatric diagnoses, we want to examine the effects of marijuana in a sample that will be similar to that of the general population of veterans with PTSD. The investigators will assess depression as a secondary measure along with the primary measure of PTSD symptoms, as noted in the study objectives (pp. 11) and outcome measures (p. 17-18).

INCLUSION/EXCLUSION CRITERIA: DEFINITION OF TREATMENT RESISTANCE

As stated in pp. 15-16 of the protocol, the study will enroll veterans with treatment-resistant PTSD arising from their service in the US military, with treatment resistance defined as still meeting criteria for PTSD diagnosis after treatment either with psychotherapy or pharmacotherapy. While we are willing to use a more stringent definition that requires treatment-resistance to both pharmacotherapy and psychotherapy, this would produce an unrepresentative sample since many veterans with PTSD have underutilized care for PTSD available to them or have not received appropriate care.

INCLUSION/EXCLUSION CRITERIA: MARIJUANA EXPERIENCED AND MARIJUANA NAIVE SUBJECTS

The study will enroll participants with and without any experience with marijuana, so long as they have not used marijuana within the month prior to study enrollment (p. 17 in the protocol). Marijuana is the most commonly used illicit drug in the US and a significant percentage of people with PTSD have used it (see p. 8 in the study protocol). To be representative of the larger population of veterans with PTSD the study needs to include subjects who have had previous experience with marijuana. If the study were limited only to subjects who had never used marijuana, the subjects would not be representative and recruitment would be seriously compromised.

SAFETY PROCEDURES

To ensure that both marijuana-naïve and marijuana-experienced subjects are prepared for the subjective experience of the specific potency of marijuana that they will receive in each of the two four week medication periods, the protocol includes a four-hour introductory session on each of two days in a row. In these introductory sessions, subjects gradually self-administer marijuana under supervision and with the support of research staff. Subjects will be administered the same potency they will receive during their four-week medication period using the same delivery

system, smoked or vaporized. This identical procedure of two four-hour introductory sessions will be repeated before the four-week cross-over period. Should any subject experience substantial anxiety during the introductory sessions or adverse effects of a persistent nature beyond the time of the introductory sessions, the subject could withdraw from the study and/or the Principal Investigator could decide to exclude the subject from further participation. Subjects will be administered the Columbia Suicide Severity Rating Scale (CSSRS) at frequent intervals throughout the study and will meet with study staff on a weekly basis. Psychotherapists will be available should either subjects or experimenters request psychotherapeutic sessions due to increased signs of suicidality.

BLINDING

One of the major methodological challenges of medical marijuana research, indeed research with any psychoactive drug, is conducting a successful double-blind. We believe that almost all or perhaps even all subjects will be able to correctly guess whether they have been randomized to either an inactive placebo group or an active drug group. However, we are going to test that assumption in this specific subject population. As a result, this pilot study is designed as a dose-response study randomizing subjects to one of five potencies of marijuana, 0 % THC (inactive placebo), 2% THC, 6% THC, 6% THC and 6% CBD, and 12% THC. Subjects will be administered marijuana for a one-month daily dosing period followed by a two-week medication cessation period.

This study is designed to explore whether a dose-response design actually results in an effective double-blind in which the subjects, the Principal Investigator who interacts directly with each subject, and independent rater are indeed blinded to dose. In this protocol, we will ask all the subjects, the Principal Investigator, and the independent rater to guess which potency of marijuana the subject was randomized to receive.

We anticipate that subjects receiving the inactive placebo will accurately guess that they have received the inactive placebo, if not in the first few days, then sometime during the four-week medication period, and that the PI and independent rate will also guess correctly. In contrast, we anticipate that the subjects receiving one of the four doses of marijuana will demonstrate a substantial proportion of inaccurate guesses as to the dose they received, as will the PI and independent rater.

CROSSOVER DESIGN DETAILS

One of the main objectives of this study is to compare the effects of the two cannabinoids delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) on PTSD symptoms. In the crossover period, we are primarily interested in learning more about the differences between 6% THC and 6% THC and 6% CBD, and also whether 12% THC will be well-tolerated by the subjects. We therefore plan to drop the inactive placebo which we anticipate will be accurately identified by the subjects, PI and independent rater. We also plan to drop the 2% THC doses from the crossover period since we anticipate 2% THC will show minimal efficacy and we want to learn more about CBD. Subjects who received 6% THC in the initial four-weeks will be assigned the

6% THC, 6% CBD marijuana in the crossover, and subjects who received the 6% THC, 6% CBD marijuana will be assigned the 6% THC marijuana in the crossover. Subjects who received either the inactive placebo or the 2% THC marijuana or the 12% THC will be randomized to either the 6% THC, 6% THC, 6% CBD, or 12% THC marijuana.

The partial crossover is a means of conducting a within-subjects comparison of the effects of marijuana with and without CBD. In addition, the blind will likely be even stronger in Stage 2 since all participants will be receiving marijuana containing at least 6% THC.

TWO-WEEK DRUG WASHOUT BETWEEN CROSSOVERS

The study contains a two week washout period of medication cessation to gather information on whether symptom relief, if any, fades during this time. In both Stage 1 and the crossover Stage 2, primary and secondary outcome measures will be collected and compared after the four-week period of marijuana use and after the two week washout period. In addition, the two week washout period ensures that the effects of the marijuana administered during the Stage 2 crossover period are from that potency rather than the potency administered during the Stage 1 dosage period.

SUBJECT SELF-TITRATION

A secondary objective of this exploratory study (p. 11) is to gather information about the range of dosing schedules and amounts that different PTSD patients chose to self-administer. Different subjects may have different sensitivities to the effects of marijuana. Some subjects may use only at night before bed, others may use throughout the day. Some subjects may vary times of use and amounts on a daily basis as symptoms vary. Subject self-titration is an accepted part of drug development research, especially in exploratory protocols such as this one where there is an absence of prior data about the safety and efficacy of a range of doses.

Data about all of the individual subject dosing preferences would be lost with a fixed dosing schedule. Furthermore, some subjects could be required to use more marijuana than they needed for symptom relief, creating the possibility of adverse events due to the fixed dosing schedule.

Study participants will be permitted to smoke or vaporize up to two of NIDA's marijuana cigarettes per day (each about .9 gram), permitting self-titration but with an upper limit imposed for diversion control purposes. While having an upper limit on the amount of marijuana that can be used is not ideal from a dose-response perspective, we feel it is an acceptable compromise to conduct this exploratory study with a limit of two NIDA marijuana cigarettes per day. Should a substantial number of subjects use all of the marijuana allocated per day and indicate that they would have preferred more medication, we can adjust the amounts in subsequent studies if the data from this study justifies further research.

Participants will be instructed to save any unused marijuana each day in the packages provided, to be returned each week for the next week's supply. The remaining material is weighed each week and the amount of marijuana used will be assessed. Serum cannabinoid levels will be

assessed weekly, permitting another means of estimating cannabinoid levels in each subject. The data analysis will use weight of remaining material as a covariate to assess self-titration across conditions (p. 43 of the protocol)..

In FDA drug development research with Sativex, an oral-mucosal spray that is 50% THC, 50% CBD, patient self-titration of the number of sprays is part of the protocol. For example, in a multi-site study of Sativex for pain relief in individuals with advanced malignancy, used a three-arm design, with low, medium and high doses. In each arm, patient self-titration of dosing was permitted, with the low arm permitting patients to decide to use a range of 1-4 sprays per day, the medium arm permitted 6-10 sprays per day, and the high arm permitted 11-16 sprays per day (see http://www.nextbio.com/b/search/individualtrial.nb?id=NCT00530764). In the Phase 3 studies with Zoloft for PTSD, subject self-titration was also part of the protocol, within limited ranges. These drug development designs included both self-titration and upper limits on medicine, as in our marijuana/PTSD study.

OUTPATIENT SETTING

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Prior to starting the study, all participants will undergo two four-hour supervised training sessions where they experience the effects of the specific potency of marijuana they will receive using the specific dose delivery approach, either smoked or vaporized. After two four-hour training sessions, participants will commence using study marijuana at home rather than being restricted to an inpatient facility. The sponsor and investigators are seeking to examine changes in PTSD symptoms over a three month or longer period of time. Requiring subjects to live in an in-patient treatment facility for three or more months would fundamentally compromise subject recruitment and, if subjects could be found, be both cost prohibitive and involve research with a non-representative sample of subjects.

DIVERSION CONTROL AGREEMENT WITH FDA CONTROLLED SUBSTANCES STAFF

Multiple means of preventing and discouraging diversion are in place, through a multi-step process approved by FDA's Controlled Substances Staff. These include setting an upper limit of a maximum of two NIDA marijuana cigarettes that each subject can use per day, giving subjects only a one week supply at a time, and requiring subjects to store unused marijuana in a secure, locked box. In addition, all subjects will be required to record every time they medicate via portable digital camera that we will loan to them for the duration of the study, and every week they will bring in the video recording for review by experimental staff before being administered the next week's supply. Subjects will also be required to complete a Daily Marijuana Use Diary, and return any unused marijuana in the separate packages for each day's supply. The experimenters will also verify subject use by contacting another individual chosen by subject and agreed on by the experimenters, and also by taking weekly blood cannabinoid levels.

At the end of the cross-over medication period and the two week period of medication cessation, the subjects have the option to request that the unused marijuana be returned with the study extended ("Optional Stage 3") for the period of time it takes for the remaining marijuana to be

used. This further reduces concerns that subjects will use more marijuana than they need for symptom control or will divert unused marijuana.

With these procedures in place, the FDA Controlled Substances Staff approved the outpatient design permitting subjects to self-administer study marijuana in their homes safely and with acceptable risk of diversion.

SPONSOR RESPONSIBILITIES TO GATHER, MONITOR, REPORT ON DATA.

This study is a drug development study. Unlike academic research, the sponsor is expected to maintain the data and analyze it, maintaining data in "locked" or tamper-proof formats. Specific procedures are followed to make sure the data is accurate, and once these are performed, the database is locked to prevent future alteration. The sponsor is committed to analyzing the data and submitting a Final Report to FDA. Consultation can be sought from individuals who are not part of MAPS, but the responsibility for the conduct of the study and for the gathering, monitoring and analyzing of the data rests with the sponsor.

Please do not hesitate to contact us with any questions about the study design that emerge in the course of your review. We look forward to working with you on the review of this protocol.

Sincerely

Sue Sisley MD
Study Principal Investigator

Rick Doblin PhD
Executive Director, MAPS