The safety and efficacy of naltrexone and scopolamine utilized in combination in the treatment of major depression: A double blinded, randomized, controlled pilot study

Protocol Identifying Number: 701

Sponsor: Neal S. Taub, MD

Principle Investigator: Neal S. Taub, MD

Funded by: The Taub Group

Version Number: 1.0

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Statement of Compliance

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without documented approval from the Institutional Review Board, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed the Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principle Investigator: Neal S. Taub, MD

Signed: _____Date: _____

Title: The safety and efficacy of naltrexone and scopolamine utilized in combination in the treatment of major depression: A double blinded randomized controlled pilot study.

Precis: A double blinded randomized controlled trial utilizing oral scopolamine and naltrexone will be performed in subjects who have current major depression. The trial duration will be 4 weeks of active treatment or placebo. The placebo group will subsequently have the option of crossing over to active treatment.

Objectives: The primary objectives of this study are to determine the safety and efficacy of oral scopolamine and naltrexone utilized in combination in the treatment of depression.

Endpoint: The MADRS tool will be utilized throughout the study to determine medication responses and remission from depression. Side effects noted by participants be recorded to determine the safety and tolerability of the medication combination. Pre and post study blood chemistries and ECGs will similarly be collected and monitored for significant changes.

Population: The sample size will be a total of 40 subjects randomized into control and active groups. Subject ages will be between 18 and 65. Subjects included will be in reasonably good health as interpreted by the Principle Investigator. The subjects will live no further than 40 miles from the research site. The male: female ratio of the study will likely be approximately 1:2 as noted in the population with major depression at large. All demographic groups will likely be represented in proportion to the local population.

Phase: Scopolamine and naltrexone are FDA approved medications that have been utilized off label for the indication of depression. The side effect profile with this combination is anticipated to be *less* than that noted with each medication utilized separately as the doses utilized in this study are significantly lower than those utilized in their respective current indications when each medication is administered alone. The study is therefore exempt as defined in 21CFR312.2, and eligible for expedited review.

Number of Sites enrolling participants:

The Taub Group—principle and only site

3535 Randolph Road Suite 208

Charlotte, NC 28211

Description of Study Agents: Scopolamine HBR will be utilized 0.15mg P.O. B.I.D with naltrexone HCL 1mg P.O. B.I.D. The scopolamine and naltrexone will be compounded in 60% propylene glycol with 40% anhydrous ethanol by the Principle Investigator. These doses are both lower than those utilized currently when the medications are utilized independently. The drops will be placed on a spoon and then placed on the tongue by the participant. The participant will be instructed not to swallow for 30 seconds in order to maximize buccal absorption of the drops before they are swallowed. The dosing of the scopolamine and naltrexone drops can be modified as noted in section 6.1.

Study Duration: Estimated time from initiation of trial to data analyses—18 months.

Participant duration: 10 weeks from initial screening to final follow up.

Schematic of Study Design:

Week 1/ Day 1 – Week 4/Day 6—Screening, randomization and Baseline Assessments

1. Participants to be enrolled 20 per group; 20 active and 20 control
2. History and physical to determine appropriateness with CBC, CMP and ECG. Principle Investigator to screen all participants.
3. Obtain informed consent from included participants.
4. Participants randomized by Study Supervisor

Week 5/Day 1-6—Study Intervention

1. Medication provided to participants with administration instructions and documentation by Principle Investigator
2. MADRS questionnaires completed
3. Study director follow up via telephone/email days 2-6 of study as needed

Week 6/Day 1-6—Follow-up Assessments

1. First office follow-up with Principle Investigator—Documentation of side effects and subjective progress.
2. MADRS questionnaires completed

Week 7/Day 1-6—Follow-up Assessments

1. Follow-up visit with Principle Investigator—Documentation of side effects and subjective progress.
2. MADRS questionnaires completed

Week 8/Day 1-6—Follow-up Assessments

1. Follow-up visit with Principle Investigator—Documentation of side effects and subjective progress.

2. MADRS questionnaires completed

Week 9/Day 1-6—End of Study Assessments

1. Final visit with Principle Investigator

2. Repeat CBC, CMP, ECG collected
3. Final MADRS questionnaires completed

Week 10/Day 1-6—Follow-up Telephone Call

1. Discussion regarding continuing active treatment or crossing over to active treatment by subjects receiving placebo treatment.

1 Key Roles

1.1 Neal S. Taub, MD—Principle Investigator

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2 Introduction: Background Information and Scientific Rationale

2.1 Background Information

Naltrexone is an opioid antagonist FDA approved for treatment of ethanol use disorder as well as opioid use disorder. Naltrexone Hydrochloride is a competitive opioid antagonist at both mu and delta opioid receptors. An oral dose of 50-100 mg can reverse opioid overdoses. Paradoxically, ultra-low dose naltrexone(less than 1 mcg) enhances the effects of opioid agonists. Naltrexone binds to the C-terminal pentapeptide of the scaffolding protein filamin A with strong avidity which may prevent or reverse a change in G-protein signaling in G-coupled receptor systems, such as the mu opioid receptor after prolonged stimulation by an agonist. Low dose naltrexone has additionally been anecdotally found to be helpful in many disorders, including fibromyalgia, which has symptom overlap with depression. Naltrexone has recently been noted in a pilot study to be effective in treating depression relapse in patients utilizing dopaminergic antidepressants (1).

Scopolamine has been demonstrated to be a rapid acting antidepressant administered both as an IV infusion as well as dosed orally. Interest in the muscarinic cholinergic system in mood disorders stemmed initially from evidence suggesting hypersensitivity of the cholinergic system plays a role in the pathophysiology of depression. Researchers have shown increasing cholinergic activity exacerbates depressive symptoms. Two studies have demonstrated that scopolamine administered both IV and orally result in rapid remission from major depression in a majority of patients (2-4). The principle investigator has utilized scopolamine in the treatment of depression and anxiety IV and orally with a high level of efficacy and minimal side effects.

The Principle Investigator believes that a combination approach, much like that utilized in oncology for decades, will have the highest likelihood of producing rapid remission from major depression. An acceptable side effect profile is hypothesized, as well as a lower rate of relapse than that noted with the use of single agents. This treatment approach will additionally be very cost effective, utilizing two inexpensive generic medications, which can be easily compounded in inexpensive buccal drops.

2.2 Rationale

Depression is currently a silent pandemic, and according to the World Health Organization accounts for more disability worldwide than any other medical problem. Most individuals with depression do not receive treatment. Those that do are treated with many modalities with only fair efficacy. More than a third of treated patients do not achieve remission with current treatments. A number of recent studies have utilized antidepressant medications in combination and generally synergy is noted with increased levels of response and remission reported, often with no increased adverse effect burden.

This study will utilize the oral route of administration in order to maximize convenience and cost effectiveness. The 1mg B.I.D. naltrexone dose and 0.15 mg B.I.D. dose of scopolamine combination has been chosen based on our clinical experience with the medications, and our desire to maximize both efficacy and tolerability.

The 4 week trial period has been chosen in order to have an adequate time period to determine efficacy while reducing the risk of subject attrition and reduce research costs. The study will be a double blinded, randomized parallel design control group study to maximize the validity of the study data accrued.

2.3 Potential Risks and Benefits

Compared with placebo, scopolamine administration generally results in higher rates of drowsiness, blurred vision, dry mouth, lightheadedness. The side effects are generally self-limited.

Other anticholinergic adverse effects are less common and include urinary retention. Scopolamine use is contraindicated in angle closure glaucoma as well as allergy to scopolamine or significant hypersensitivity. Pregnancy and breast-feeding are similarly contraindications.

Compared with placebo, naltrexone administration generally results in higher rates of insomnia. Other potential side effects include anxiety, headaches, stomach upset, nausea, sneezing, nasal stuffiness, muscle pain, decrease in libido, blurred vision, ringing in the ears, weakness or tiredness. Contraindications to use of naltrexone are allergy to naltrexone or significant hypersensitivity. Increased liver function tests have been noted in high-dose naltrexone however this is unlikely to be an issue at the proposed low dose schedule.

2.3.1 Known Potential Risks

There are potential economic risks should additional medical care be required due to medication induced side effects. There are potential psychological risks should the intervention worsen the subjects' underlying depression.

Immediate risks mainly relate to medication side effects, as noted above.
Any long term risks utilizing scopolamine are unknown. Naltrexone has a very favorable profile utilized long term by patients.

This study is a clinical trial and therefore of requires human subjects. In the opinion of the Principle Investigator, the potential benefits far outweigh the risks. Major depression is a life threatening disease and this combination of medications may provide a high rate of response and remission with a positive safety profile.

2.3.2 Known Potential Benefits

Naltrexone and scopolamine have been demonstrated to be effective agents in the treatment of depression both in clinical trials and in the clinic of the Principle Investigator.

Potential short and long term benefits of this study may be short and/or long term remission from major depression if participants continue treatment after the conclusion of the study.

3 Objectives and Purpose

The primary objectives of this study are to determine the safety and efficacy of naltrexone and scopolamine utilized in combination for the treatment of depression.

4 Study Design and Endpoints

4.1 Description of the Study Design

The trial will be a placebo-controlled, double blinded, randomized study. The trial will be a single center study. There will be one control group and one active agent group. The doses noted will remain fixed during the entirety of the study except as noted in section 6.1. There will be the opportunity for crossover of the placebo control group to active treatment. There will be the opportunity for subjects receiving the active treatment to continue treatment after the trial.

4.2 Study Endpoints

4.2.1 Primary Endpoint

The primary endpoint will be to measure remission from depression and responses to medication. The MADRS questionnaire is a validated tool utilized in many depression studies to measure affective changes correlated with remission from depression. This questionnaire will utilized throughout the study. These questionnaires will generate granular data which can be easily analyzed with simple statistical tools. The group sizes are expected to generate data with adequate statistical power to determine whether or not the intervention is effective. Remission from depression will be considered a 50% reduction in MADRS score. A response to treatment will be considered a 25% reduction in MADRS score.

4.2.2 Secondary Endpoint

There is no secondary endpoint in this trial.

4.2.2 Exploratory Endpoints

The exploratory endpoint is to determine the relative safety of this medication combination. A standardized questionnaire will be utilized at all visits to determine the presence and severity of side effects or adverse reactions. These data will be pooled and the relative incidence of side effects and adverse reactions in the active group will be compared to the control group.

5 Study Enrollment and Withdrawal

5.1 Participant Inclusion Criteria

Individuals must meet all of the inclusion criteria that follow in order to be eligible to participate in the study. Women and members of minority groups and their subpopulations will be included in accordance with the NIH Policy on Inclusion of Women and Minorities as Participants in Research Involving Human Subjects. The inclusion criteria are as follows:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the trial
3. Male or female, aged 18-65
4. In good health other than depression as evidenced by medical history
5. Diagnosed with depression and exhibiting signs and/or symptoms of depression as noted on physical exam findings and MADRS or other validated questionnaires
6. Stable signs of depression noted for at least the preceding 8 weeks.
7. A negative serum pregnancy test in women with reproductive potential and agreement to utilize appropriate contraception during the trial (e.g., Licensed hormonal or barrier method)
8. Generally normal CBC, CMP, and ECG tests as interpreted by the Principle Investigator

5.2 Participant Exclusion Criteria

Individuals meeting any of the exclusion criteria at baseline will be excluded from study participation. The exclusion criteria are as follows:

1. Uncontrolled anxiety
2. Uncontrolled hypertension
3. Severe renal impairment
4. Severe hepatic disease
5. Determination that the subject is currently a danger to himself/herself or others
6. Diagnosed schizophrenia
7. Febrile illness within 4 weeks
8. Pregnancy or lactation
9. Known allergic reactions or hypersensitivity to scopolamine or naltrexone
10. Treatment with an investigational drug within 8 weeks
11. Current use of antipsychotic medications
12. Current use of MOA inhibitor
13. Current use of opioids
14. Glaucoma

5.3 Strategies for Recruitment and Retention

Participants will be recruited utilizing advertisements on The Taub Group and The Charlotte Ketamine Center websites (included with this protocol), as well as through their respective Facebook pages. Similar advertisements will be sent to psychiatrists and psychologists within a 30 mile radius of the study site periodically. It is anticipated that utilizing these strategies will allow the accrual of 40 appropriate subjects over a 6-12 month period.

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely suspended or prematurely terminated, the Principle Investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

1. Determination of unexpected, significant or unacceptable risk to participants
2. Demonstration of efficacy that would warrant stopping
3. Insufficient compliance to protocol requirements
4. Data that are not sufficiently complete and/or evaluable
5. Determination of futility

The study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the Principle Investigator.

6 Study Agents

The control medications consist of inactive drops prepared by the Principle Investigator consisting of 60% propylene glycol and 40% anhydrous ethanol. In the active group, naltrexone and scopolamine will be compounded by the principle investigator and added to the drops.

6.1. Dose adjustments/Modifications/Delays

The scopolamine/naltrexone and control drops dose will be modified in case of side effects or lack of efficacy. After the first three days of treatment in the study, the participants will be queried by the Study Supervisor. If the participant notes significant side effects, such as sedation, dizziness, severe dry throat or other problematic side effects, the dose of the drops will be reduced by 50% for the remainder of the trial. If the participant notes no improvement in affect and notes no significant side effects, the dose of drops will be increased by 50%.

6.2 Duration of Therapy

Four weeks appears to be the minimum duration within which significant responses would be noted with the two active agents if a response or remission is likely to occur.

6.3 Tracking of Dose

The patients will be seen weekly and will bring their medications with them. The Study Supervisor or Research Assistant will review the dosing with participants each visit to ensure adherence to prescribed dosing.

6.4 Study Agent Accountability Procedures.

Naltrexone HCL USP powder and scopolamine HBR USP powder will be obtained from Letco Medical. Compounding will be performed by The Principle Investigator. The medications will be and labeled and beyond use dates assigned as per USP chapter 795. The finished medication will be stored in the compounding area in a locked cabinet. The active drops will then be cataloged by the Study Supervisor, with an equal number of controls cataloged. The medications will be dispensed to participants by the Principle Investigator after the drops are randomized into actives and controls by the Study Supervisor, in order to assure blinding of the Principle Investigator and subjects. The catalog will be stored electronically and a hard copy placed in a locked place in the office.

Patient information handouts for each of the medications will be given to participants and reviewed carefully with each participant. Each subject will be provided with 6cc of naltrexone/scopolamine drops or 6cc of placebo drops.

Any remaining medication will be collected at the end of the study by the Study Supervisor and destroyed.

7 Study Procedures and Schedule

7.1 Study Specific Procedures

1. A medical history will initially include a detailed questionnaire completed by prospective participants with the Principle Investigator or Study Supervisor. This will include a MADRS questionnaire, detailed prescription and over the counter medication history, past medical history, allergies, review of systems, illicit substance use history. Assessment of eligibility will include a review of permitted and prohibited medications.

2. If the prospective participant is tentatively deemed eligible for further evaluation, then a physical examination will be performed by the Principle Investigator. This will include weight and height, blood pressure, pulse and respiratory rate. Further physical exam will include a general survey, chest exam, cardiovascular exam, and a neurological exam.

3. An ECG will subsequently be performed and interpreted by the Primary Investigator.

4. A blood specimen from the prospective participant will be collected by the Research Assistant and sent to Quest Laboratory and a CBC and CMP obtained to assess primarily renal and hepatic function. The laboratory results will be interpreted by the Principle Investigator. A urinalysis and a urine drug test will be performed to assess for illicit substance use. A serum pregnancy test will be performed in women with reproductive potential.

5. The prospective participant will be counseled regarding the nature of the study, and requirements for study agent adherence.

6. Accepted participants will be evaluated on a weekly basis. Each will complete a questionnaire detailing effects of the medication, side effects, and a repeat MADRS questionnaire. A brief physical examination will be performed.

7.2 Prohibited Medications

The following medications will not be permitted in study participants:

1. Pimozide
2. anticholinergics
3. MOA inhibitors

7.3 Rescue Medications, Treatments and Procedures

Participants will be treated by the Principle Investigator in accordance with the prevailing standard of care if significant adverse reactions occur during the study. Study medication(s) reduction or withdrawal will be considered in these circumstances.

7.4 Participant Access to Study Agent at Study Closure

The control group will have the option of crossing over to the active treatment for an additional 4 week trial at the end of the initial 4 week trial. Active group participants will have the option of continuing treatment if was deemed beneficial by the participant. At that point, the participant will be responsible for the cost of medication and office visits.

8 Assessment of Safety

8.1 Specification of Safety Parameters

Safety parameters recorded will include all adverse effects note by participants and the Principle Investigator. In particular, adverse events requiring medication dose modification or medication withdrawal will be recorded. Any adverse events requiring actual intervention or hospitalization will be recorded.

8.1.1 Definition of Serious Adverse Events

An adverse event or suspected adverse reaction is considered serious if, in the view of the Principal Investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, or a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.2 Definition of Unanticipated Problems.

An incident, experience, or outcome that meets the definition of an unanticipated problem may warrant consideration of changes to the protocol or consent in order to protect the safety, welfare, or rights of participants. Examples of corrective actions or changes that might need to be considered in response to an unanticipated problem include:

1. Modification of inclusion or exclusion criteria to mitigate the newly identified risks
2. Implementation of additional safety monitoring procedures
3. Suspension of enrollment of new participants or halting of study procedures for all participants
4. Modification of informed consent documents to include a description of newly recognized risks

5. Provision of additional information about newly recognized wrist to previously enrolled participants

Unanticipated problems involving risk to participants include any incident, experience or outcome that meets all of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given the research protocol described in protocol related documents, such as the IRB approved research protocol and informed consent documents; and be unexpected taking into account the population been studied;
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggest that the research places participants at a greater risk of harm, including physical, psychological, economic or social harm than was previously known or recognized

8.2 Classification of Adverse Events

8.2.1 Severity of Event

All adverse events will be assessed by the principal investigator using a protocol defined grading system as follows:

1. **Mild**-events require minimal or no treatment and do not interfere with the participants daily activities.
2. **Moderate**-events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
3. **Severe**-events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

All adverse events will have their relationship to the study agents and study participation assessed by the principal investigator. The adverse event will be rated either related or not related. All adverse events will have their relationship to the study agents assessed by the principal investigator. Definitions of causation are as follows:

1. **Related**--The adverse event is known to occur with the study agents, there is a reasonable possibility that the study agents causing adverse event, or there is a temporal relationship between the study agents and event. The reasonable possibility means that there is evidence to suggest a causal relationship between the study agents and the adverse event.
2. **Not related**- there is not a reasonable possibility that the administration of the study agents cause the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

8.2.3 Expectedness

Expected adverse reactions are adverse events that are common and known to occur with the study agents being studied and will be collected in a format which discusses the magnitude of the reaction.

Expected adverse events have been noted previously as potential side effects of the medications and are noted in the informed consent as well.

An adverse event or suspected adverse reaction is considered unexpected if it is not listed in the informed consent or in the overview of expected risks with the medications noted. The Principal Investigator will be responsible for determining whether an adverse event is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described with study agents.

8.3 time period and frequency for event assessment and follow-up

Adverse events and suspected adverse events will be identified and followed by the Principle Investigator through frequent follow-up visits, and telephone contact and e-mail contact. These events will be recorded in the medical records of the participants and also in the research log. Treatment and follow-up of adverse events and suspected adverse events will be the responsibility of the Principal Investigator and will follow the standard of care.

Adverse events will be solicited through the utilization of a review of systems questionnaire that will be completed by the participants at each follow-up visit and is included with this protocol.

The occurrence of an adverse event or suspected adverse event may come to the attention of study personnel during study visits and interviews of study participants presenting for medical care, or upon review by the Principal Investigator. All adverse events including local and systemic reactions not meeting the criteria for solicited adverse events will be captured in the research log and in the participant's medical record. Information to be collected will include event description, time of onset, the Principal Investigator's assessment of severity, relationship to study agents, as well as time of resolution/stabilization of the event. All adverse events will be followed by the Principal Investigator to adequate resolution.

Any medical condition that is present at the time that the participant's intake screen will be considered baseline and not reported as an adverse event. However, if the study participant's condition deteriorates at any time during the study, it will be reported as an adverse event. Unexpected events will be recorded in the research log as well as in the participant's medical record throughout the study.

Changes in the severity of an adverse event will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Adverse events characterized as intermittent will be documented at each onset and the duration of each episode will be documented.

The Principal Investigator will report all reportable events with start dates occurring any time after informed consent is obtained up to 30 days after the last day of study participation. At each study visit, as previously noted, the Principal Investigator will inquire about the occurrence of adverse events since the last visit.

8.4 Reporting Procedures

8.4.1 Adverse Event Reporting

The Principal Investigator will report adverse events to the IRB within one week of occurrence.

8.4.2 Serious Adverse Event Reporting

Serious adverse events will be reported by the Principal Investigator to the IRB within one week.

8.4.3 Pregnancy

If a study participant become pregnant during the study than the principal investigator will taper and discontinue all medications over a one-week period.

8.5 Study Halting Rules

Consideration will be given by the Principal Investigator to halting the study if two severe adverse events are noted. An unexpected frequency of adverse events in general may trigger termination or suspension of the study. The principal investigator will serve as the medical monitor and be responsible for safety oversight.

9 Clinical Monitoring

Clinical site monitoring will be conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable and that the conduct of the trial is in compliance with the currently approved protocol, with GCP, and consistent overall with the current standard of care.

1. The Principal Investigator will conduct on site monitoring on a monthly basis to assure 100% data collection and verification as well as to ensure ongoing appropriate training of personnel.
2. Independent audits will not be performed in order to reduce cost.

10 Statistical Considerations

10.1 Statistical and Analytical Issues

10.1.1 Statistical Methods

All study practices and statistical methods are based on the ICH document Statistical Principals for Clinical Trials.

Data be summarized by treatment group. All baseline, demographic, safety and efficacy output data will be summarized by treatment group. In summary tables of the categorical variable, counts and percentages will be utilized. The denominator for each percentage will be the number of subjects within the population treatment group unless otherwise specified.

All hypothesis testing will be carried out at the 5% two-sided significance level unless otherwise specified. P- Values will be rounded to 3 decimal places.

The treatment label for all tables, listings and figures will be:

Treatment	Label
4 weeks of treatment with scopolamine and naltrexone	Active Treatment
4 weeks of placebo Treatment	Placebo
All Treatments	**Total**

Where any of the statistical methods described herein prove unsuitable during analysis, more appropriate methods will be used. All changes and methodology will be documented in the clinical study report.

Additional ad hoc analyses may be conducted as deemed suitable.

10.1.2 Dropouts and Missing Data

Subject inclusion/exclusion criteria will be determined at the baseline visit, and subjects that did not meet all of the criteria will not be entered into the study. Those subjects deemed eligible to participate will be allocated a 3 digit number at randomization prior to the initial treatment.

If a participant discontinues the study at any time after entering the study, the Principle Investigator will ensure this does not affect the patient's care. The reasons for withdrawal will be reported in the research log and will be included in the final report. Failure to attend two follow-up visits will result in participant removal from the trial.

10.1.3 Determination of Sample Size

The primary objective of the study is to assess changes in depression symptoms in patients treated with Naltrexone and scopolamine. No previous study to our knowledge has assessed this combination in human subjects however clinical experience has demonstrated anecdotally a high response and remission rate from depression. Because no study to our knowledge has systematically assessed depression symptomatology response to this combination, there are no data available for a statistical power calculation. Review of other depression studies and the studies utilizing these medications independently have demonstrated trials with approximately 6-60 participants. It is therefore the opinion of the Principal Investigator that a trial with 40 participants will be sufficient to assess whether this medication combination is more efficacious than placebo.

10.2 Subject Characteristics

10.2.1 Subject Disposition

The subject disposition table will summarize the following and will be presented for all subjects by treatment group and overall.

1. The number and percentage of subjects entered into the study after baseline visit

2. The number and percentage of subjects in the active treatment group withdrawn before treatment completion
3. The number and percentage of subjects in the control group withdrawn before week 4 of active treatment
4. The number and percentage of subjects to complete the study

The number and percentage of subjects to complete and withdraw from the study and the primary reason for withdrawal will be summarized in the treatment group and overall for all subjects.

10.2.2 Background and Demographic Characteristics

Demographic data presented will be age and gender.

10.2.3 Prior and Concomitant Medications

Prior and concomitant medications taken by a subject will be reported. Prior medications are defined as a medication that started and stopped before baseline. Concomitant medications are defined as the medications that started before baseline and are continued into the study.

10.2.4 Medical History

The Principal Investigator will document all significant affective disorders that the subject has experienced in the past.

10.3 Efficacy Analyses

10.3.1 Primary Efficacy Variable

The primary efficacy endpoint for depression remission is the achievement of a 50% reduction in MADRS score at the end of the 4 week treatment cycle and a response represents a 25% reduction in MADRS during the 4 week treatment cycle.

The comparison of the MADRS scores of the treatment arm versus the control arm will be reported as mean values along with standard error. Means will be reported for initial score, final score, and interim scores.

10.3.3 Exploratory Variable

A review by the Principal Investigator of adverse effects will be performed qualitatively and results compared with the agents studied individually in previous trials.

11 Source Documents and Access to Data/documents

The clinical site will maintain appropriate medical and research record for this trial, and compliance with ICH E6 and regulatory requirements will be assured for the protection of confidentiality of participants.

Source data are all information, original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to medical records, office charts, memoranda, medication dispensing records, in addition to the research log. All documentation will be available to the IRB to

examine. Otherwise only the principal investigator, study supervisor and research assistant will have access to these records

12 Ethics/Protection of Human Subjects

12.1 Institutional Review Board

The protocol, informed consent, recruitment materials and all participant materials will be submitted to the IRB for review and approval. Approval of the protocol and consent form as well as additional materials will be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB improved; a determination will be made regarding whether previous consented participants need to be reconsented.

12.2 Informed Consent Process

Informed consent will be required for all participants of this study. The Principal Investigator will comply with guidelines noted in ICH GCP. The consent documents are included with this protocol.

12.2.1 Consent Procedures and Documentation

Informed consent is a process that will be initiated prior to the individual's agreement to participate in the study. It also continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families by the study supervisor and/or research assistant. The consent forms will be IRB approved and the participant will be asked to read and review the document. The principal investigator will explain the research study to the participant and answer any questions that may arise.

All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study and their rights as research participants. The participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent documented prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected it they decline to participate in the study.

12.3 Participant and Data Confidentiality

Participant confidentiality will be maintained as per standard medical practice and per HIIPA guidelines. The research data will similarly be maintained utilizing standard medical record confidentiality security measures. The study supervisor and Principal Investigator will have access to the research data and the research assistant and study supervisor will have access to medication codes until broken at the end of the study. All data will be stored electronically and password protected. Hard copies of research and medical documents will be stored in a locked office.

A certificate of confidentiality will be provided to each participant as well as per typical HIIPA confidentiality procedures. The participants' confidentiality will be strictly held in trust by the participating investigators, their staff and agents. This confidentiality is extended to cover testing biological samples and clinical information relating to participants. Therefore the study protocol, documentation, data, and all information generated will be held in confidence. No information concerning the study or the data will be released to any unauthorized or party without prior authorization and approval of the Principal Investigator.

Representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records and medication dispensing records for the participants in the study. The study site will permit access to such records.

The study participants' contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for at least 3 years.

12.4 Study Records Retention

All records pertaining to this study will be maintained for minimum of 3 years.

12.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly. These practices are consistent with ICH E6.

13 Publication and Data Sharing Policy

This clinical trial will be registered with www.clinicaltrials.gov. The results of the study will be utilized to further optimize treatment of severe depression. Similarly, the results will be prepared in article format and submitted to an appropriate peer reviewed Journal.

14 Conflict of Interest Policy

The independence of the study from any actual or perceived influence is critical. Therefore any actual conflict of interest of a person who has a role in the design, performance, analysis, publication or any aspect of his trial is noted below. The design of the trial, participation of the study supervisor as well as IRB oversight will in the opinion of the Principle Investigator minimize any chance of bias. The perceived possible conflicts of interest are as follows:

1. The principal investigator is the owner of the Taub Group, which is supporting this study. The naltrexone/scopolamine buccal drops are dispensed directly to patients by Dr. Taub at a nominal charge.

15 References

1. Mischoulon, David et al. Randomized, proof-of-concept trial of low dose naltrexone for patients with breakthrough symptoms of major depressive disorder on antidepressants. Journal of Affective Disorders. 2017; 208: 6-14.
2. Han, Changsu et al. Oral scopolamine augmentation for major depression. 2013; Expert Review Neurother; 13(1), 19-21.
3. Drevets, Wayne et al. Antidepressant Effects of the Muscarinic Cholinergic Receptor Antagonist Scopolamine: A Review. 2013 June 15: 73 (12): 1156-1163.
4. Furey, Maura et al. Antidepressant Efficacy of the Antimuscarinic Drug Scopolamine. 2006. Arch Gen Psychiatry: 63 1121-1129.