

# CLINICAL TRIAL PROTOCOL

## Light and Ion Treatment to Enhance<sup>+</sup> Medication Efficacy in Depression

### (The LITE+MED Trial)

#### *A Randomized Controlled Trial of Light Treatment and Fluoxetine in Patients with Nonseasonal Major Depressive Disorder*

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##### **A. Study Objectives**

The **primary objectives** of this study are to test the hypotheses that, in patients with nonseasonal major depressive disorder (MDD) of at least moderate severity: 1) light treatment with a fluorescent light box (10,000 lux white light for 30 minutes daily) is more effective than a placebo control condition, and 2) combined light treatment and antidepressant medication (fluoxetine) is more effective than placebo and both monotherapies.

The **secondary objectives** of this study are to investigate the effects of bright light treatment and fluoxetine on clinical response and remission rates, adverse events, quality of life, work productivity, and health services utilization.

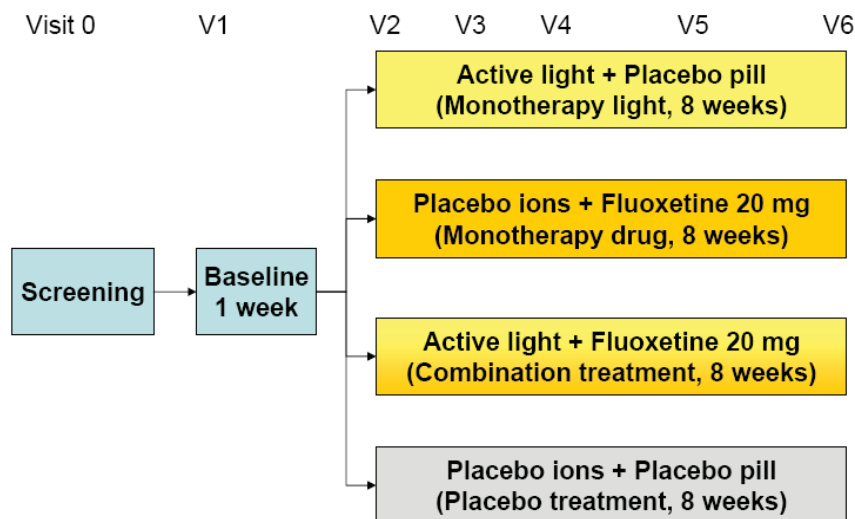
##### **B. Overall Study Design (see Figure 1)**

This trial has been designed as a multicentre, double-blind, placebo-controlled, randomized, parallel-design study. A total of 216 patients meeting entry criteria will be enrolled at 6 centres over a 3 year period.

**Phase I** is a one week baseline phase without treatment to quantify baseline pre-treatment measures (see Figure 1). In **Phase II**, subjects will be randomized to 1 of 4 treatment conditions for 8 weeks: 1) active light treatment using a fluorescent light box (10,000 lux white light for 30 minutes daily) plus a placebo pill, 2) placebo inactive negative ion generator (30 minutes daily) with fluoxetine 20 mg/d, 3) placebo inactive negative ion generator (30 minutes daily) plus placebo pill (double placebo), or 4) combined active light treatment using a fluorescent light box (10,000

lux white light for 30 minutes daily) plus fluoxetine 20 mg/d. Randomization will be conducted centrally via a web-based computerized system and stratified by sex and centre.

Figure 1. Protocol Summary (also see Appendix 1 – Summary of Procedures)



The primary measure of efficacy will be change score (baseline to termination) on the Montgomery-Asberg Depression Rating Scale (MADRS). Secondary measures of efficacy will include clinical response (50% or greater improvement in MADRS scores) and remission (final MADRS score of 10 or less), scores on the 24-item Hamilton Depression Rating Scale (Ham-24), the CGI, the Quick Inventory of Depressive Symptoms (QIDS-SR, Rush 2003), the Lam Employment Absence and Productivity Scale, and the Quality of Life, Enjoyment and Satisfaction Questionnaire. All of these outcome measures are widely used in depression research studies, are sensitive to change, and have been well validated (e.g., Lam et al, 2005). Safety and adverse events data will also be systematically recorded and compared across conditions. Utilization of health services data will be captured to estimate cost-effectiveness of each active treatment condition compared to placebo.

### C. Outcome Measures (see Appendix 1)

1. Montgomery-Asberg Depression Rating scale (MADRS, Montgomery and Asberg, 1979). This interview-rated 10-item is also used widely for depression studies and is sensitive to change in clinical trials. Reliability is enhanced by using the Structured Interview Guide for the MADRS (SIGMA, Williams et al, 2008). To further increase reliability and maintain integrity of the blind, patients will be rated by telephone raters blind to treatment condition. The telephone rating method is widely used in depression studies, has been validated against face-to-face interviews, and has been used regularly at several centres in this trial. The MADRS is more reliable than the Ham-D in telephone ratings.
2. Hamilton Depression Rating Scale (Ham-D, Hamilton, 1967). The interviewer-rated Ham-D is the most widely used measure of outcome in depression studies. To enhance reliability, a semi-structured interview, the Structured Interview Guide for the Hamilton Depression Rating Scale

- (SIGH, Williams et al, 1988). The SIGH generates scores for several versions of the Ham-D, including the 17-item Ham-D (Ham-17), which is the most widely used outcome measure in depression clinical trials. The SIGH also generates a 7-item atypical symptom addendum, for a 24-item total (Ham-24). This atypical addendum was developed because the original Ham-17 does not rate depressive symptoms such as hypersomnia, increased appetite, and weight gain.
3. Quick Inventory of Depressive Symptoms, Self-Rated version (QIDS-SR, Rush et al, 2003). This self-rated depression inventory is also widely used and validated in depression studies. It will provide a basis for comparison to the results from the large U.S. STAR\*D trial.
  4. Clinical Global Impression scale, Severity and Improvement (CGI, Guy 1976). The CGI adds an overall clinical impression to the continuous outcome measures, and is useful as a global measure of change.
  5. The Adult ADHD Self-Report Scale (ASRS-v1.1) is a self-rated scale that assesses the severity of 18 symptoms associated with Attention Deficit/Hyperactive Disorder (ADHD) (Kessler et al., 2005). This scale is used as a screening tool for adults who exhibit symptoms of ADHD, and provides information to the clinician regarding the need for more in-depth clinical interview (Schweitzer et al., 2001; Barkley, 1998). The questions in the ASRS v1.1 are consistent with the DSM-IV criteria and manifestations of ADHD symptoms, and has high validity and reliability (Adler et al., 2006; American Psychiatric Association, 2000).
  6. Adverse Events Scale (CANMAT, 1999). Developed by the Canadian Network for Mood and Anxiety Treatment for use in the Emergency Drug Release program, this self-rated scale assesses both frequency and severity of 32 adverse events (including a category for “other”). This scale provides a more comprehensive and systematic evaluation of adverse events than is usually conducted in antidepressant clinical trials, and was used in the CIHR-funded CAN-SAD light treatment versus fluoxetine study (Lam et al, 2006).
  7. Lam Employment Absence and Productivity Scale (LEAPS, Lam, 2007). This 10-item self-report scale assesses absenteeism and presenteeism (work productivity) and has recently been validated in depressed patients.
  8. Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q, Endicott et al, 1993). The Q-LES-Q is a 16-item self-report questionnaire developed and validated for use in depressed outpatients. There are also single items that rate “overall life satisfaction and contentment” and “satisfaction with medications (if any are taken).” The Q-LES-Q has good test-retest reliability and is sensitive to change in clinical status.
  9. Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The PSQI is a subjective instrument used to assess the quality and pattern of sleep in adults. Patients score themselves on seven areas of sleep, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The PSQI has good reliability and validity for use in adults across all health care settings (Buysse et al.).
  10. Fatigue Severity Scale (FSS, Krupp et al., 1989). This 9-item scale is designed to differentiate fatigue from clinical depression, as they exhibit similar symptoms. This scale is also a practical

measure due to its brevity and ease of administration/scoring (Friedberg & Jason, 1998; Krupp et al., 1989).

11. Health Economic Assessment (HEA, Fantino et al, 2007), to assess health care utilization and costs associated with the various treatment conditions.
12. Seasonal Pattern Assessment Questionnaire (SPAQ, Rosenthal et al, 1987). The SPAQ is widely used as a screening tool for SAD and to assess seasonality as a dimensional construct.
13. Morningness-Eveningness Questionnaire (MEQ, Horne and Ostberg, 1976). This questionnaire has been used in many studies to establish a chronotype – the propensity for optimal mood and alertness to occur in the morning or evening. Scores on the MEQ have been significantly correlated with physiological measures of circadian phase.
14. Relationship Styles Questionnaire (RSQ, Griffin & Bartholomew, 1994). This questionnaire assesses general orientations and attachment styles in close relationships. This instrument has good internal consistency and test-retest reliability, and results correlate well with attachment data provided by other informants pertaining to the respondent (Creasey et al., 2004; Griffin et al., 1994). The RSQ is frequently used as a screening tool for attachment styles across a variety of clinical settings, and has good convergent validity with other attachment scales (Creasey et al., 2004; Eames & Roth, 2000).

## **D. Study Population**

### Entry Criteria

Clinical trials for depression have always used clinic samples of patients rather than epidemiologically sampled patients, because of convenience. Results are then generalizable to those patients who are willing to seek help (epidemiological studies show that 50% of people who suffer from major depression do not seek help). An advertising strategy will be used to recruit patients for this study. We and others have been using this strategy for clinical trials that require rapid recruitment. Patients recruited through advertisement are similar to those recruited from the clinic, but are not usually as resistant to treatment.

Participation will be voluntary. The nature of the study will be fully explained to the patient. The patient must have an educational level and degree of understanding such that he/she can communicate with the investigator and research staff intelligently. An informed consent document (ICD) will be signed by the patient and retained by the investigator. A signed copy will be given to both the patient and to the Study Coordinator. Patients should be reliable and must agree to keep appointments for clinic visits and all tests and examinations required by the protocol. All patients will be screened using the Mini International Neuropsychiatric Interview (MINI, Sheehan et al, 1998) to confirm the diagnosis and to rule out other primary illnesses (such as bipolar disorder, other depression/anxiety disorders, substance abuse, etc.). All patients will also be evaluated for risk of suicidality, using the Columbia Classification Algorithm of Suicide Assessment (C-CASA, Posner et al, 2007).

### *Inclusion Criteria*

1. Male and female outpatients aged 19-60 years.
2. Patients will meet criteria for major depressive episodes as determined by a structured interview (Mini Neuropsychiatric Interview, MINI, Sheehan et al, 1998).

3. A score of 20 or greater on the clinician-rated Ham-17, indicating at least moderately severe depression, comparable to previous depression treatment studies.
4. Competency to give informed consent.

#### *Exclusion Criteria*

1. Pregnant women, lactating women and sexually active women of childbearing potential who are not using medically accepted means of contraception.
2. Serious suicidal risks as judged by the clinician, the MINI, the Ham-17, and the C-CASA.
3. The following DSM-IV diagnoses (to ensure a homogenous diagnostic group):
  - Major depressive disorder, recurrent, with a seasonal pattern
  - Organic mental disorders
  - Substance abuse/dependence, including alcohol, active within the last year
  - Schizophrenia, Paranoid or Delusional Disorders, or any other psychotic features
  - Obsessive-Compulsive Disorder, Post-Traumatic Stress Disorder
  - Panic disorder, Generalized Anxiety Disorder, if a primary diagnosis
  - Bipolar Disorder
  - Bulimia Nervosa; Anorexia Nervosa
4. Serious illness including cardiac, hepatic, renal, respiratory, endocrinologic, neurologic and hematologic disease that is not stabilized, or a past history of convulsions.
5. Any retinal disease or systemic illness with active retinal involvement (e.g. diabetes) that precludes the use of bright light.
6. Patients who have a history of severe allergies and multiple drug adverse reactions.
7. Regular or current use of other psychotropic drugs including lithium and tryptophan.
8. Patients treated with beta blocking drugs.
9. Hypertensive patients being treated with guanethidine, reserpine, clonidine or methyldopa (because of possible mood-altering effects of those drugs).
10. Use of monoamine oxidase inhibitors within 14 days of Visit 1 (to ensure no drug interactions between fluoxetine and MAOIs), or use of heterocyclic antidepressant within 7 days of Visit 1 (to ensure adequate washout period of two weeks between stopping previous drug and start of treatment at Visit 2).
11. Previous use of fluoxetine or light therapy.
12. Treatment resistance in the current episode, as defined by failure (lack of clinically significant response) of two or more antidepressants given at therapeutic doses for at least 6 weeks.
13. Patients who started formal psychotherapy (e.g. cognitive-behavioural or interpersonal psychotherapy) within 3 months of Visit 1, or who plan to initiate such psychotherapy during this study.
14. Patients involved in any other form of treatment for depression.

#### Sample Size

Based on a power analysis using a minimal clinically important difference (MCID) and data derived from the largest and highest quality study of light and medication treatment for MDD (Martiny et al, 2005), we propose a sample size of 216 patients overall, or at least 54 randomized to each of the 4 groups with allowance for a 20% dropout rate (the average in our previous studies), recruited over 3 years. With regard to the primary hypothesis, this sample size will allow us to detect a difference of 3.5 points on the MADRS (widely regarded as a MCID in depression

treatment studies) between conditions with 80% power at two-sided testing at a Bonferroni-corrected  $\alpha=0.017$  (3 planned comparisons: fluoxetine vs. placebo, light vs. placebo, light+fluoxetine vs. placebo).

For the secondary hypotheses, a sample size of 216 patients will allow us to detect a risk difference in response or remission rates of 15% between conditions. It also allows us to detect a minimal difference between means of at least 5 points on scale scores such as quality of life measures, based on an anticipated pooled standard deviation of 8 points (based on previous studies, e.g., Michalak et al, 2005), at 80% power and an alpha of 0.05 on two-sided testing. Again, these differences are considered clinically meaningful and are similar to the effect sizes seen in meta-analyses of antidepressant drugs vs. placebo.

## **E. Treatments**

### Treatment Device Method

The active treatment consists of a fluorescent (4000 Kelvin broad spectrum) light box that emits 10,000 lux ( $2600 \mu\text{w}/\text{cm}^2$ ) white light measured by digital photometer at the level of the cornea when subjects are positioned at 18 inches from the screen. The light box will be fitted with a screen that filters out wavelengths below 400 nm (ultraviolet wavelengths).

Subjects will be given standardized instructions on how to use the light box (supplied by Uplift Technologies, Canada). In summary, subjects will be instructed about properly positioning themselves and the light box to maintain the correct distance to the light source. A measuring cord attached to the light box will be used to ensure that the distance is properly maintained. They will be instructed to stay awake with their eyes open during light exposure, but they will not be required to look directly at the light source, i.e., they can read or eat during the light treatment. The instructions will be repeated at each clinic visit. Subjects will take home the light box and sit under the light box for 30 minutes, within 15 minutes of arising from habitual wake time.

The placebo control treatment consists of a negative ion generator (SphereOne Inc.) modified to emit an audible hum, but which is deactivated so no negative ions are emitted. This credible placebo condition has been used in previous studies by our group and others (Desan et al, 2007; Eastman et al, 1998; Goel et al, 2005).

The same instructions as used for the light box will be used for the ion generator. Patients will be instructed to use the ion generator for 30 minutes, within 15 minutes of arising from habitual wake time.

To improve and monitor adherence to the protocol, each treatment device will be fitted with a computer chip that records the time when the device is turned on. This will provide a post hoc assessment of treatment adherence.

### Antidepressant Medication Method

Study drugs will be administered on a once-a-day (morning) treatment regimen. At each visit patients will be given bottles from their randomly assigned patient kits. Each capsule will contain either fluoxetine (20 mg), or placebo. A capsule count will be taken at each visit throughout the study and recorded on the web-CRF (Case Report Form).

## F. Procedures and Methods (also see Summary of Procedures, Appendix 1)

The study begins with a screening visit to establish eligibility for the study and to obtain informed consent. A script will be used to explain the study objectives to subjects. They will be told that the study will involve taking active or inactive treatments, including a placebo pill, and that we are studying different light and ion treatments that may or may not be effective. A similar script and procedure has been approved by the IRB in previous UBC light treatment studies.

Once patients have agreed to participate in the study by signing the ICD, the following will then be completed and recorded:

1. Full medical and psychiatric history, including the MINI.
2. Structured Interview Guide for the Hamilton Depression Rating Scale (HAMD), which generates the Ham-17 with established reliability.
3. CGI-Severity
4. Seasonal Pattern Assessment Questionnaire (SPAQ).
5. Adult ADHD Self-Report Scale (ASRS)
6. Relationship Styles Questionnaire (RSQ)

### Study Phase I

Study Phase I, lasting one week, is an initial observation period to establish baseline pre-treatment routines. It commences at Visit 1 (screening) and finishes at Visit 2 (randomization). Subjects will keep track of sleep times, treatment device times, and times spent outdoors in a daily log that will be collected at each weekly visit. Visits for other health-related services (family physician, emergency room, etc) will also be tracked using the Health Economic Assessment.

### Study Phase II

Study Phase II is an 8-week, “double-blind” treatment period that commences at Visit 2 (randomization visit). Subsequent evaluation will be scheduled at one-week intervals for the first 2 visits, then two-week intervals for the next 3 visits, concluding at Visit 7, or upon termination. During this treatment phase, patients will take one tablet of study medication (fluoxetine 20 mg, or placebo) daily and will use the treatment device (light box or ion generator) for 30 minutes daily.

At Visit 2, patients will be discontinued from the study if they show significant spontaneous response. Spontaneous response is defined as greater than 25% reduction of Ham-17 between Visit 1 and Visit 2, or if the Ham-17 at Visit 2 is 19 or less.

At Visit 2, subjects will be instructed on the use of the assigned treatment device and medication, and will then complete an Expectation of Response questionnaire modeled on a questionnaire by Borkovec and Nau (1972). Subjects will take home the treatment device to use for the duration of the study. Adherence to the protocol will be reinforced and monitored at each study visit. A daily log will be completed by subjects to record their use of the treatment device, and they will telephone the Centre and leave a time-stamped voice-mail message each day when using the device. These logs will be inspected at each visit throughout the study and recorded on the web-CRF.

In summary, the following clinical efficacy parameters will be recorded at Visit 2.

1. Expectation of Response Questionnaire (Visit 2 only)
2. Ham-17



The following clinical efficacy and safety parameters will be repeated at Visits 2 through 7.

1. Combined MADRS/Ham-24 (by telephone with a rater blind to treatment condition using the SIGMA/SIGH-SAD)
2. CGI (Severity and Improvement)
3. QIDS-SR
4. Adverse Events Scale
5. Health Economic Assessment
6. LEAPS (Visits 2, 5 and 7 only)
7. QLESQ (Visits 2, 5, and 7 only)
8. MEQ (Visits 2, 5, and 7 only)
9. Weight (Visits 2, 5, and 7 only)
10. FSS (Every 2 weeks)
11. PSQI (Visits 2, 5, and 7 only)

Patients will be encouraged to contact the investigator or a member of the research staff at any time between visits concerning adverse events or worsening of symptoms. Adverse Events will be classified as mild, moderate or severe. These are defined according to widely used criteria in antidepressant clinical trials as follows:

1. Mild event - noted change in patient condition that does not affect activity.
2. Moderate event - mild disruption in usual activity.
3. Severe - major disruption in usual activity. The investigator shall promptly report all adverse events to the Study Coordinator by prompt submission of the web-CRF. **IF THE ADVERSE EVENT IS ALARMING, IT SHALL BE REPORTED TO THE STUDY COORDINATOR IMMEDIATELY BY TELEPHONE.** Serious events requiring immediate notification by telephone to the Study Coordinator are those events which:
  - a) Result in death
  - b) Are life threatening
  - c) Are severely or permanently disabling
  - d) Require inpatient hospitalization or prolongation of an existing hospital stay
  - e) Result in an incidence of cancer
  - f) Result from a drug overdose or reaction after drug withdrawal.

The following compliance parameters will be collected/reviewed at Visit 2 through Visit 7.

1. Daily logs of time spent using treatment device
2. Capsule counts from medication blister packs.

## **G. Concomitant Therapy**

Drugs which may be taken by the subject include any prescription or over-the-counter medication not specifically excluded in the protocol. These may include aspirin, birth control pills, vitamins, etc.

Drugs that must **NOT** be taken by the subject during the course of the study include: sympathomimetics; CNS depressants; narcotics; monoamine oxidase inhibitors; antidepressants; amino acids (including tryptophan and tyrosine); hypnotics; modafinil; melatonin or melatonin agonists; beta blocking drugs; other psychotropic drugs including lithium, psychostimulants (e.g.,

d-amphetamine, methylphenidate), antipsychotics and benzodiazepines, and herbaceuticals (e.g., St. John's wort). Patients requiring excluded concomitant drugs will be discontinued from the study.

## **H. Data Safety Monitoring Committee**

An independent physician and biostatistician not involved in the trial will comprise the Data Safety Monitoring Committee (DSMC). Although we do not anticipate serious adverse events, the DSMC will monitor all adverse events reports. They will have access to the randomization codes, if necessary, to determine if a particular condition is associated with serious adverse events.

## **I. Quality Assurance**

### Compliance Monitoring

Methods for quality assurance will be strictly observed. A start-up videoconference involving the study site personnel (principal investigators, co-investigators, and research assistants) and the Study Coordinator will be held prior to commencing the study. During this meeting, great care will be taken to fully explain the study procedures and web-CRF completion.

Inter-rater reliability for the MADRS/Ham-24 will be established and confirmed for the telephone raters using taped interviews. Previous studies by the co-investigators have established the reliability of these outcome measures.

Each year throughout the study, the Study Coordinator will regularly visit each site to ensure that accurate and complete data are collected and properly recorded. At least 25% of all records will be randomly selected and the web-CRF will be manually audited against original charts and documents.

The web-CRF will be constructed to collect the data required by the protocol (see Data Management section). All data and information requested on the web-CRF must be completed by the investigator and/or their research staff, including results of clinical examinations. Completion of each web-CRF will be verified weekly by the Study Coordinator.

### Concealment of Allocation and Maintenance of Blinded Assignment

There will be a central computerized randomization process, stratified for site and randomized in random blocks of 4 or 8. Concealment of allocation will be accomplished using a computerized web-based system that reveals the treatment allocation only after the subject is assigned a unique subject number. Site-specific randomization codes will be kept at each site, with 24-hour availability in the (very unlikely) event that the blind needs to be broken for urgent medical reasons.

During the protocol, specific measures will be taken to maintain the blind for subjects. Subjects will be instructed not to talk about their treatment device. Subjects will not be scheduled for appointments at the clinic at the same time, so they will not be able to talk among themselves. Research personnel will minimize time with the subject and will not discuss the treatments with them.

### Data Management

Data will be managed and analyzed by the Verity Strategy Group Inc. This group has extensive experience in managing large datasets and procedures in place to ensure integrity and

verification of data handling and analysis. They will design the web-Case Report Form (CRF) as a web-based dataform on a secure web site, for direct data entry by research staff.

## **J. Early Terminations**

Every effort will be made to keep the subject in the study for the duration of the study. Acceptable reasons for premature discontinuation include the following:

1. Request of subject.
2. Decision of the investigator.
3. Serious adverse events.
4. Protocol variance (e.g. non-compliance).

## **K. Data Analysis**

All randomized subjects who receive treatment will be included in the analysis based on intent-to-treat, defined as randomized subjects who have at least one follow up rating. Ineligible subjects who are inappropriately randomized will be excluded from the analysis. Eligibility will be reviewed by the independent adjudication committee (chaired by Dr. Lam) blind to assigned treatment and response.

For the analyses the treatment variables will remain coded and the analysts and investigators will remain blinded to variable identity during analysis and interpretation.

The change from baseline to Week 8 (or termination) in the MADRS is the primary endpoint. In order to preserve comparability with previous depression treatments studies, a similar method of analysis will be used. Missing data will be imputed using last observation carried forward (LOCF). An ANOVA on the change scores will be conducted using preplanned pairwise contrasts.

The secondary outcomes will also be analyzed using a similar ANOVA analysis, when appropriate. Categorical data (such as proportions of the sample with adverse events) will be analyzed using binary logistic regression with preplanned pairwise contrasts, chi-square tests and Fisher's exact test where cell sizes warrant.

A secondary confirmatory analysis will also be conducted using a mixed-effects model with repeated measures (MMRM), under the missing at random framework (Gueorguieva and Krystal, 2004). The baseline MADRS score will be used as a covariate under this model. This model will include treatment condition and visit factors as class fixed effects and subject as random effect as well as two interaction terms between treatment condition by visit and covariate by visit, and subject as random. The treatment condition factor will have 4 levels (two monotherapies, one placebo condition, and one combination condition) and the visit factor will have 4 levels (each of the 4 treatment visits). This model using all available post-baseline evaluation in Phase II will provide the baseline adjusted least-squares means (LS-means) estimates at Week 8 by treatment condition, as well as the differences of these estimates versus placebo conditions, with their corresponding standard errors, degrees of freedom, t-test statistics and associated 95% confidence intervals. The t-test statistic at Week 8 will be used to determine the statistical significance of the primary efficacy comparisons of active versus placebo conditions.

## **L. Informed Consent and Ethical Considerations**

The investigator will prepare a written Informed Consent Document (ICD). The subject will read the ICD and the investigator will answer any questions he/she may have. The subject must indicate willingness to participate in the study by signing the ICD. The document must also be signed by a witness and an investigator. A copy of the signed ICD will be submitted to the Study Coordinator.

This study will be conducted according to guidelines established by Good Clinical Practice (Food and Drug Administration, [www.fda.gov/oc/gcp/regulations.html](http://www.fda.gov/oc/gcp/regulations.html)). The Institutional Review Boards (IRBs, or research ethics committees) of each participating site must approve the protocol and ICD. Each investigator will provide the Study Coordinator with evidence that their IRB has approved the study before subjects are entered at that site.

## **M. Publications and Communications**

This trial will be registered at [www.clinicaltrials.com](http://www.clinicaltrials.com) and at the Cochrane Collaboration clinical trials registry in accordance with the policy from the International Committee of Medical Journal Editors (De Angelis et al, 2004). The results of this trial will be presented at scientific conferences and published, using the CONSORT guidelines, in a peer-reviewed scientific journal.

## **N. List of Trial Site Investigators**

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## **O. References**

Please refer to Research Proposal, p.12 of the Research Module.

**P. Appendix**

## Summary of Procedures

Item	Visit 1 Screen	Visit 2 Week 0	Visit 3 Week 1	Visit 4 Week 2	Visit 5 Week 4	Visit 6 Week 6	Visit 7 <sup>a</sup> Week 8
Physician: ICD signed	X						
Physician: MINI/C-CASA	X						
Physician: Eligibility	X						
Physician: Demographic info	X						
Physician: Ham-17	X	X					
Study Coordinator (SC): SPAQ*/ASRS*/RSQ*	X						
SC/Web: Expectation of Response*		X					
Telephone: MADRS+Ham-24		X	X	X	X	X	X
Physician: CGI (-S and -I)		X	X	X	X	X	X
SC: Health Economic Assessment		X	X	X	X	X	X
SC/Web: QIDS-SR*		X	X	X	X	X	X
SC/Web: Adverse Events Scale*		X	X	X	X	X	X
SC/Web: FSS*		X		X	X	X	X
SC/Web: LEAPS*		X			X		X
SC/Web: Q-LES-Q*		X			X		X
SC/Web: PSQI*		X			X		X
SC/Web: MEQ*		X			X		X
SC: Weight		X			X		X
SC: Height		X					
SC: Device/drug instructions		X	X	X	X	X	
SC: Handout/return device		X					X
Physician: Debrief							X

<sup>a</sup> or Termination visit, if patient withdraws.

\* patient-rated.