NCT02720198

Study Proposal Full Protocol

Title: A randomized, rater-blinded trial comparing efficacy and tolerability and changes in neurocognition and apathy of a switch to levomilnacipran extended release (ER) versus adjunctive quetiapine extended release for patients who have shown inadequate relief with Selective Serotonin Reuptake Inhibitors (SSRIs) in Major Depressive Disorder (MDD).

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I. BACKGROUND AND RATIONALE:

As increasing number of antidepressants has become generically available, the generic penetration of the antidepressant market in the US has increased from about 41% in 2004 to about 73% in 2010 (Ventimiglia and Kalali, 2010). Although generic SSRIs are widely used, they continue to suffer from several limitations including variability of response, intolerable side effects and high discontinuation rates. In real world settings, clinicians frequently switch patients between different antidepressants for efficacy and/or tolerability reasons.

The efficacy of extended-release (ER) levomilnacipran has been established for major depressive disorder (MDD) in doses ranging from 40 mg/day to 120 mg/day (Sambunaris et al, 2014; Asnis et al, 2013). Levomilnacipran is the most noradrenergically active of the SNRI class of antidepressant drugs. Levomilnacipran was found to have twofold greater potency for norepinephrine relative to serotonin reuptake inhibition, and 17 and 27 times higher selectivity for norepinephrine reuptake inhibition compared with venlafaxine and duloxetine, respectively (Auclair et al, 2013).

Cognitive dysfunction in MDD is common and associated with greater impairment in functioning and quality of life. Given the similarities in mechanisms of action, it is possible for levomilnacipran to have beneficial effects on neurocognition. Apathy is considered a disorder of motivation and can occur in neuropsychiatric syndromes as well as depression. It is associated with neurocognitive disturbances and functional impairment. It remains understudied in depression.

Augmentation by adjunctive atypical antipsychotics is recommended as one of the clinical strategies on par with antidepressant switch in the APA guidelines to treat MDD. Quetiapine (extended release) is an atypical antipsychotic approved as adjunct to antidepressants for treatment of MDD in doses between 150-300 mg/day and has been extensively used in clinical practice.

Needs assessment: There is a significant unmet clinical need in terms of patients with MDD who show inadequate response and remission with SSRI treatment. Scientific evidence that guides appropriate treatment strategies in terms of further steps of switching or augmentation of medications will improve clinical care in patients with MDD who do not show adequate response to SSRIs.

II. STUDY OBJECTIVE(S):

Primary:

1. To compare the efficacy and tolerability of switching to levomilnacipran ER (40-120 mg/d) versus augmentation with quetiapine 150-300 mg/day to the patients' existing treatment for patients with inadequate relief on generic SSRIs in patients with MDD.

Secondary:

1. To examine the response and remission rates following the switch from generic SSRI to levomilnacipran ER and augmentation with quetiapine.
2. To examine changes in neurocognitive and apathy measures after switching from SSRI to levomilnacipran and after augmentation with quetiapine in MDD

III. STUDY DESIGN and PLAN:

Methodology:

This is an 8-week, randomized rater blinded parallel group, 2-arm trial to comparing a switch to levomilnacipran ER versus augmentation with quetiapine.

Participants who meet inclusion/exclusion criteria for inadequate response to existing antidepressants will be randomly assigned (1:1 ratio) to either levomilnacipran ER or augmentation with quetiapine and their existing antidepressants in the same dose for 8 weeks. A flexible dose regime of levomilnacipran ER 40-120 mg/d mg per day will be employed with titrating doses starting at 20 mg/d on Days 1-2, increasing to 40 mg/d on Days 3-7 in week 1, then flexibly dosed between 40 mg/d -120 mg/d during weeks 2 through 8. FDA approved package insert guidelines will be followed for the adjunctive

quetiapine dosing. Quetiapine will be started at 50 mg/d on Day 1-2, increasing to 150 mg/d on Days 3-7 in Week 1 and then flexibly dosed between 150-300 mg/d during Weeks 1 through 8 along with their current antidepressant. Patients who cannot tolerate the higher dose of levomilnacipran ER or quetiapine will have their dose reduced to a lower dose per the investigator's judgment. The primary efficacy measure rating will be performed by a blinded rater.

IV. STUDY POPULATION:

A. A total of 60 subjects (n=30 in each group) will be studied at 2 sites. A total of 40 subjects will be screened for a total of 30 eligible subjects to be enrolled at Duke.

B. Potential participants will be identified by self-referral via the printed ad, phone Script, the patients' physicians, local health providers, mental health providers, or Duke providers; if not self-referred, the potential participant will have the study introduced by a care provider known to them as meeting the inclusion criteria will be offered basic information about the protocol by the PI or Study Coordinator and if interested, provided with an appointment for the purposes of obtaining informed consent and screening assessments.

During the phone screen interview the study coordinator will collect specific protected health information (PHI) for ascertaining subject eligibility and to determine if an appointment should be set up. If the is ineligible to participate or decides not to participate in the study, the PHI will be destroyed. The PI or Study Coordinator will also clearly explain to them that a refusal to participate in the study will not affect their participation to treatment at their regular treating physician or Duke University Medical Center (DUMC).

C. Inclusion Criteria

- Male or Female - ages 18-65 years of age inclusive
- Current diagnosis of Major Depressive Disorder based on DSM-IV criteria

- Able to understand study rules and procedures and willing to sign written informed consent for study participation

- Inadequate response to antidepressants: having a score of ≥14 on the 17-item HAMD and not having a ≥ 50% reduction in HAMD or CGI-S scores from baseline after a retrospective confirmation of an adequate trial of a single antidepressant (defined as a minimum 6-week trial of acceptable therapeutic dose (daily dose ≥ 40 mg of fluoxetine, 40 mg of paroxetine, 20 mg of citalopram, 10 mg of escitalopram, 37.5 mg of paroxetine CR, 150 mg of sertraline, 100 mg of fluvoxamine).

If female, nonpregnant/nonlactating status

- Duration of current MDD ≥ 4 weeks and < 24 months

  Not more than 2 treatment failures of adequate antidepressant trials for current episode of MDD

D. Exclusion Criteria

- Has previously participated in a levomilanacipran ER or quetiapine XR or quetiapine clinical study in previous 12 months
- Has 1 or more the following: Current or past history of: manic or hypomanic episode, schizophrenia or any other psychotic disorder defined in the DSM- 5
- Diagnosis of alcohol or other substance use disorder (except nicotine and caffeine) as defined in the DSM-5 that has not been in sustained full remission for at least 6 months prior to screening (participant must also have negative urine drug screen prior to baseline).
- Presence or history of a clinically significant neurological disorder (including epilepsy)
- Poorly controlled Hypertension or Diabetes
- uncontrolled narrow-angle glaucoma
- hypersensitivity to levomilnacipran, milnacipran , quetiapine or quetiapine XR
- Neurodegenerative disorder.
- Has a thyroid stimulating hormone value outside the normal range at the Screening Visit that is deemed clinically significant by the investigator.

- Has clinically significant abnormal vital signs as determined by the investigator.
- Has a clinical significant abnormal electrocardiogram.
- Has screening laboratory values greater than 2.5 times the upper or lower limits of normal range or judged to be clinically significant
- Has a disease or takes medication that, in the opinion of the investigator, could interfere with the assessments of safety, tolerability, or efficacy or prevent the individual from completing the study. Female subjects of childbearing potential not on adequate contraception methods in the opinion of the investigator
    - If the female is childbearing, she must agree to use appropriate contraceptive measures for the duration of the study and for one month afterwards. Medically acceptable contraceptives include: (1) surgical sterilization (such as tubal ligation of hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants, or injections), (3) barrier methods (such as condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B ™, sold for emergency use after unprotected sex, are not acceptable methods for routine use. If the female does become pregnant during this study she must inform the study physician immediately.
- Has a significant risk of suicide according to Columbia Suicide Severity Rating Scale (CSSRS) or in the clinical judgment of the investigator
- History of suicide attempt in the previous 12 months
- MDD with postpartum onset, psychotic features or seasonal features
- Hamilton Anxiety Scale (HAM-A) baseline score ≥ 24
- Failure of ≥ 3 adequate trials of different antidepressants for the current episode of MDD
- ≥ 3 episodes major depression in previous 12 months or ≥ 8 lifetime episodes of MDD
- Current or previous use of an atypical or typical antipsychotic agent for augmentation of major depression or treatment of psychotic depression, mania psychosis, or agitation. Previous use of antipsychotics for insomnia will be permitted.

V. STUDY PROCEDURES

A. Blinding and Controls:

The study will be rater blinded, randomized, parallel study. Patients will be randomized in 1:1 ratio to levomilnacipran ER switch arm or adjunctive quetiapine arm. Subjects will be instructed not to discuss any clinical issue with the blinded rater. The blinded rater will be specifically instructed to perform specified ratings only and not to address or ask any other study related questions.

B. Drugs, Dosages, and Regimens:

All allowed concomitant medications will be unchanged throughout the study. Other psychotropic medications will require a 2-4 week washout, depending on the half life of the applicable medication after the subject is deemed eligible after the screening visit. Subjects will be monitored weekly by phone for side effects or symptom worsening during the taper. Subjects randomized to the Levomilnacipran switch arm will have their SSRI tapered over 2-4 weeks after they are determined to be eligible for the study to avoid risk of discontinuation syndrome. Subjects randomized to the adjunctive quetiapine arm will have their pre-existing antidepressants continue unchanged at baseline. A flexible dose regime of levomilnacipran ER 40-120 mg/d mg per day will be followed with the FDA approved package insert. Initial titration dose will bet 20 mg/d Days 1-2, increasing to 40 mg/d from Days 3-7 in week 1, flexibly dosed between 40 mg/d - 120 mg/d week 2 to week 8. FDA approved package insert guidelines will be followed for adjunctive quetiapine dosing. Adjunctive quetiapine will be started at 50 mg/d Day 1-2, increasing to 150 mg/d Days 3-7 and flexibly dosed between 150-300 mg/d week 1-8. Patients who cannot tolerate the higher dose of levomilnacipran ER or quetiapine will have their dose reduced to the lower dose per the investigator's judgment. At the end of the 8-week trial, subjects in each group will have 1-week taper of study drug. A week 9 follow up safety assessment will be performed. Subjects will be told how to safely restart their

prior medication or can be provided with a referral for continued treatment as needed.

Any new medication started during the study will be evaluated by the investigator to determine its effect on study integrity and subject safety. Subjects and primary raters will be blinded to study drug and doses.

Arm I: Levomilnacipran ER flexible dose regime (40-120 mg/d): titration dose of 20 mg po once a day from days 1-2, then 40 mg po once a day, 80mg po once a day or 120 mg once a day.

Arm II: Quetiapine flexible dose regime: 50 mg po once a day as initiating dose, 150 mg po once a day (during the period that the subjects will be titrated on 150 mg; they will be given 1-50mg tab and 1-100 mg tab with instructions to be taking once per day) (, then 300 mg po once a day.

C. Visit specific procedures and sequence:

This is an 8-week trial with a 1 week (week 9) safety follow up visit. Visits will be planned to occur at the screening visit and weeks 0, 1, 2, 3, 4, 6, 8 and 9.

The following activities and/or assessments will be performed at/during the Screening visit (Week -4 to Week 0):

- Obtain written informed consent prior to performing any of the formal screening procedures.
- Administer the M.I.N.I
- Administer the C-SSRS, MADRS, ASEX, HAM-D, HAM-A, DSST, CGI-S, RVLT, Spontaneous Reported AEs and Sheehan Disability
- Record demographic information
- Obtain medical and surgical and psychiatric history
- Record prior and concomitant medications
- Record vital signs (temperature, heart rate, supine and orthostatic blood pressure), body height and body weight
- Perform a complete physical examination
- Perform a 12-lead ECG

- Collect blood and urine samples for evaluation of standard laboratory safety test (chemistry, hematology, and urinalysis)
- Assess all applicable inclusion and exclusion criteria
- Schedule the baseline visit for those subjects that do not require washout of prohibited medications
- Subjects requiring washout of prohibited medication will be provided washout requirements
    - Subjects in adjunctive quetiapine arm will be permitted to continue their pre-existing antidepressants if FDA approved for depression; if not FDA approved, they will be switched to an FDA approved medication for the duration of the study but will undergo washout of other prohibited medications
- Provide instructions on washout of prohibited medication(s), including the duration of the washout period (if needed)
- Assess for and record AEs and concomitant medications

Once potential eligibility is confirmed, the investigator, or a person designated by the investigator, will contact the subject by telephone at or during the Randomization/Baseline (Week 0):

- Determine appropriate duration of the washout period of prohibited medication(s), taking into account any labeling requirements for tapering of medication dose(s), as well as the minimal washout requirements
    - Weekly phone calls will include a Symptom Checklist, consistent with symptoms of Major Depression, suicidal risk and adverse events, which the Study Coordinator will review with the subject. Any potential concerns will be reviewed with the subject. Any potential concerns will be discussed with the PI and appropriate interventions for subject safety will be planned. The same symptom checklist and monitoring plan for the subjects will be used at the Duke and the non-Duke site.
- Assess all applicable inclusion and exclusion criteria

- Administer the C-SSRS, MADRS, ASEX, HAM-A, DSST, CGI-S, RVLT, AES, Spontaneous Reported AEs and Sheehan Disability
- Assess for and record AEs and concomitant medications
- Dispense study medication

The following activities and/or assessments will be performed at Weeks 1 through Weeks 6:

- Assess for and record AEs and concomitant medications
- Administer the C-SSRS, MADRS, ASEX, HAM-A, DSST, CGI-S, RVLT, AES, Spontaneous Reported AEs and Sheehan Disability
- Collect study medication and review medication compliance
- Dispense study medication

The following activities and/or assessments will be performed at Week 8: End of Study or Early Termination:

- Assess for and record AEs and concomitant medications
- Collect study medication and review medication compliance
- Record vital signs (temperature, heart rate, supine and orthostatic blood pressure), and body weight
- Collect blood and urine samples for evaluation of standard laboratory safety tests
- Administer the C-SSRS, MADRS, ASEX, HAM-A, DSST, CGI-S, RVLT, AES, Spontaneous Reported AEs and Sheehan Disability
- Perform a 12-lead ECG

The following activities and/or assessments will be performed at the Week 9/ Safety Follow-Up Visit:

- Assess for and record AEs and concomitant medications
- Administer the C-SSRS, Spontaneous Reported AEs and the DSST

After all study assessments has been completed or if the participant completes an early term visit, the participants will be referred back to their outpatient treating physician for

psychiatric care. Participants who are uninsured will be referred to Lincoln Community Health Center or Durham Access. Results of the subject's participation will not be available to the subject before they return to their treating doctor.

Patient termination will occur if the patient experiences a clinically significant worsening of MADRS scores in two successive visits or any worsening on CSSRS on two consecutive visits, or based on clinician judgment or patient preference.

D. Concomitant Medications and Therapy:

All medications for pre-existing medical conditions will be permitted to continue unchanged provided subjects are on a stable dose of at least 12 weeks. Subjects on prohibited concomitant mood stabilizers or atypical antipsychotics will require a 2-4-week washout of the prohibited medication after the subject meets all eligibility criteria at the screening visit. Washout of prohibited medication will be determined by the ½ life of the drug. Subjects on a minimum of 3 months of stable dose of hypnotics (e.g. zolpidem 10 mg per day or benzodiazepine dose of ≤ 2 mg per day of lorazepam or trazodone ≤ 100 mg per day) will be allowed to continue their hypnotic medication at the same dose. Over the counter medications will be permitted if in the opinion of the investigator, they are not considered to have any significant impact on the study. Any medication that has the potential to cause a clinical significant drug interaction with levomilnacipran ER or quetiapine in the judgment of the investigator will require a washout.

VI. STUDY MEDICATION

A. Description and Dispensing

a. Description and Dispensing

Levomilnacipran and quetiapine will be dispensed/administered at specified study visits.

b. Storage

All study medications will be stored in a double-locked cabinet in the Civitan Building. With available access only to the study investigator and research coordinator.

VII. CLINICAL ASSESSMENTS

Diagnostic Evaluation: The Mini-International Neuropsychiatric Interview (MINI) (version 6.6) for DSM-5 Axis I Disorders to establish diagnosis.

Study Parameters/Efficacy:

Efficacy:

The primary outcome measure will be:

Change from Baseline to end of treatment in Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score.

Secondary outcome will be:

Change from baseline to end of treatment in

Clinical Global Impression Scale- Severity (CGI-S) and Improvement (CGI-I) scores

Hamilton Anxiety Rating Scale (HAM-A) scores

Hamilton Depression Rating Scale (HAM-D) scores

Sheehan Disability Scale (SDS) total score.

Scores on Digit symbol substitution test (DSST)

Scores on Reyes Verbal Learning Test (RVLT).

Scores on Apathy Evaluation Scale (AES).

Safety/Tolerability:

Safety and tolerability will be assessed by spontaneously reported adverse events, Columbia Suicide Severity Rating Scale (CSSRS) Arizona Sexual Experience Scale (ASEX) scores, vital signs, weight and BMI measurements and clinical laboratory assessments and evaluating reasons for dropout from the trial.

Adverse event: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected adverse reaction: any adverse event for which there is a reasonable possibility that the drug caused the adverse event

Serious Adverse Event (SAE)

A serious adverse event is one that:

- Results in death
- Is an immediate threat to life?
- Requires inpatient hospitalization, or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect.

Causality Assessment

For all AEs, the Investigator must provide an assessment of causal relationship to the IP. Causal relationship must be assessed by answering the following question:
Is there a reasonable possibility the IP caused the event?
Yes: There is a possible or probable relationship (i.e., there is a reasonable or strong temporal relationship, and the events are unlikely to be attributable to other drugs, underlying diseases, or other factors). Challenge and/or rechallenge (if available) is positive.
No: The relationship is unlikely or nonexistent (i.e., there is no strong temporal relationship and/or the use of other drugs, underlying diseases, or other factors provide plausible explanations for the event), or the patient did not take the IP.

Reporting of Adverse Events:

All spontaneously reported and observed adverse events will be recorded in the source and CRF documents. The Principal Investigator will inform Actavis/Forest Global Drug Safety of all SAEs within 24 hours of first knowledge of any AE that meets one of the criteria for an SAE, on a SAE report form. If, during follow-up, any nonserious AE worsens and eventually meets the criteria for an SAE, that AE will be recorded as a new SAE.
The study centers will transmit the SAE report form to the SAE fax number (631) 858-7906) within 24 hours of first awareness of the event at the study center. Supplemental information will be submitted as soon as available and may include laboratory results,

radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

Reporting of Pregnancy to Allergan, Inc. / Forest Research Institute

Study center personnel will report every pregnancy on a pregnancy report form as soon as possible (within 24 hours of first awareness of the pregnancy to the Allergan, Inc. pregnancy fax number, (631) 858-7906), even if no AE has occurred, and follow it to term. If, however, the pregnancy is associated with an SAE (e.g., if the mother is hospitalized for dehydration), in addition to the pregnancy report form, a separate SAE report form will be filed.

Any Serious Adverse Event will also be reported to the Duke IRB, to the FDA within 24 hours. The FDA Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The FDA uses AERS to monitor for new adverse events and medication errors that might occur with these marketed products.

VII. STATISTICAL EVALUATION

A. Power analysis:

The proposed design levomilnacipran switch has never previously been studied in either a randomized or open-label design. Thus no direct pilot data exist upon which to base a power analysis. As is recommended for cases where pilot data are absent or minimal, clinical trials can be powered to detect clinically meaningful effect sizes. What is clinically meaningful depends on the illness and outcome being studied. According to mainstream resources, such as British National Institute for Health and Clinical Excellence (NICE), it is generally accepted that small effect sizes are not clinically meaningful, while medium effect sizes are. If one uses standardized effect sizes (Cohen's d) to determine clinical significance, the British National Institute for Health and Clinical Excellence (NICE) has suggested that d=0.50 should be the standard general threshold for "clinical significance" in drug treatments (www.nice.org.uk). This standard has been applied to assessing efficacy in RCTs with antidepressants in MDD (Kirsch et al., 2008).

Sample Size calculations for two-sided log rank test in survival analysis

Power	Proportion Response: Drug	Proportion Response: Placebo	Alpha	Number in each group
0.90	.33	.17	0.05	44
0.80	.33	.17	0.05	28
0.90	.45	.27	0.05	48
0.80	.45	.27	0.05	31

Using Cohen's d effect size to determine sample size, in Cohen's standard text on statistical power (Cohen, 1988), using the NICE definition of a d=0.5 or larger, we obtain an estimated sample size (given a two-sided alpha = 0.05 and 1 – Beta = 0.800) of n= 30 per arm or 60 for the study. A power analysis was also conducted based on an effect size estimate derived from the drug-placebo difference in primary outcome of MADRS scores in published levomilnacipran trials (Citrome, 2013). The summary of Least square mean change between drug and placebo at 95% CI was -4.9 ($p<.0001$). With a two-tailed alpha= =0.05, a sample size of n= 60 provides a power of 0.80.

B. Randomization Method

Randomization will occur with randomly generated computer lists held at the Duke site. This group will assign subjects according to a computer-generated the randomization sequence (without blocking or stratification) for each site. After the study coordinator determines eligibility, the participant will be randomized to one of two different arms. Drug capsules will be placed in standard medicine bottles. Each bottle will be dispensed individually by the study coordinator at the appropriate visit. Rater unblinding will be done at the end of the study after data lock. In case of any AEs or SAEs or other emergencies that require the blind to be broken, the pharmacy will have a 24-hour on call support service.

Power analysis was performed using an internet based software program. The results showed that a sample size of n=60 (n=20 in each of the 3 groups) could detect a strong effect with $\alpha = .05$, unless the true mean difference is quite minimal.

C. Plan of Data analysis

Subjects will be defined as able to be evaluated by two methods. The primary method will be an intent-to-treat analysis, including those who discontinue drug due to lack of efficacy or due to side effects. The secondary method will be completer analysis. The intent-to-treat (ITT) group will include randomly assigned patients receiving study drug with a post baseline efficacy assessment. The safety population will comprise all patients receiving study drug with a post baseline safety assessment.

Primary efficacy analysis will be conducted in the ITT population using the last-observation-carried-forward (LOCF) method. Treatment group comparisons will base on changes in MADRS from baseline to week 8/end of treatment from repeated measures ANOVA or analysis-of-covariance (ANCOVA) model containing treatment site, gender and baseline MADRS score included as a covariate.

Secondary efficacy analysis: Repeated measures ANOVA or ANCOVA models will be used to analyze change from baseline in secondary measures. Response and remission rates at end of treatment will be compared using the Cochran-Mantel- Haenszel test. No formal hypothesis testing will be performed on safety data. Safety outcomes will be summarized by treatment group and study visit (observed cases) using descriptive statistics. Any clinically significant findings among patients who terminated early will be discussed separately. All analyses will be conducted using SAS Version 9.1.3 (SAS Institute, Inc.; Cary, North Carolina). Statistical comparisons of efficacy outcomes will be 2-sided and considered significant at $P < .05$. Comparisons for secondary endpoints will be not adjusted for multiplicity.

D. Definition of Evaluable Subject (Safety and Efficacy)

Subjects will be defined as able to be evaluated by two methods. The primary method will be an intent-to-treat analysis, including those who discontinue drug due to lack of efficacy or due to side effects. The secondary method will be completer analysis.

XI: ETHICAL AND REGULATORY CONSIDERATIONS

A. Institutional Committee Approval

Duke University Health Systems Institutional Review Board (DUHS IRB) will need to approve the protocol at the Duke site. Dr Sambunaris' site will use an external IRB (e.g. Copernicus, Western) and provide Duke with a copy of its approval.

B. Informed Consent

Participation in this study is voluntary and at no cost to the subjects. All potential participants interested in this study must be thoroughly informed of the details of the study. Prior to study participation in this trial, each subject will have an opportunity to ask questions and will sign an approved informed consent form. The signed consent forms will be filed with the investigator's copies of the Case Report Forms for each subject and a copy provided to the subject. Any subject may voluntarily withdraw from the study at any time without prejudicing treatment.

C. Document Storage and Retention

Documents will be stored at the offices of the respective Principal Investigator Dr. Patkar at Duke and Dr Sambunaris at Atlanta. Medical records will be kept in accordance with Duke University Medical Center requirements. All research records and information obtained in this study will be kept in locked files and will be available only to research staff, Duke Institutional Review Board, the FDA, and personnel from Allergan, Inc. Computers will be password protected. Except when required by law, subjects will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Duke University Health System (DUHS).

The study results will be retained in the subject's research record for at 6 years after the study is completed, whichever is longer. At that time either the research information not already in the subject's medical record will be destroyed or information identifying the subject will be removed from such study results at

DUHS. Any research information in the subject's medical record will be kept indefinitely.

D. Protocol Amendments

Any protocol amendments will be accompanied by IRB approval and appropriate revisions of consent form documents.

E. Confidentiality of Data and Subject Records

Subject research charts will only be identifiable by initials and numbers when disclosed outside of the study site. No subjects will be identifiable in any published data produced from this study. HIPPA compliant deidentification procedures will be followed for any data analysis or dissemination.

F. Monthly Protocol Communication

Before subject enrollment, the PI's at Duke and the non-Duke site will plan a schedule of monthly teleconferences to review the following: Subject Enrollment, Screening Issues, Subject Compliance, Assessment Scales and Primary/Secondary Efficacy and Safety Measures, Adverse Events and Serious Adverse Events, Study Drug Storage and Dispensing, Data Collection and Data Entry.

Any potential concerns that may impact on subject safety, or study integrity, will be reviewed to decide if any protocol modifications and/or urgent communication with sites are necessary. If required, a Modified Protocol and Consent Form will be submitted to IRB for approval. The teleconferences will also include discussion of interim blinded data analysis and results.

ADDITIONAL INFORMATION REGARDING STUDY CONDUCT

A. Case Report and Other Forms

All case report and other forms will be contained in the study research chart of each subject.

B. Quality Assurance Audits

Charts will be made available as requested to the sponsor, the participating site IRBs, sponsor and the FDA or other federal regulatory bodies for quality assurance purposes.

C. Study Discontinuation/Termination

Patients will be discontinued from the study for the following reasons:

1. Initiation of any concomitant medications that are excluded from the trial
2. Development of any psychiatric or medical condition that are exclusion criteria.
3. Development of any side effects or adverse events that are sufficiently clinically significant in the opinion of the investigator to warrant discontinuation.
4. Clinical worsening sufficient to require hospitalization or other medication interventions in the judgment of the investigator.
5. Patient noncompliance with medications or appointments
6. Patient voluntarily withdraws consent or is lost to follow up.

X: REFERENCES:

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2014.

Auclair AL, Martel JC, Assié MB, et al. Levomilnacipran (F2695), a norepinephrine-preferring SNRI: profile in vitro and in models of depression and anxiety. Neuropharmacology. 2013; 70:338-347.

Asnis GM, Bose A, Gommoll CP, Chen C, Greenberg WM. Efficacy and safety of levomilnacipran sustained release 40 mg, 80 mg, or 120 mg in major depressive disorder: a phase 3, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2013; 74:242-248.

CItrome L Levomilnacipran for major depressive disorders. A systematic review of the efficacy and safety profile of this newly approved antidepressant. What is the number needed to treat and number needed to harm. Int J Clin Practice 2013; 67:1089-1104

Guy W. Clinical Global Impressions (028-CGI). In: ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: National Institute of Mental Health; 1976:216–222.

Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.

Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50–55.

Hawley CJ, Gale TM, Sivakumaran T; Hertfordshire Neuroscience Research group. Defining remission by cut off score on the MADRS: selecting the optimal value. *J Affect Disorder*. 2002; 72(2):177–184.

Hindmarch I, et al: Pharmacodynamics of milnacipran in young and elderly volunteers.Br. J. Clin. Pharmacology. 2000; 49: 118–125.

Kanetani K, et al: Therapeutic effects of milnacipran (serotonin noradrenalin reuptake inhibitor) on depression following mild and moderate traumatic brain injury. J. Nippon Med. Sch. 2003; 70: 313–320.

Marin RS, Biedrycki RC, Firiciogullari S. Reliability and validity of the apathy evaluation scale. Psychiatry Res 1991; 38:143–162.

McGahuey CA, Gelenberg AJ, Laukes CA, Moreno FA, Delgado PL, McKnight KM, Manber R. The Arizona Sexual Experience Scale (ASEX): reliability and validity. J Sex Marital Therapy 2000 Jan-Mar; 26(1):25-40.

Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979; 134(4):382–389

Zimmerman M, Posternak MA, Chelminski I. Defining remission on the Montgomery-Asberg Depression Rating Scale. *J Clin Psychiatry*. 2004; 65(2):163–168.

Posner K, Brent D, Lucas C, et al. Columbia-Suicide Severity Rating Scale (C-SSRS). http://www.cssrs.columbia.edu/docs/ C-SSRS_1_14_09_Baseline.pdf. Accessed September 22, 2011.

Sambunaris, A., Bose, A.,Gommoll, C., Chen, C., Greenberg, WM, Sheehan, DV. A Phase III Double-blind, Placebo-Controlled, Flexible-Dose Study of Levomilnacipran ER in Patients with Major Depressive Disorder. J Clinical Psychopharmacology 2014 34; 1.

Rickels K, Athanasiou M, Robinson D, Gibertini M, Whalen H, Reed C. Evidence for efficacy and tolerability in the treatment of major depressive disorder: A randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009; **70**(3):326-333.

Ventimiglia J, Kalali A. Generic penetration in the retail antidepressant market. *Psychiatry (Edgmont)* 2010; **7**(6):9-11.

XI: STUDY TIMELINE:

A startup period of 3 months for contract and IRB approval is anticipated. The projected enrollment is to be completed in 12 months, at a rate of 4 patients/month. With an 8 week trial, it will take 2 additional months for the last subject to complete last visit. It will take 2 additional months for the study data to be analyzed and ready for presentation. We anticipate he total time period for the trial to be 18 months.

All data will be analyzed by the Duke site. The PI and Co-Is are solely responsible for data analysis, interpretation of results, presentation and publication of data produced by this study. The results of this study will be presented at national Conferences (APA, NCDEU) and published in peer reviewed journals (Journal of Clinical Psychiatry).

XII: PUBLICATION PLAN:

Presented at APA Annual meeting 2017, NCDEU annual meeting 2017 and article submitted to Journal of Clinical Psychiatry end 2016.

XIV. SCHEDULE OF EVENTS:

STUDY VISIT SCHEDULE

Test	Week -4 Screening	Week 0: Randomization/ Baseline	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8: End of Study or ET	Week 9: Safety Follow-Up
Informed Consent	X								
Eligibility Criteria	X	X							
Demographic Data	X								
Medical/Surgical History	X								
Physical Exam	X							X	
Vital Signs	X							X	
Blood Samples & Laboratory tests	X							X	
Urine Samples Collect.	X							X	
ECG	X							X	
Psychiatric History/MINI	X								
Prior/concomitant meds	X	X	X	X	X	X	X	X	X
Washout instructions	X	X							
MADRS	X	X	X	X	X	X	X	X	
Columbia Suicide Severity Rating Scale	X	X	X	X	X	X	X	X	X
ASEX	X	X	X	X	X	X	X	X	
HAM-A	X	X	X	X	X	X	X	X	
HAM-D	X								
RVLT	X	X	X	X	X	X	X	X	
Spontaneous Reported AEs	X	X	X	X	X	X	X	X	X
DSST	X	X	X	X	X	X	X	X	
Sheehan Disability	X	X	X	X	X	X	X	X	
CGI-I and CGI-S	X	X	X	X	X	X	X	X	
Adverse event reporting	X	X	X	X	X	X	X	X	X
Drug Dispense/Account/Adjust		X	X	X	X	X	X	X	