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| Document Title: | **Statistical Analysis Plan** |
| Version: | 3.0 |
| Date: | April 1, 2021 |
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| Protocol Number: | |
| Study Title: | **Mood Stabilizer Plus Antidepressant versus Mood Stabilizer Plus Placebo in the Maintenance Treatment of Bipolar Disorder – Randomized Trial Phase** |
| Sponsor-Investigator: | Lakshmi N. Yatham |

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# 1.0 INTRODUCTION

## 1.1 Study Description

Patients with bipolar I disorder (BD) experience depression 3 times more frequently than mania, and antidepressants are prescribed as adjuncts to mood stabilizers in up to 70% of patients. However, no placebo-controlled trials have assessed the efficacy or safety of modern antidepressants in combination with mood stabilizers in the maintenance treatment of BD. This study is to assess the safety and the efficacy of antidepressants combined with mood stabilizers

in comparison to placebo plus mood stabilizers in the maintenance treatment of bipolar disorder.

## 1.2 Trial Design

The study is a multicenter, randomized, double-blind clinical trial to compare mood stabilizer plus antidepressant (escitalopram or bupropion XL) to mood stabilizer plus placebo in the maintenance treatment of Bipolar disease (BD). This trial consists of two separate phases: Open-label Acute Treatment Phase and Double-blind Maintenance Treatment Phase. This SAP is for the Double-blind Maintenance Treatment Phase (DBMTP).

Patients may enter the DBMTP either: (1) following successful completion of the open-label phase, defined as have adequately tolerated the combination of antidepressant plus mood stabilizer, and is currently in remission for ≥ 2 weeks and ≤ 8 weeks, (2) directly (without having been enrolled in the open-label phase) if there is evidence that the patient had entered remission with antidepressant plus antimanic mood stabilizing medication and the remission was within 2 to 8 weeks.

The patients continue treatment with their anti-manic medication(s), and will be randomized to 1) the "8 week arm": the antidepressant is tapered in a double-blind manner beginning at 6 weeks, and will be substituted with placebo by 8 weeks and continued up to 52 weeks; or 2) the "52 week arm": the antidepressant medication is continued up to 52 weeks. Randomization was stratified in permuted blocks of size 4 within combinations of:

- antidepressant type (escitalopram or bupropion XL)
- anti-manic medication(s)
- study site (Canada, India, Korean)

Patients visits occurs at baseline then week 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and a final visit at week 52 (or when they withdraw from the study).

## 1.3 Objectives

### 1.3.1 Primary

To assess whether continuing antidepressant treatment for 12 months reduces the risk of relapse into any mood episode, including depression, mania, and hypomania, compared to discontinuing the antidepressant and substituting it with placebo after 2 months.

### 1.3.2 Secondary

1) Does continuing antidepressant treatment for 12 months reduce the risk of relapse into depression?
2) Does continuing antidepressant treatment for 12 months increase the risk of developing a manic or hypomanic episode?
3) Do rates of subsyndromal mood symptoms and adverse events differ between patients who continue antidepressant treatment for 12 months compared to those who stop the antidepressant after 2 months?
4) Does 12-month antidepressant treatment improve overall health and quality of life for patients, compared to stopping treatment after 2 months?

### 1.4 Eligibility Criteria

#### 1.4.1 Inclusion

1) Taking escitalopram 10-30 mg/day or bupropion XL 150-450 mg/day, in addition to either a mood stabilizing medication (lithium, serum level 0.6-1.2 mEq/L, divalproex, serum level 350-700 mM or carbamazepine, serum level 20-50 umol/L), an SGA (risperidone 1-6 mg/day; olanzapine 5-30 mg/day; quetiapine IR or XR 150-900 mg/day; aripiprazole 10-30 mg/day; or ziprasidone 80-160 mg/day), two mood stabilizers, a mood stabilizer plus an SGA (including asenapine 5-20 mg/day), or a mood stabilizer or SGA plus lamotrigine (100-400 mg/day).
2) Has adequately tolerated the combination of antidepressant plus mood stabilizer and is currently in remission for ≥ 2 weeks and ≤ 8 weeks.
3) If female and of childbearing potential, is using an adequate method of contraception.

#### 1.4.2 Exclusion

If a patient meets **any** of following criteria, she/he was excluded from the study:

1) Has a history of rapid cycling, defined as ≥ 4 mood episodes in the preceding 12 months.
2) Has current manic, hypomanic, or subsyndromal hypomanic symptoms, defined as a YMRS score ≥ 8 at the screening or baseline visits.
3) Has active substance dependence, other than caffeine or nicotine dependence, in the preceding 3 months. Otherwise, patients with comorbid substance abuse or other comorbid psychiatric illnesses will be eligible to participate in the study.
4) Is at high risk for suicide, as defined by a score of ≥ 4 on the suicide item of the MADRS, or in the opinion of the investigator.
5) Has an unstable medical illness, as defined by a change in medication or other treatment in the past 4 weeks, or in the opinion of the investigator.
6) Has significant abnormalities on an electrocardiogram.
7) Is pregnant or lactating.
8) Has experienced an episode of mania, hypomania, or a mixed episode during antidepressant treatment of the acute depression, defined as a YMRS score of ≥ 16 at any open-label study visit, or in the opinion of the study psychiatrist.

## 2.0 DATA SUMMARIES AND ANALYSES

### 2.1 Data analysis general information

Study data will be analyzed using the most updated SAS version and/or R in PC environment. All statistical tests will be two-sided, with significance levels of 0.05.

### 2.2 Trial Information and Patient Disposition

The following information will be presented:

- number of participants enrolled
- number of participants completing each visit of follow-up
- median follow-up time
- frequency table for the reasons for going off-study (from the “Off Study” CRF)
- frequency table for the reasons for discontinuation (from the “Permanent Discontinuation

from Protocol" CRF)
- a CONSORT Flow Diagram

## 2.3 Baseline and Demographic Variables

Summary statistics such as the mean, median, standard deviation, minimum, maximum and inter-quartile range for continuous variables and the number and percentage of participants with various levels of categorical variables will be calculated for ***all participants enrolled*** for the following variables. All summary statistics will be calculated for each treatment group individually as well as for all treatment groups combined. Also, these summaries will be computed separately for the escitalopram and bupropion XL groups.

| CRF | Field |
|---|---|
| E.g., Screening - Demographics | • Age<br>• Gender<br>• Ethnicity<br>• Marital status<br>• Occupational status<br>• Treatment location (inpatient versus outpatient)<br>• Age at onset of illness<br>• Numbers of previous depressive, manic, and hypomanic episodes<br>• Length of current depressive episode<br>• Drug combination<br>• Baseline MADRS, IDS-S, IDS-CR, HAM-A, YMRS, CGI-S-BD, and QLESQ scores |

## 2.4 Primary Outcome

### 2.4.1 Primary Analysis

The primary outcome is time to occurrence of any mood episode (manic, hypo-manic, depressive). Occurrence of mood episode was defined as any one of following:

1) hypomanic episode defined as a YMRS score ≥ 16;
2) manic episode defined as a YMRS score of ≥ 20;
3) depressive episode defined as a MADRS score ≥ 20;
4) a CGI-S-BD of ≥ 4;
5) hospitalization for a mood episode;
6) additional treatment required for a mood episode in the judgment of the treating psychiatrist;
7) a MADRS suicide item score ≥ 4;
8) attempted or completed suicide.

Kaplan-Meier curve will be used to summarize the time to any mood episode by treatment arm. Ae Cox proportional hazards model will be used to compare the outcome between the two arms with adjustment for drug combinations (anti-manic medication and antidepressants), age and sex.

The time origin of the survival analysis is the time of enrollment. A patient who do not experience a primary outcome will be censored at the time of the patient's last visit.
Results will be reported using hazard ratios with 95% confidence intervals, and the number needed to treat to avoid one outcome event by 52 weeks.

### 2.4.2 Sensitivity Analyses

To account for the intervention being identical in the two arms during the first six weeks, the primary analysis will be repeated with all events prior to and including the six-week follow-up visit excluded and the time origin of the survival analysis is set to the six-week follow-up visit.

### 2.4.3 Subgroup Analyses

Subgroup analyses for the primary outcome will be conducted for the two antidepressant medications (escitalopram or bupropion). Country will be included to check if the conclusions similar using data from India alone.

## 2.5 Secondary Outcome

- Time to manic or hypomanic episode
- Time to depressive episode
- Time to study discontinuation for any reason (e.g. onset of mood episode, intolerable side effects, patient or clinician decision)

Analogous to the primary analysis, Kaplan-Meier curves and Cox proportional hazard models will be used to summarize and to compare the time to each of these events of interest between the two arms. Patients who do not experience the event of interest will be censored at the time of the last follow-visit.

- The number of weeks the patient was "healthy" (defined as MADRS <=8)

Poisson regression will be used to compare two arms. If a substantial number of patients have no subsyndromal symptoms (or overdispersion observed), negative binomial regression will be used instead.

- The percentage of patients who experience subsyndromal symptoms
- The percentages of patients who experience any mood episode, a manic or hypomanic episode, or a depressive episode
- Rates of adverse events and SAEs
- Mean endpoint scores on the clinical rating scales.

Summary statistics will be provided by groups.

## 2.6 Other Outcomes

## 2.7 Sub-Studies in the Appendix of the Protocol

## 2.8 Interim Analyses

N/A

### 2.9 Safety Data

#### 2.9.1 Adverse Events (AEs)

Number (proportions) of AEs defined in the proposal in each group will be summarized and reported by groups

#### 2.9.2 Serious Adverse Events (SAEs)

Number (proportions) of SAEs defined in the proposal in each group will be summarized and reported by groups

### 2.10 Concomitant Medications

All concomitant medications must be documented on the Case Report Form (CRF)

## 3.0 ADDITIONAL METHODOLOGICAL DETAILS

### 3.1 Statistical Tests

Cox proportional hazard model
Linear-mixed effect model

### 3.2 Software to be Used

Study data will be analyzed using the most updated SAS version and/or R

## 4.0 REVISION HISTORY

| Version | Date | Summary of Changes |
|---|---|---|
| 2.0 | May 22, 2020 | Separate open-label phase and double blinded phase |
| 3.0 | April 1, 2021 | Finalized selection of adjustment variables |
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