

**A Randomized, Parallel-group, Placebo-controlled, Double-blind Clinical Trial to
Evaluate the Efficacy and Safety of Ethosuximide in Chinese Patients with
Treatment-Resistant Depression**

Statistical Analysis Plan

(Registration Number: 2019-716)

Version Number: 2.0 Date:12 April 2019 (Protocol version Number: 3.0)

1. Study purpose

The aim of this study is to evaluate the clinical efficacy and safety of ethosuximide in patients with treatment-resistant depression.

2. Study design

2.1 Study Overview

This is a randomized, parallel-group, placebo-controlled and double-blind study conducted by a single center. In the study, ethosuximide or placebo will be given for 2 weeks in experimental group or control group and escitalopram will be given for the next 4 weeks in each group.

usage and dosage:

Ethosuximide, 2 times/day, take it orally after breakfast/dinner; take 500mg in the morning and 500mg in the evening on day1, 500mg in the morning and 750mg in the evening on day2, 750mg in the morning and 750mg in the evening on day3, 750mg in the morning and 1000mg in the evening on day4, 1000mg in the morning and 1000mg in the evening on day5, maintain this dose until the end of treatment for 2 weeks.

The usage and dosage of placebo are the same as above.

Escitalopram, 1 time/day, 20mg/day, take it orally after breakfast, take it for 4 weeks without interruption.

2.2 Sample Size

We will recruit 40 subjects, 20 in the experimental group and 20 in the control group.

3. Analytical parameters

3.1 Validity Index

3.1.1 Main efficacy measures

Changes of Montgomery–Asberg Depression Rating Scale (MADRS) score at therapeutic visit point compare with baseline.

3.1.2 Secondary efficacy measures

Changes of Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR) score at therapeutic visit point compare with baseline.

Changes of Hamilton Anxiety Rating Scale (HAMA) score at therapeutic visit point compare with baseline.

Changes of individual score of MADRS at therapeutic visit point compare with baseline.

Changes of Young Mania Rating Scale (YMRS) score at therapeutic visit point compare with baseline.

Efficacy after 2 and 4 weeks of treatment.(Efficacy means that the score of MADRS decreasing by more than or equal to 50% compares with its baseline score)

Remission rate after 2 and 4 weeks of treatment.(Remission means that the total score of MADRS is less than 10.)

3.2 Safety Index

Adverse events, Vital signs, Physical examination, Laboratory tests(Including complete blood count, routine urine, blood biochemical examination, prolactin), ECG: 12 leads cardiogram, Scale evaluation.

4. Patient population analysis

4.1 Efficacy Set

Efficacy Set contains a set of subjects that meet all the following requirements.

- 1) All patients who are received study drug.
- 2) Patients who have scale scoring data at least at one time point after drug administration.

The Efficacy Set will be used for analysis of the efficacy of drugs.

4.2 Safety Set

Safety Set contains a set of subjects that meet all the following requirements.

- 1) All patients who are received study drug.
- 2) All patients who have safety data.

The Safety Set will be used for analysis of demographic and baseline characteristics and the safety of drugs.

5. Statistical method

5.1 General Principles

The analysis will be performed after data collection is completed. Statisticians and relevant researchers of the study group will use the latest version of SPSS statistics for data analysis, and all data analysts are blinded to treatment allocation.

The research data are mainly analysed on the basis of intention-to-treat (ITT) principle. All randomized participants are analysed according to the intervention to which they are randomized initially in the ITT analysis. The per-protocol (PP) analysis is another analysis method. In the per-protocol (PP) analysis, participants who do not receive treatment or do not provide any follow-up data should be excluded and grouped to analyse according to the intervention they actually received.

5.2 Handling of Missing data

Unless otherwise specified, missing values will not be imputed.

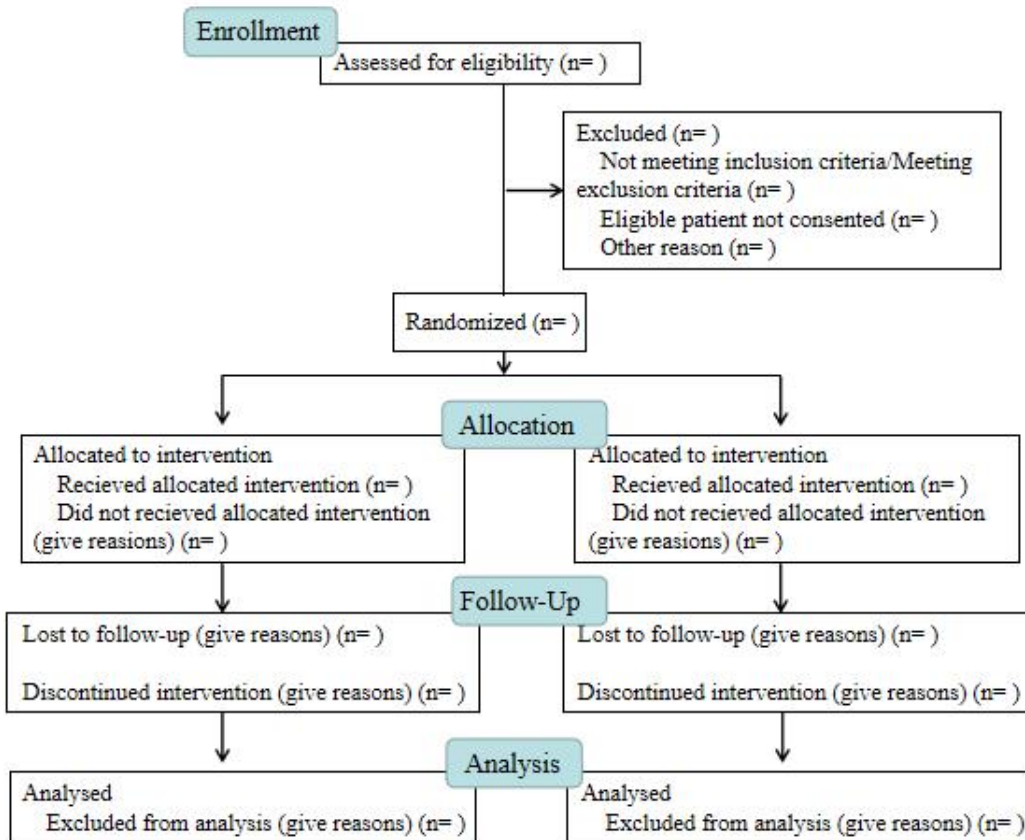
5.3 Subjects Characteristics

5.3.1 Subjects Disposition

Subject enrollment and disposition will be summarized.

The number and percentage of completed and withdrawn subjects will be summarized.

The details of incomplete study subjects will be listed.



5.3.2 Demographic and Baseline Characteristic

Baseline characteristics

	Ethosuximide + Escitalopram(n)	Placebo + Escitalopram(n)
Age, years		
Sex, F (% n/N)		
BMI, kg/m ²		
Years of education		
Vital signs		
Blood pressure (sitting position)		
Heart rate		
Respiratory rate		
Body temperature		
Physical examination of clinical significance		

Abnormal values of laboratory examination

Abnormal results of 12-Lead Electrocardiograms

Age at onset of first major depressive episode (years)

Lifetime number of major depressive episodes

Duration of current episode (weeks)

Montgomery–Åsberg Depression Rating Scale (MADRS) score

Young Mania Rating Scale (YMRS) score

Hamilton Anxiety Rating Scale (HAMA) score

Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR) score

5.4 Clinical Efficacy of Drug Treatment Analysis

The efficacy of drugs will be judged by analyzing the changes from baseline to treatment point in each scale score. Two-way Repeated Measures Anova will be used to compare the efficacy between experimental and control group; intervention measures will be defined as inter-group variables, and time points of scale evaluation as inner-group variables. First, the scale scores of each participant at baseline and each treatment point be listed (Table 2), and the average value of each group will be calculated. Then, values of sum of squares of deviation from mean, degree of freedom and mean square will be calculated. After calculating F values of inter-group factors or inner-group variables, the corresponding P values by querying F value threshold table and statistical inferences will be determined. It should be noted that the degree of freedom of inner-group variables needs to be corrected in the statistical test.

5.5 Safety Analysis

5.5.1 Adverse events

Adverse events occurred in experimental and control group will be summarized according to following contents.

1. Any treatment emergent adverse events
2. Related treatment emergent adverse events

3. Serious treatment emergent adverse events
4. Adverse Events Leading to Treatment Discontinuation
5. Adverse Events Leading to Death
6. Any treatment emergent adverse events by severity
7. Related treatment emergent adverse events by severity

These events will be displayed in data lists.

5.5.2 Vital signs

Summary tables will be created to present the descriptive statistics (n, mean, standard deviation, median, minimum, maximum) for vital signs values (temperature, pulse, systolic and diastolic blood pressure) in experimental and control group at baseline and each treatment point.

5.5.3 Physical examination

Physical examination of clinical significance will be listed at baseline and each treatment point.

5.5.4 Laboratory tests

Abnormal values or values of clinical significance according to researchers will be listed at baseline and changes of these values from each treatment point to baseline will be listed in table.

5.5.5 12-Lead Electrocardiograms (ECG)

Abnormal values or values of clinical significance according to researchers will be listed at baseline and changes of these values from each treatment point to baseline will be listed in table.

5.5.6 Systematic Assessment for Treatment Emergent Events (SAFTEE)

In the study, summary tables will be created to present treatment emergent events of subjects at baseline and each treatment point.

6. Instructions

This statistical analysis plan(SAP) is to develop from the research protocol (Protocol

version Number: 3.0). The contents of SAP may be modified with the deepening of the study.