Protocol Title:

A Two-Part Study of CLE-100 as an Adjunct Therapy in Subjects With Major Depressive Disorder

NCT04103892

03 December 2021

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- Names of study personnel, investigators, or institutions.
- Proprietary instruments, scales, coding systems, or other methodologies designated as confidential.
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A Two-Part Study of CLE-100 as an Adjunct Therapy in Subjects With Major Depressive Disorder

Investigational Product: Oral immediate-release esketamine tablet

Protocol Number: CLE100-MDD-201

Sponsor:

Clexio Biosciences Limited

[redacted]

Version Number: 6.0

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[redacted]

Amendment 5: 03 December 2021

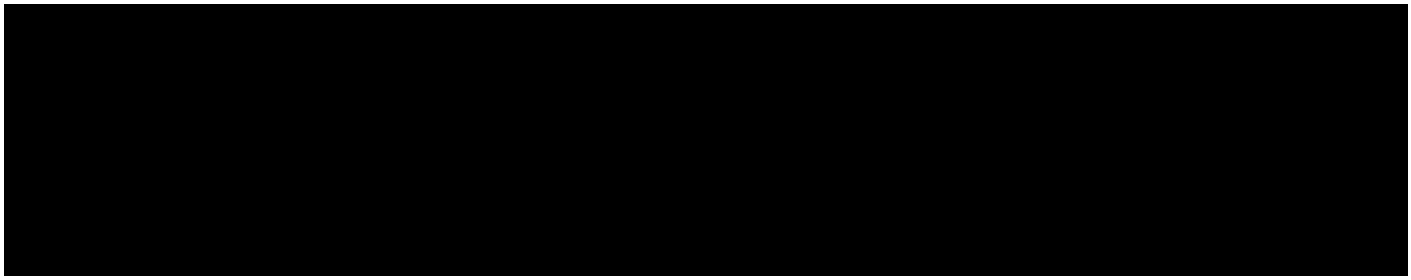
Confidentiality Statement

SIGNATURE PAGE

STUDY TITLE: A Two-Part Study of CLE-100 as an Adjunct Therapy in Subjects With Major Depressive Disorder

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature Date



INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Clexio Biosciences Limited to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Clexio Biosciences Limited and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Clexio Biosciences Limited, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and International Council for Harmonisation Guidelines for Good Clinical Practices.

SYNOPSIS

TITLE: A Two-Part Study of CLE-100 as an Adjunct Therapy in Subjects With Major Depressive Disorder

PROTOCOL NUMBER: CLE100-MDD-201

INVESTIGATIONAL PRODUCT: Oral immediate-release esketamine tablet

PHASE: 2

INDICATION(S): CLE-100 is being investigated as an adjunct therapy for patients with major depressive disorder (MDD) with an inadequate response to standard antidepressant therapy.

OBJECTIVE:

The study objective is to assess the safety, efficacy, and tolerability of 40 mg CLE-100 for the treatment of MDD in subjects with an inadequate response to standard antidepressant therapy.

Part A

The objectives for Part A of this study are to:

- Evaluate the safety and tolerability of 40 mg CLE-100 administered to subjects with MDD, once daily for 7 days.
- Evaluate the full pharmacokinetic (PK) profile of 40 mg CLE-100 in plasma.
- Assess key cognitive functions important for driving.

Part B

The primary objective for Part B of this study is to assess the efficacy of 40 mg CLE-100 compared to placebo in improving depressive symptoms in subjects with MDD with an inadequate response to standard antidepressant therapy, as assessed by change from Baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) to Week 4 (Day 29).

The secondary objectives for Part B of this study are to assess the efficacy of 40 mg CLE-100 compared to placebo in improving depressive symptoms and associated disability in subjects with MDD with an inadequate response to standard antidepressant therapy, as assessed by the following:

- Change in the self-rated Symptoms of Depression Questionnaire (SDQ) from Baseline to Week 4 (Day 29).
- Change in the Sheehan Disability Scale (SDS) from Baseline to Week 4 (Day 29).
- Change in the MADRS score from Baseline to Week 2 (Day 15).
- Change in the Clinical Global Impression – Severity (CGI-S) from Baseline to Week 4 (Day 29).

Another secondary objective for Part B of this study is to assess the safety of 40 mg CLE-100 compared to placebo in subjects with MDD with an inadequate response to standard antidepressant therapy.

POPULATIONS:

The population for Part A is subjects suffering from MDD currently treated with an antidepressant therapy.

The population for Part B is subjects suffering from MDD with an inadequate response to at least 2 standard antidepressant therapies in the current major depressive episode (MDE).

INCLUSION AND EXCLUSION CRITERIA:

Part A

Inclusion Criteria

1. Is a male or female between 18 to 60 years of age, inclusive, at Screening.
2. Is diagnosed with MDD, single or recurrent, without psychotic features, in the current or previous episode(s), according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The diagnosis of MDD must be supported by the Mini-International Neuropsychiatric Interview (MINI) Screen 7.0.2 for DSM-5.
3. Is currently experiencing an MDE.
4. Has an MADRS score of ≥18 at Screening.
5. Has been on a stable dose of the current oral antidepressant medication for ≥4 weeks by the time of randomization. If on fluoxetine, dose has been stable for ≥5 weeks.
6. Has a body mass index (BMI) between 18 and 40 kg/m^2, inclusive.
7. Is able and competent to read and sign the informed consent form (ICF).

Exclusion Criteria

1. Has a high risk of suicide based on any of the following:

2. Has a length of current MDE >5 years.
3. Has a lifetime history of any substance use disorder per DSM-5 criteria, except for tobacco use disorder.
4. Has a positive urine test for drugs of abuse at Screening or upon admission to the inpatient unit on Day 0 (eg, cannabinoids, cocaine, amphetamine, methamphetamine, benzodiazepines, morphine/opiates, phencyclidine [PCP], barbiturates, methadone, ecstasy). A positive urine test for cannabinoids at Screening will not necessarily exclude the subject as long as the Investigator deems the positive result does not meet DSM-5 criteria for substance use disorder. In addition, a subsequent negative test will be required during the screening phase. Note: At the discretion of the Investigator, a positive benzodiazepine drug screen in subjects prescribed benzodiazepines will not be considered exclusionary from the study.
5. Has a history or current diagnosis of bipolar disorder, schizophrenia, or schizoaffective disorders.
6. Has a current binge eating disorder or history of (binge) eating disorders within 1 year of Screening.
7. Has dementia, delirium, amnesia, or any other significant cognitive disorder.
8. Has posttraumatic stress disorder, obsessive compulsive disorder, or any other mental disorder (including personality disorders) that at Screening are either clinically predominant to their MDD or

have been predominant at any time within 6 months prior to Screening based on clinical judgment, or that would interfere with the subject's ability to participate in the study in the judgment of the Investigator.

9. Has a history of seizure disorder or unexplained loss of consciousness (subjects who suffered childhood febrile seizures are allowed).
10. Has a significant medical condition(s) or symptom(s) that, in the opinion of the Investigator, would prevent the subject from safely participating in the study, interfere with protocol compliance, or interfere with the safety or efficacy assessments.
11. Has a positive test for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) at Screening.
12. Has a chronic lung disease, including asthma, that is not well controlled at Screening.
13. Has a lifetime history of surgical procedures involving the brain or meninges, encephalitis, meningitis, hydrocephalus, degenerative central nervous system (CNS) disorders, epilepsy, mental retardation, or any other disease/procedure/accident/intervention associated with significant injury to or malfunction of the CNS, or a history of significant head trauma (defined as any loss of consciousness) within the past 2 years.
14. Has angina pectoris, had a recent myocardial infarction (within 1 year), or congestive heart failure >Stage 2, based on New York Heart Association Criteria, at Screening.
15. Has systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg that does not resolve on up to 3 repeated measurements. Note: At the discretion of the Investigator, subjects may be started on antihypertensive treatment during the screening phase to lower blood pressure into the allowed range with the expectation the antihypertensive medication will be stable by the time of randomization and remain at a stable dose during the double-blind phase of the study.
16. Has any medical condition for which an increase in blood pressure or intracranial pressure poses a serious risk (eg, aneurysmal vascular disease, arteriovenous malformation, or history of intracerebral hemorrhage).
17. Has a heart rate <50 or >105 beats per minute (bpm) at Screening. Note: Physically fit subjects with a heart rate <50 bpm may be enrolled with Sponsor approval in cases where clinically significant bradycardia can be ruled out.
18. Has evidence of second or third degree atrioventricular (AV) block, or first degree AV block (PR interval >200 msec), left bundle branch block (LBBB), or right bundle branch block (RBBB) at Screening.
19. Has a heart rate-corrected QT interval ≥450 msec for males and ≥470 for females at Screening using Fridericia's formula (QTcF).
20. Has uncontrolled hyperthyroidism or hypothyroidism at Screening, as defined by thyroid-stimulating hormone (TSH) levels outside the normal reference range or change in thyroid medications within 3 months prior to Screening.
21. Has uncontrolled diabetes mellitus defined as glycosylated hemoglobin (HbA1c) >8.5% at Screening.
22. Has narrow angle glaucoma.
23. Has alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >2.5 × the upper limit of normal or known hepatic insufficiency or chronic liver disease at Screening.
24. Has chronic cystitis.

25. Has known allergies or sensitivity to any anesthetic or to the excipients contained in the study drug or placebo.
26. Has had poor tolerability or sensitivity to esketamine, ketamine, or other N-methyl-D-aspartate receptor (NMDAR) antagonists.
27. Has failed to respond to ketamine or esketamine for depression (including treatment received in a clinical trial).
28. Is a female of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) who is not willing to use at least 1 highly effective birth control method throughout the study.
    - Female subjects will be considered to be of childbearing potential if they have begun menstruation.
    - Female subjects will not be considered to be of childbearing potential if they are:
        - Postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle-stimulating hormone [FSH] level >40 IU/mL).
        - Permanently sterilized (eg, have undergone a hysterectomy, bilateral oophorectomy, or tubal ligation ≥26 weeks prior to Screening).
        - Otherwise incapable of pregnancy.
29. Is a female that is pregnant or breastfeeding.
30. Is a female with a positive pregnancy test at Screening or upon admission to the inpatient unit on Day 0.
31. Is currently enrolled in or has not yet completed a period of at least 30 days since ending another investigational device or drug trial(s).
32. Is unsuitable for participating in the study, in the opinion of the Investigator.
33. Is taking prohibited concomitant medications or foods.

Part B

Inclusion Criteria

1. Is a male or female between 18 to 65 years of age, inclusive, at Screening.
2. Is diagnosed with MDD, single or recurrent, without psychotic features, in the current or previous episode(s), according to the DSM-5. The diagnosis of MDD must be supported by the MINI Screen 7.0.2 for DSM-5.
3. Is currently experiencing an MDE that began at least 12 weeks prior to Screening. [redacted]
4. Has an MADRS score of ≥24 at Screening [redacted]
5. Has, at Screening, a history of failure to achieve a satisfactory subjective response [redacted] to at least 2 treatment courses of a therapeutic dose of an antidepressant medication therapy, [redacted]

[redacted]

6. Has a BMI between 18 and 40 kg/m^2, inclusive.
7. Is able and competent to read and sign the ICF.

Exclusion Criteria

1. Has a history of failure to achieve a satisfactory subjective response [redacted] to more than 5 treatment courses of a therapeutic dose of an antidepressant medication therapy [redacted]
2. [redacted].
3. Has a length of current MDE >5 years.
4. Has a high risk of suicide based on any of the following:

   [redacted]

5. Has a current substance use disorder or history of any substance use disorder per DSM-5 criteria within 12 months prior to Screening, except for tobacco use disorder.
6. Has a positive urine test for the following drugs of abuse at Visit 1 (Screening) or Visit 2 before randomization: cocaine, PCP, methadone, or ecstasy. For benzodiazepines, amphetamines, methamphetamines, barbiturates, morphine/opiates, and tetrahydrocannabinol, refer to the flowchart in Appendix H, which provides special considerations for these drugs.
7. Has a history or current diagnosis of bipolar disorder, schizophrenia, or schizoaffective disorders.
8. Has dementia, delirium, amnesia, or any other significant cognitive disorder.
9. Has posttraumatic stress disorder, obsessive compulsive disorder, or any other mental disorder (including personality disorders, eating disorders, etc.) that at Screening are either clinically predominant to their MDD or have been predominant at any time within 12 months prior to Screening based on clinical judgment, or that would interfere with the subject's ability to participate in the study in the judgment of the Investigator.
10. Has a failure to respond to adequate treatment with electroconvulsive therapy during the current depressive episode. Determination of inadequate treatment is based on the opinion of the Investigator and with approval of the Medical Monitor.
11. Has received vagus nerve stimulation at any time prior to Screening.
12. Has a history of seizure disorder or unexplained loss of consciousness (subjects who suffered childhood febrile seizures are allowed).
13. Has a significant medical condition(s) or symptom(s) that, in the opinion of the Investigator, would prevent the subject from safely participating in the study, interfere with protocol compliance, or interfere with the safety or efficacy assessments.
14. Has a known history of positive test for HIV or has an active or chronic infection with HBV, or a positive test for HCV (however, a subject with documented proof of cure from HCV can be enrolled).

15. Has a chronic lung disease, including asthma, that is not well controlled at Screening.
16. Has a lifetime history of surgical procedures involving the brain or meninges, encephalitis, meningitis, hydrocephalus, degenerative CNS disorders, epilepsy, mental retardation, or any other disease/procedure/accident/intervention associated with significant injury to or malfunction of the CNS, or a history of significant head trauma (defined as any loss of consciousness) within the past 2 years.
17. Has angina pectoris, had a recent myocardial infarction (within 1 year), or congestive heart failure >Stage 2, based on New York Heart Association Criteria, at Screening.
18. Has systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg that does not resolve on up to 3 repeated measurements. Note: At the discretion of the Investigator, subjects may be started on antihypertensive treatment during the screening phase to lower blood pressure into the allowed range with the expectation the antihypertensive medication will be stable by the time of randomization and remain at a stable dose during the double-blind phase of the study.
19. Has any medical condition for which an increase in blood pressure or intracranial pressure poses a serious risk (eg, aneurysmal vascular disease, arteriovenous malformation, or history of intracerebral hemorrhage).
20. Has a heart rate <50 or >105 bpm at Screening. Note: Physically fit subjects with a heart rate <50 bpm may be enrolled with Sponsor approval in cases where clinically significant bradycardia can be ruled out.
21. Has evidence of second or third degree AV block, LBBB, or RBBB at Screening.
22. Has a QTcF interval ≥450 msec for males and ≥470 msec for females at Screening.
23. Has hypothyroidism or hyperthyroidism, unless stabilized on appropriate medication with no change in dosage for at least 3 months prior to Screening. Euthyroid subjects and subjects with controlled thyroid dysfunction may be enrolled if they meet one of the following criteria:
    - TSH levels within normal reference range; or
    - TSH ≥0.75 × the lower limit of normal and ≤1.25 × upper limit of normal AND with no clinical signs/symptoms of thyroid disease AND normal free triiodothyronine (T3) and thyroxine (T4).
24. Has uncontrolled diabetes mellitus defined as HbA1c >8.5% at Screening.
25. Has narrow angle glaucoma.
26. Has ALT and AST >2 × the upper limit of normal or known hepatic insufficiency or chronic liver disease at Screening.
27. Has chronic cystitis (subjects with acute cystitis can be enrolled after successful treatment).
28. Has undergone a bariatric surgery for weight loss.
29. Has known allergies or sensitivity to the excipients contained in the study drug or placebo.
30. Has had poor tolerability or sensitivity to esketamine or ketamine.
31. Has been randomized in Part A of this study.
32. Has had previous non-response for treatment of depression to esketamine or ketamine with an adequate dose and duration per the Investigator's judgment.

33. Is a female of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) who is not willing to use at least 1 highly effective birth control method throughout the study and for 1 month after study ends.
    - Female subjects will be considered to be of childbearing potential if they have begun menstruation.
    - Female subjects will not be considered to be of childbearing potential if they are:
        - Postmenopausal, as determined by:
            a. >45 years of age with amenorrhea for at least 12 months without an alternative medical cause.
            b. ≤45 years of age with amenorrhea for at least 12 months and a serum FSH level >40 mIU/mL without an alternative medical cause.
        - Permanently sterilized (eg, have undergone a hysterectomy, bilateral oophorectomy, or tubal ligation ≥26 weeks prior to Screening).
        - Otherwise incapable of pregnancy.
34. Is a female that is pregnant or breastfeeding.
35. Is a female with a positive pregnancy test at Screening or Visit 2.
36. Is a male who is sexually active with a female of childbearing potential, has not had a vasectomy, and does not agree to use an effective method of birth control (eg, condom with spermicide), or does not agree to refrain from donating sperm during the study and for 3 months after receiving the last dose of study drug.
37. Is currently enrolled in another investigational device or drug trial(s), or has not yet completed a period of at least 60 days or 5 half-lives since the last dose of the previous investigational drug, whichever is longer, before the administration of the first dose of the study drug in this study.
38. Is unsuitable for participating in the study, in the opinion of the Investigator.
39. Is taking prohibited concomitant medications or foods.
40. Is receiving any medication(s) given to augment the efficacy of his/her antidepressant therapy (eg, anticonvulsants, mood stabilizers including lithium, atypical antipsychotics, psychostimulants, and thyroid hormones) at the time of randomization.
41. Is known to experience, based on the Investigator's judgment, clinically significant sedation from any concomitant medication planned to be taken during the 4-week treatment period.
42. Is unwilling or unable to comply with the driving instructions of the study protocol.

STUDY DESIGN AND DURATION:

This is a 2-part, Phase 2 study in subjects with MDD currently treated with an oral antidepressant medication. In both parts, all subjects will remain on their current oral antidepressant monotherapy with no dose change during the study. Part A will be an inpatient study to assess the safety, tolerability, and PK of 40 mg CLE-100. Part B will be an outpatient study to assess the safety, efficacy, and tolerability of 40 mg CLE-100.

Fifteen subjects will be randomized into Part A and approximately 122 subjects will be randomized into Part B of this study.

Part A

Part A will comprise 3 phases:

- Screening phase that will last up to 35 days (Days -35 to -1).
- Inpatient double-blind treatment phase composed of admission on Day 0, dosing on Days 1 to 7, and discharge on Day 8 (Discharge Day) (Days 0 to 8).
- Outpatient posttreatment safety follow-up phase of 1 week after last study drug administration (Days 9 to 14).

During Screening, subjects will be assessed for study eligibility and will wash out from disallowed drugs, if needed. In addition, during this period it will be determined whether the subject's current dose of oral antidepressant medication has been stable for at least 4 weeks. Evidence of compliance should include either documented compliance from the subject's medical or pharmacy records or a report from the subject's treating clinician or pharmacist. If this is not the case, subject compliance will be observed for a minimum of 4 weeks before randomization. Eligible subjects will be randomized using a 4:1 allocation scheme to receive either 40 mg CLE-100 or placebo once daily, respectively. Subjects will be admitted to the inpatient unit on Day 0. Subjects will receive the study drug orally once daily in the morning (Days 1 to 7).

Subjects will be frequently monitored postdosing for potential neuropsychiatric effects using a comprehensive set of scales to identify sleepiness, alertness/sedation, and psychotomimetic or dissociative effects.

Key cognitive functions important for driving will also be assessed on Days 1 and 7 with a pencil and paper Digit Symbol Substitution Test (DSST), as well as with the Cogstate battery of cognitive tests. The Cogstate battery will include the Detection Test (psychomotor function), Identification Test (attention), One Back Test (working memory), Groton Maze Learning Test (executive function), and Chase Test (visual motor control). In addition, blood pressure and heart rate will be measured repeatedly after each dosing. Symptoms of suicidal ideation, self-harm, and suicidal behavior will be monitored repeatedly using the C-SSRS. The MADRS will be repeatedly administered and evaluated as an exploratory assessment. Pharmacokinetic sampling will be performed daily during the inpatient period except on Day 0. Subjects will be discharged in the morning on Day 8 pending approval by a physician. Before discharge, the subject and the Investigator will be asked separately whether they believe the study drug could be safely administered at home based on their experience with dosing during the inpatient stay.

There will be an outpatient safety follow-up of 1 week after the last study drug administration. During this period, there will be a remote assessment of the 20-item Physician Withdrawal Checklist (PWC-20) by telephone on Day 10 and a follow-up visit on Day 14.

At the conclusion of Part A, an independent Data Safety Monitoring Board (DSMB) will review the data from Part A. The outcome of the DSMB review will be submitted to the Food and Drug Administration before proceeding with Part B.

Part B

Part B will comprise 3 phases:

- Screening phase that will last up to 28 days (Days -28 to -1).

- Four-week double-blind treatment phase (4 weeks of dosing and an end of treatment [EOT] visit; Days 1 to 29).
- Posttreatment safety follow-up phase of 2 weeks after last study drug administration (Days 30 to 42).

During Screening, subjects will be assessed for study eligibility and will taper and/or wash out from benzodiazepines, benzodiazepine-like drugs, prescription sleeping aids, and other disallowed drugs, if needed. Eligible subjects will be randomized to receive either placebo or 40 mg CLE-100 once daily in addition to their current oral antidepressant monotherapy for 4 weeks.

Subjects will receive study drug orally once daily (Days 1 to 28).

[redacted]

[redacted]

The subject will also be provided an information sheet with instructions for the administration of study drug at home. The Investigator or key clinical staff will be available 24 hours a day/7 days a week for the duration of the study, and the relevant phone number will be provided on the information sheet. The subject will also be informed at discharge that an early refill will only be given under special circumstances and upon approval by the Sponsor on a case-by-case basis.

[redacted] and to not use benzodiazepines, benzodiazepine-like drugs, or sleeping aids (either prescription or over-the-counter). [redacted]

Instructions about driving and operating machinery and warning about the use of sedative drugs during the study treatment period, as well as information on available car services, will be included on the information sheet provided to the subject at discharge at Visit 2.

[redacted]

There will be weekly on-site visits (Visits 3 to 5) [redacted]

Suicidal ideation, self-harm, and suicidal behavior will be monitored once weekly using the C-SSRS. Pharmacokinetic sampling will be performed at each on-site visit during the 4-week treatment period.

The DSMB will evaluate the unblinded safety data during Part B of the study at intervals predetermined in the DSMB charter. The DSMB will provide their recommendation for the continuation or discontinuation of the study as planned or whether protocol changes are warranted.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

CLE-100 is an oral, immediate-release (IR) formulation of esketamine hydrochloride for once daily administration [redacted]. For this study, 40 mg IR tablets of CLE-100 will be used.

Part A

In Part A, subjects will be randomized in a 4:1 ratio to the following 2 treatment groups:

- 40 mg CLE-100 (12 subjects).
- Placebo (3 subjects).

Part B

In Part B, at Visit 2 predose, subjects will be randomized in a 1:1 ratio to the following 2 treatment groups:

- Placebo (61 subjects).
- 40 mg CLE-100 (61 subjects).

The study drug will be administered in addition to the subject's current oral antidepressant monotherapy that must be kept at a stable therapeutic dose throughout study participation.

EFFICACY VARIABLES IN PART B:

The primary efficacy endpoint for Part B of this study is the change from Baseline to Week 4 (Day 29) in the MADRS score.

The key secondary efficacy endpoints for Part B of this study include the following:

- Change in the self-rated SDQ from Baseline to Week 4 (Day 29).
- Change in the SDS from Baseline to Week 4 (Day 29).
- Change in the MADRS score from Baseline to Week 2 (Day 15).
- Change in the clinician-administered Clinical Global Impression – Severity (CGI-S) rating from Baseline to Week 4 (Day 29).

In Part B, other secondary efficacy endpoints include the following:

- Responder rate [redacted] at Week 4 (Day 29).
- Remission rate [redacted] at Week 4 (Day 29).
- Clinician-administered Clinical Global Impression – Improvement rating at Week 4 (Day 29).
- Change in the General Anxiety Disorder 7-item Scale from Baseline to Week 4 (Day 29).

SAFETY VARIABLES:

Safety and tolerability variables measured in both Part A and Part B of this study will include the following:

- AEs.
- Clinical laboratory evaluations (hematology, chemistry, and urinalysis).
- Physical examination findings.
- Vital signs (blood pressure, heart rate, and body temperature).
- 12-lead electrocardiogram findings.
- Self-reported KSS.
- MOAA/S.
- CADSS.
- C-SSRS.
- 4-item BPRS.
- Cognitive function evaluated by Cogstate battery (Part A only)
  - Detection Test.
  - Identification Test.
  - One Back Test.
  - Groton Maze Learning Test.
  - Chase Test.
- DSST.
- PWC-20.
- Withdrawal rates, including days and reason(s) for withdrawals.
- Bladder Pain/Interstitial Cystitis Symptom Score (Part B only).

STATISTICAL ANALYSES:

Part A

Fifteen subjects will be randomized into Part A using a 4:1 assignment ratio to treatment with either 40 mg CLE-100 (12 subjects) or placebo (3 subjects), respectively.

The overall safety and tolerability of CLE-100 treatment will be assessed in Part A by evaluating the safety variables for the Safety Analysis Set for Part A.

Part B

Approximately 122 subjects will be randomized into Part B using a 1:1 assignment ratio to treatment with either placebo (61 subjects) or 40 mg CLE-100 (61 subjects).

The significance level for Part B of this study will be 0.05 2-sided.

For Part B, a fixed sequence gatekeeping (hierarchical) approach will be applied to adjust for multiplicity and to control type I error due to multiple efficacy endpoints testing of the primary and key secondary endpoints. The sequence order is according to the defined order of the primary and key secondary endpoints. If the primary analysis is statistically significant at the 2-sided 0.05 level, the key secondary endpoints will be analyzed sequentially according to their defined order. A key secondary endpoint will be considered statistically significant at the 2-sided 0.05 level only if the previous key secondary or primary

endpoint in the hierarchy is significant at the 2-sided 0.05 level.

The primary estimand for Part B of this study is based on the efficacy assumption (de jure) using the hypothetical strategy. The treatment effect will be attributed to eligible and randomized subjects who have both a Baseline and at least 1 post-Baseline MADRS total score measurement while the subjects are on study drug and hypothetically received study medication for 4 weeks.

An evaluation of the possible impact of missing values on the primary analysis results will be performed.

The treatment policy estimand strategy will also be evaluated as a secondary estimand and is based on the effectiveness assumption (de-facto). The treatment effect will be attributed to eligible and randomized subjects regardless of early treatment discontinuation.

The change in the MADRS total score from Baseline to Week 4 (Day 29) in Part B will be analyzed using Mixed Models Repeated Measures analysis. [redacted]

The model will use the unstructured covariance matrix, the Restricted Maximum-Likelihood (REML) estimation method, and the Kenward-Roger adjustment method for the degrees of freedom. In the case that the model does not converge, the Maximum-Likelihood estimation method will be used instead of the default REML. If the model still does not converge, then a simpler covariance structure with fewer parameters will be used according to the following order: heterogeneous autoregressive (1), heterogeneous compound symmetry, autoregressive (1), and compound symmetry.

All data collected while the subject is on study drug for all randomized subjects who received at least 1 dose of study drug and have a Baseline MADRS total score will be included in the primary efficacy analysis.

[redacted]

SAMPLE SIZE DETERMINATION:

Part A

No prospective calculations of statistical power were made for Part A. The sample size was selected to provide information on safety, tolerability, and PK following administration of multiple doses of CLE-100.

Part B

The sample size for Part B was determined based on the following assumptions [redacted] a randomization ratio of 1:1. [redacted] a power of 80%, a 2-sided alpha level of 0.05, [redacted]

Under the above assumptions, the estimated number of subjects required for this study is 122 (61 subjects on placebo and 61 subjects on 40 mg CLE-100).

SITES: [redacted]

SPONSOR:

Clexio Biosciences Limited