Study Title:

A Phase 2a Study to Evaluate the Kappa Opioid Receptor As a Target for the Treatment of Mood and Anxiety Spectrum Disorders by Evaluation of Whether CERC-501 Engages Key Neural Circuitry Related to the Hedonic Response

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Statistical Analysis Plan

Fast-Fail Trials in **M**ood and **A**nxiety **S**pectrum Disorders **(FAST-MAS)**
Kappa **O**pioid **R**eceptor Phase **2**a (**KOR2**)

Version Date: December 18, 2017

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STUDY SYNOPSIS

Title:	A Phase 2A Study to Evaluate the Kappa Opioid Receptor as a Target for the Treatment of Mood and Anxiety Spectrum Disorders by Evaluation of Whether LY2456302 Engages Key Neural Circuitry Related to the Hedonic Response
Indication:	Mood and Anxiety Spectrum Disorders
Location:	1. Baylor College of Medicine 2. Case Western Reserve University 3. Duke University 4. Indiana University 5. Mount Sinai School of Medicine 6. Yale University
Rationale:	We chose to focus on anhedonia as an endpoint for this study because: 1) the available data suggest that anhedonia is the dimension of mood and anxiety spectrum disorders that is most likely to be improved by KOR antagonists; 2) anhedonia is associated with measurable neurobiological mechanisms which can be studied with available methodologies that could be used to establish POC in terms of engagement of relevant neural circuitry; and 3) anhedonia allows us to accomplish our goal of studying an important aspect of dysfunction that cuts across mood and anxiety spectrum disorders, consistent with the NIMH's RDoC framework.
Objectives:	To assess the effects of LY2456302 compared to PBO in adults age 21-65 years with mood and anxiety spectrum disorders
Study Design:	This study will be a six-site randomized, double-blind, PBO-controlled, parallel-group mono-therapy study to assess the effects of LY2456302 compared to PBO in adults age 21-65 years with mood and anxiety spectrum disorders. We will recruit a total of 90 subjects, of which 45 will be randomized to LY2456302 and 45 to placebo for 8 weeks of treatment.
Primary Objectives:	**Primary Specific Aim:** To establish POC for KOR antagonism by evaluating the impact of LY2456302 10 mg relative to Placebo (PBO) on reward-related neural circuitry in terms of ventral striatal fMRI activation during anticipation of reward during the Monetary Incentive Delay (MID) Task
Secondary Objectives:	**Secondary Specific Aim 1 (Clinical Anhedonia Measure):** To determine if 10 mg of LY2456302 is superior to PBO in improving a clinical, self-report measure of anhedonia, the Snaith Hamilton Pleasure Scale (SHAPS), in patients with mood and anxiety spectrum disorders. **Secondary Specific Aim 2 (Behavioral Anhedonia Measure)***:* To evaluate the impact of LY2456302 relative to PBO on a behavioral measure of anhedonia, the Probabilistic Reward Task (PRT), in patients with Mood and Anxiety Spectrum Disorders.
Exploratory Objectives:	To assess the effects of LY2456302 relative to placebo on: • Ventral striatal fMRI activation during anticipation of loss during the MID Task

	• Resting state delta EEG current density in the rostral anterior cingulate. • Resting state fMRI connectivity • Self-rated affective responses to cues and feedback during the MID Task • The Effort-Expenditure for Rewards Task (EefRT) • The Visual Analogue Scale for Anhedonia (VAS) • The Temporal Experience of Pleasure Scale (TEPS) • The Hamilton Depression Rating Scale (HAM-D) • The Hamilton Anxiety Scale (HAM-A) • Clinical Global Impression – Improvement (CGI-I) • Clinical Global Impression – Severity (CGI-S) • The Cognitive and Physical Functioning Questionnaire (CPFQ) To assess the safety and tolerability of LY2456302 on systematically collected and spontaneously reported adverse events.

STUDY FLOW CHART

SCREENING: Day -30 to Day -1

Subjects who sign informed consent will undergo rigorous screening including: a medical, psychiatric, medication, and treatment history, vital signs, physical examination, pregnancy test, ECG, urine drug screen, MINII, Snaith-Hamilton Pleasure Scale (SHAPS), Temporal Experience of Pleasure Scale (TEPS), Visual Analog ue Scale for Anhedonia (VAS), Columbia Suicide Severity Rating Scale (CSSRS), and a battery of clinical laboratory tests, Urea Breathe Test, Mock MRI scanning session

RANDOMIZATION: Day 0

Subjects who qualify will be randomly assigned to receive LY2456302 or PBO in a 1:1 ratio using IVRS randomization within the EDC

Baseline visit (day 0, prior treatment initiation)

The Baseline Assessment Visit will occur within 30 days of screening. During this visit, all primary and secondary outcome measures will be assessed. Vital signs (pulse rate, blood pressure, height, weight) will be collected at Baseline. Blood samples will be collected, and fMRI and QEEG imaging sessions will be scheduled at Baseline.

Double-Blind Treatment Period: Week 2,4,6,8

2, 4, 6, 8 week treatment visits (± 1 week)

During these visits, all primary and secondary outcome measures will be assessed. Vital signs (pulse rate, blood pressure, height, weight) will be collected. Adverse events will be assessed. Blood samples will be collected, and fMRI and QEEG imaging sessions will be scheduled at 8 weeks (endpoint) after treatment initiation.

Post Medication Follow-up: Week 12

During this visit, vital signs (pulse rate, blood pressure, height, weight) will be collected. Interval history will be assessed. Snaith-Hamilton Pleasure Scale (SHAPS), Temporal Experience of Pleasure Scale (TEPS), Visual Analogue Scale for Anhedonia (VAS), Columbia Suicide Severity Rating Scale (CSSRS) will be assessed. Adverse events will be collected using the Patient Reported Inventory of Side-Effects (PRISE). Clinical Global Impression – Severity Scales (CGI-S) and Clinical Global Impression – Improvement (CGI-I) will be assessed At the conclusion of this visit, subject participation in the study will **END**.

2. HYPOTHESES AND AIMS

2.8 Primary Aim

We will conduct a multicenter, randomized, parallel-group, placebo-controlled, Phase 2A trial of 10 mg of LY2456302 in 90 adults with mood and anxiety spectrum disorders in order to achieve the following aims.

Primary Specific Aim (Proof of Concept/Engagement of Neural Circuitry Related to Anhedonia): to establish POC for KOR antagonism by evaluating the impact of LY2456302 10 mg relative to Placebo (PBO) on reward-related neural circuitry in terms of ventral striatal fMRI activation during anticipation of reward during the Monetary Incentive Delay (MID) Task.

This will be achieved by comparing pre- to post-treatment changes in LY2456302 and PBO groups on ventral striatal fMRI activation during anticipation of reward during the monetary incentive delay task (MID).

We **hypothesize** that compared with PBO, LY2456302 will increase monetary incentive delay task-associated fMRI activation in the ventral striatum. This will be the primary outcome measure for the proposed study

1.2 Secondary Aims

Secondary Specific Aim 1 (Clinical Anhedonia Measure): To determine if 10 mg of LY2456302 is superior to PBO in improving a clinical self-report measure of anhedonia, the Snaith Hamilton Pleasure Scale (SHAPS) across 8 weeks of treatment.

We **hypothesize** that LY2456302 will result in improvement in anhedonia relative to PBO, as determined by a pre- to post-treatment decrease in the score on the Snaith-Hamilton Pleasure Scale (SHAPS) across 8 weeks of treatment.

Secondary Specific Aim 2 (Behavioral Anhedonia Measure)*:* To evaluate the impact of LY2456302 relative to PBO on a behavioral measure of anhedonia, the Probabilistic Reward Task (PRT).

We **hypothesize** that LY2456302 will result in statistically significant improvement in anhedonia relative to PBO, as reflected in a pre- to post-treatment increase in Reward Responsiveness (i.e., the ability to modulate behavior as a function of reinforcement history) as assessed by the Probabilistic Reward Task (PRT), which has been found to be related to the proposed primary outcome measure, over 8 weeks of treatment in adults with mood and anxiety spectrum disorders.

1.3 Exploratory Aims

The **Exploratory Aims** of this study are:

To assess the effects of LY2456302 relative to placebo on:

- Ventral striatal fMRI activation during anticipation of loss during the MID Task
- Resting state delta EEG current density in the rostral anterior cingulate
- Resting state fMRI connectivity
- Self-rated affective responses to cues and feedback during the MID Task
- The Effort-Expenditure for Rewards Task (EefRT)
- The Visual Analogue Scale for Anhedonia (VAS)
- The Temporal Experience of Pleasure Scale (TEPS)
- The Hamilton Depression Rating Scale (HAM-D)
- The Hamilton Anxiety Scale (HAM-A)
- The Cognitive and Physical Functioning Questionnaire (CPFQ)
- Clinical Global Impression Severity and Improvement (CGI-S and CGI-I) Ratings

To assess the safety and tolerability of LY2456302 on systematically collected and spontaneously reported adverse events

2. BACKGROUND AND RATIONALE

The available treatments for patients with mood and anxiety disorders have significant limitations (Rush, 2007; Denys and de Geus, 2005). There is a need to develop new treatments for people with these disorders. Many research studies carried out in animals and a few preliminary studies carried out in humans suggest that medications which block kappa opioid receptors (KOR) have potential for being effective new treatments for patients with mood and anxiety spectrum disorders (see below). These medications have shown particular promise for improving one important type of difficulty experienced by many patients who suffer from mood and anxiety spectrum disorders referred to as anhedonia, which is an impairment in reward-related function. In this study we will test the hypothesis that KOR antagonism is a promising means of improving anhedonia in patients with mood and anxiety spectrum disorders. We will do so by evaluating whether we can establish Proof of Concept (POC) that a relatively selective KOR antagonist, LY2456302 (see Investigator Brochure), engages neural circuits involved in mediating reward-related function in patients with mood and anxiety spectrum disorders with anhedonia. We are attempting to establish POC in this study in order to determine whether there is a sufficient basis for pursuing future work evaluating whether KOR antagonism has therapeutic effects on clinical and behavioral measures of reward-related functioning.

In addition to being a relatively selective KOR antagonist, LY2456302 is also well-suited for this study based on its pharmacologic and safety profiles (see Investigator Brochure). The 10 mg dosage of LY2456302 was chosen for evaluation because of preclinical studies, single and multiple ascending dose studies in humans, a single-dose PET study of KOR occupancy (Zheng et al., 2013), and pupillometry data obtained following administration of the mu agonist fentanyl (see Invesigator Brochure). The following sections include details of the rationale for this study.

2.1. KOR Antagonism Promising Target for Treating Mood and Anxiety Disorders

There is an extensive set of pre-clinical studies suggesting that KOR antagonists are likely to have therapeutic effects in those with mood and anxiety spectrum disorders. This includes studies indicating a role of the kappa opiate system in mediating both anxiety and depression symptoms and studies suggesting that KOR antagonists have effects on animal models of both major depression and anxiety.

A number of studies indicate that the kappa opiate system is critical for mediating the adverse effects of stress. An important aspect of stress-related pharmacology is the dynorphins, a group of opioid peptides that exert their effects primarily through binding to KOR (Bruchas et al., 2009). Evidence suggests that stress leads to anxiety by CRF1 receptor activation of dynorphins in the basolateral amygdala which then bind to KOR (Bruchas et al., 2009). Place aversion and social avoidance occurring with repeated stress is mediated via dynorphin activation in ventral striatum, an effect which can be mimicked by KOR agonists and blocked by KOR antagonists (Land et al., 2009; Schindler et al., 2012). KOR antagonists also block stress-related impairment in elevated plus maze spontaneous exploration (Peters et al., 2011).

Non-stress anxiety paradigms also suggest that KOR antagonists are likely to have anxiolytic effects. Prodynorphin knockouts (prodynorphin is the precursor protein for dynorphins) and KOR antagonists have been found to have anxiolytic-like effects in the novelty-induced hypophagia test, the defensive burying tests, the elevated plus maze test, fear-potentiated startle test, open-field test, and light-dark test (Carr and Lucki, 2010; Knoll et al., 2011; Wittmann et al., 2009).
A larger literature suggests that KOR antagonists are likely to have anti-depressant effects and may prevent the depression-like consequences of stress. Dynorphin mediates the dysphoric aspects of stress via binding to KOR and this effect is prevented by knocking out dynorphin or administering a KOR antagonist (Land et al., 2008). The depression-like behaviors caused by chronic stress, uncontrollable stress, and social-defeat stress are mediated by kappa opiate receptors and can be mimicked by KOR agonists (McLaughlin et al., 2006; Knoll and Carlezon, 2010). KOR antagonist treated mice and KOR knockout mice show a reduction of stress-induced depression-like behavior (McLaughlin et al., 2006; Knoll and Carlezon, 2010). Stress has also been found to trigger KOR activation of dorsal raphe neurons which project to nucleus accumbens and decrease dopamine release thereby diminishing reward and increasing drug seeking (Lemos et al., 2012).

More generally, rodent studies show that administering KOR antagonists or knocking out the prodynorphin gene leads to antidepressant-like effects as assessed by reduced immobility in the forced swim test and reduced learned helplessness (via nucleus accumbens and hippocampal mediated mechanisms), whereas KOR agonists have depressogenic effects in conjunction with decreasing nucleus accumbens dopamine release (Reindl et al., 2008; Shirayama et al., 2004; Carlezon et al., 2006; McLaughlin et al., 2003; Mague et al., 2003; Todtenkopf et al., 2004; Chartoff et al., 2012; Chartoff et al., 2009).

Perhaps the best recognized effect of KOR antagonists in animal models is to prevent the development of anhedonic-like states. The literature suggesting that KOR antagonists have such effects speaks to the potential of these agents to have therapeutic effects on anhedonia in humans, which is a core symptom of mood and anxiety disorders that cuts across diagnostic boundaries. In this regard, there is evidence that KOR stimulation inhibits dopamine release in the striatum (nucleus accumbens and caudate) and induces a negative mood state (Bruijnzeel, 2009). Consistent with this model, a series of studies indicate that KOR agonists decrease phasic dopamine release in the nucleus accumbens and increase intracranial self-stimulation (a model of anhedonia), whereas KOR antagonists have the opposite effect, increasing

nucleus accumbens dopamine release and decreasing self-stimulation (Ebner et al., 2010; Muschamp et al., 2011; Carlezon et al., 2006; Maisonneuve et al., 1994). Further, KOR agonists block cocaine's anti-anhedonic effect on intracranial self-stimulation (Tomasiewicz et al., 2008) and block the reinforcing/rewarding effects on drugs of abuse (Wee and Koob, 2010), whereas, giving a KOR antagonist prior to cocaine withdrawal prevented anhedonic-like intracranial self-stimulation responses (Chartoff et al., 2012).

Although data in humans on the effects of selective KOR antagonists are lacking, preliminary data from humans are consistent with the animal data in suggesting that this target is likely to have therapeutic effects in mood and anxiety spectrum disorders. In an open-label study, 6 patients who had failed antidepressant medications and ECT were found to improve with buprenorphine (a KOR antagonist and partial mu agonist) treatment (Nyhuis et al., 2008). Findings of a double-blind, placebo-controlled, pilot study in 32 patients with treatment-resistant depression treated with the combination of buprenorphine and a mu receptor antagonist (simulated kappa opiate receptor antagonist) indicate that this combination had a significant antidepressant effect (Ehrich, 2012).

Together, the available data provide a compelling indication that KOR antagonists are likely to have therapeutic effects in patients with mood and anxiety spectrum disorders. These data point to the adverse effects of stress and particularly anhedonia as therapeutic targets of interest with these agents.

2.2. Rationale for Studying Effects of KOR Antagonist on Anhedonia

We chose to focus on anhedonia as an endpoint for this study because: 1) the available data suggest that anhedonia is the dimension of mood and anxiety spectrum disorders that is most likely to be improved by KOR antagonists (see above); 2) anhedonia is associated with measurable neurobiological mechanisms which can be studied with available methodologies that could be used to establish POC in terms of engagement of relevant neural circuitry (Wacker et al., 2009; Pizzagalli et al., 2004, 2009; Treadway et al., 2012; Stoy et al., 2012; Ossewaarde et al., 2011); and 3) anhedonia allows us to accomplish our goal of studying an important aspect of dysfunction that cuts across mood and anxiety spectrum disorders, consistent with the NIMH's RdoC framework.

The data indicating that KOR antagonists are likely to improve anhedonia are strong relative to the data indicating that there will be other therapeutic effects of KOR antagonists. As a result, it seems likely that, if there are any therapeutic effects of these agents in those with mood and anxiety spectrum disorders, a therapeutic effect on anhedonia would be evident. As a result, anhedonia is an appropriate primary endpoint for a POC study with a KOR antagonist the treatment of patients with mood and anxiety spectrum disorders. Failure to demonstrate a therapeutic effect of a KOR antagonist on the neural circuitry related to anhedonia using a dosage that had been demonstrated to have acceptable kappa opiate receptor occupancy would be a reasonable indication to fail KOR antagonism as a treatment for mood and anxiety disorders.

3. STUDY DESIGN

3.1 Overview

This study will be a six-site randomized, double-blind, PBO-controlled, parallel-group mono-therapy study to assess the effects of LY2456302 compared to PBO in adults age 21-65 years with mood and anxiety spectrum disorders. We will recruit a total of 90 subjects, of which 45 will be randomized to LY2456302 and 45 to placebo for 8 weeks of treatment.

3.2 Procedures

Screening Visit: **Day -30 to Day -1 (4 – 6 hours):**

Subjects will undergo a set of screening tests to determine if they meet the inclusion/exclusion criteria for the study. These screening tests will include:

- Medical, psychiatric, and medication history
- Vital signs (temperature, blood pressure, and pulse)
- Physical examination
- Pregnancy Test (beta-HCG serum pregnancy test – females only)
- Electrocardiogram (ECG)
- Urine drug screen
- Mini-International Neuropsychiatric Interview (MINI)
- Snaith-Hamilton Pleasure Scale (SHAPS)
- Temporal Experience of Pleasure Scale (TEPS)
- Visual Analogue Scale for Anhedonia (VAS)
- Columbia Suicide Severity Rating Scale (CSSRS)
- Clinical Global Impression – Severity (CGI-S)
- Battery of clinical laboratory tests including: Complete blood count with differential, Electrolytes, Metabolic Panel, Thyroid Function Tests, Urinalysis
- Urea Breathe Test to test for the presence of *Heliobacter pylori*,
- Mock MRI scanning session

Those who qualify to continue with the study based on the screening assessment will be asked to return 1-30 days later for additional evaluations. Subjects who require medication tapering will discuss a medication tapering plan with a study physician during this visit (for details see Section 4.1. Study Overview). This plan will be designed so that subjects are free of all excluded medications at least 5 half-lives prior to the baseline visit (see Section 3.3. Exclusion Criteria). Qualifying subjects will be instructed about not using any prohibited medications during the study including substances of abuse. They will be specifically instructed about not using Salvia divinorum, which has kappa opioid agonist effects and is not an illegal substance.

Baseline: Day 0 (A0) Visit (6 – 8 hours):

Following rigorous screening, subjects will return to the clinic/research unit up to 30 days later and undergo the following assessments and procedures:

- Structural MRI, fMRI during Monetary Incentive Delay Task, Resting State Connectivity fMRI

- Interval history
- Battery of clinical laboratory tests including: Complete blood count with differential, Electrolytes, Metabolic Panel, Thyroid Function Tests, Urinalysis.
- EEG
- Vital signs (temperature, blood pressure, and pulse)
- Physical examination
- Electrocardiogram (ECG)
- Snaith-Hamilton Pleasure Scale (SHAPS)
- Temporal Experience of Pleasure Scale (TEPS)
- Visual Analogue Scale for Anhedonia (VAS)
- Columbia Suicide Severity Rating Scale (CSSRS)
- Probabilistic Rewards Task (PRT)
- Effort Expenditure for Rewards Task (EefRT)
- Hamilton Depression Rating Scale (HAM-D)
- Hamilton Anxiety Rating Scale (HAM-A)
- The Cognitive and Physical Functioning Questionnaire (CPFQ)
- Clinical Global Impression – Severity (CGI-S)
- Clinical Global Impression – Improvement (CGI-I)
- Adverse events assessment with the Patient Reported Inventory of Side-Effects (PRISE)
- Blood sample collection for tests for assessment for gastric adverse events including gastrin, and pepsinogen I/II levels.
- Blood sample collection to be sent to Rutgers for potential genetic analysis or other future analysis (optional)

At the end of this visit subjects will be randomized to LY2456302 10 mg or placebo, will be provided with enough study medication for a 2-week period and will be instructed to take the medication every morning. Subjects will also be instructed to bring all of their study drug packaging and unused study drug with them to each visit.

Week 2 Visits (4 – 6 hours per visit):

At this visit subjects will undergo the following assessments and procedures:

- Interval history
- Battery of clinical laboratory tests including: Complete blood count with differential, Electrolytes, Metabolic Panel, Thyroid Function Tests, Urinalysis
- Vital signs (temperature, blood pressure, and pulse)
- Physical examination
- Electrocardiogram (ECG)
- Snaith-Hamilton Pleasure Scale (SHAPS)
- Temporal Experience of Pleasure Scale (TEPS)
- Visual Analogue Scale for Anhedonia (VAS)
- Columbia Suicide Severity Rating Scale (CSSRS)
- Clinical Global Impression – Severity (CGI-S)
- Clinical Global Impression – Improvement (CGI-I)
- Adverse events assessment with the Patient Reported Inventory of Side-Effects (PRISE)
- Inspection of medication blister packs to assess medication adherence

- Blood sample for drug blood level testing

At the end of this visit subjects will receive enough study medication for another 2 week period, and will be instructed to take the medication each morning, to bring all study drug packing and unused study drug to the next visit, and to return to the clinic/research unit in 2 weeks.

Week 4 Visit (4 – 6 Hours):

At this visit subjects will undergo the following assessments and procedures:

- Interval history
- Battery of clinical laboratory tests including: Complete blood count with differential, Electrolytes, Metabolic Panel, Thyroid Function Tests, Urinalysis.
- Vital signs (temperature, blood pressure, and pulse)
- Physical examination
- Electrocardiogram (ECG)
- Snaith-Hamilton Pleasure Scale (SHAPS)
- Temporal Experience of Pleasure Scale (TEPS)
- Visual Analogue Scale for Anhedonia (VAS)
- Columbia Suicide Severity Rating Scale (CSSRS)
- Inspection of medication blister packs to assess medication adherence
- Blood sample for drug blood level testing
- Clinical Global Impression – Severity (CGI-S)
- Clinical Global Impression – Improvement (CGI-I)
- Adverse events assessment with the Patient Reported Inventory of Side-Effects (PRISE)
- Blood sample for tests for assessment for gastric adverse events including gastrin, and pepsinogen I/II levels.

At the end of this visit subjects will receive enough study medication for another 2 week period, and will be instructed to take the medication each morning, to bring all study drug packing and unused study drug to the next visit, and to return to the clinic/research unit in 2 weeks.

Week 6 Visit (4 – 6 Hours):

At this visit subjects will undergo the following assessments and procedures:

- Interval history
- Battery of clinical laboratory tests including: Complete blood count with differential, Electrolytes, Metabolic Panel, Thyroid Function Tests, Urinalysis.
- Vital signs (temperature, blood pressure, and pulse)
- Physical examination
- Electrocardiogram (ECG)
- Snaith-Hamilton Pleasure Scale (SHAPS)
- Temporal Experience of Pleasure Scale (TEPS)
- Visual Analogue Scale for Anhedonia (VAS)
- Columbia Suicide Severity Rating Scale (CSSRS)
- Inspection of medication blister packs to assess medication adherence
- Blood sample for drug blood level testing

- Clinical Global Impression – Severity (CGI-S)
- Clinical Global Impression – Improvement (CGI-I)
- Adverse events assessment with the Patient Reported Inventory of Side-Effects (PRISE)

At the end of this visit subjects will receive enough study medication for another 2 week period, and will be instructed to take the medication each morning, to bring all study drug packing and unused study drug to the next visit, and to return to the clinic/research unit in 2 weeks.

Week 8 Visit (6 – 8 Hours):

At this visit subjects will undergo the following assessments and procedures:

- Structural MRI, fMRI during Monetary Incentive Delay Task, Resting State Connectivity fMRI
- Interval history
- Battery of clinical laboratory tests including: Complete blood count with differential, Electrolytes, Metabolic Panel, Thyroid Function Tests, Urinalysis
- Electroencephalogram (EEG)
- Vital signs (temperature, blood pressure, and pulse)
- Physical examination
- Electrocardiogram (ECG)
- Snaith-Hamilton Pleasure Scale (SHAPS)
- Temporal Experience of Pleasure Scale (TEPS)
- Visual Analogue Scale for Anhedonia (VAS)
- Columbia Suicide Severity Rating Scale (CSSRS)
- Probabilistic Rewards Task (PRT)
- Effort Expenditure for Rewards Task (EefRT)
- Hamilton Depression Rating Scale (HAM-D)
- Hamilton Anxiety Rating Scale (HAM-A)
- The Cognitive and Physical Functioning Questionnaire (CPFQ)
- Blood sample collection to be sent to Rutgers for potential genetic analysis or other future analysis (optional)
- Clinical Global Impression – Severity (CGI-S)
- Clinical Global Impression – Improvement (CGI-I)
- Blood sample for tests for assessment for gastric adverse events including gastrin and pepsinogen I/II levels.
- Adverse events assessment with the Patient Reported Inventory of Side-Effects (PRISE)
- Inspection of medication blister packs to assess medication adherence
- Blood sample for drug blood level testing

At the end of this visit study drug will be discontinued and subjects will be instructed to return to the clinic/research unit in 4 weeks.

Week 12 Visit: Post Medication Follow-up (2 – 4 hours)

At this visit subjects will undergo the following assessments:

- Vital signs
- Interval history

- Snaith-Hamilton Pleasure Scale (SHAPS)
- Temporal Experience of Pleasure Scale (TEPS)
- Visual Analogue Scale for Anhedonia (VAS)
- Columbia Suicide Severity Rating Scale (CSSRS)
- Adverse events assessment with the Patient Reported Inventory of Side-Effects (PRISE)
- Clinical Global Impression – Severity (CGI-S)
- Clinical Global Impression – Improvement (CGI-I)

At the conclusion of this visit subject participation in the study will end.

End of Participation

At the end of the week 12 visit, participation in the study will end. The results of all of the laboratory assessments and EEGs, ECGs, and physical examinations that could affect the subject's health care will be shared with them and their health care provider if they would like this to occur. Subjects will meet with the study physician and options for treatment will be reviewed. Participants will not be informed as to their treatment assignment at this meeting.
In case a subject is lost-to-follow-up, every possible effort must be made by the study site personnel to contact the subject and determine the reason for withdrawal. The measures taken to follow up must be documented.

Subjects have the right to withdraw from the study at any time for any reason. If a subject withdraws from the study before Week 8, the subject should have a complete evaluation performed at the time of withdrawal that includes all Week 8 procedures **EXCEPT fMRI** (see Table 3 Schedule of Assessments). Subjects will be followed through Week 12 follow up unless they specifically withdraw their consent for further contact or for medical records review. When a subject withdraws before completing the study, the reason for withdrawal is to be documented on the eCRF and in the source document. Subjects who withdraw will not be replaced.

4. STUDY POPULATION

4.1 Overview of Study Population

We will enroll 90 subjects in this trial. The inclusion and exclusion criteria are listed below. We will stratify enrollment to ensure that there is ample cross-diagnostic representation so that the therapeutic effects of LY2456302 on anhedonia may be assessed independently of its effect on any particular mood and anxiety spectrum disorder. This will be accomplished by requiring that at least 33% of the subjects randomized meet the anhedonia entry criteria and have an anxiety disorder but do not currently meet major depressive disorder (MDD) criteria based on the MINI (subjects with a past history of MDD but who do not currently meet diagnostic criteria could be included). Anhedonia is a core symptom of MDD and one of its diagnostic criteria but this is not the case for anxiety disorders. As a result, we are including a requirement for inclusion of patients with anxiety disorders because without such a criterion, we run the risk of only including subjects with anhedonia occurring in the setting of MDD, which would result in our being unable to distinguish an antidepressant effect which included a beneficial effect on anhedonia from an anhedonia-specific effect.

4.2 Inclusion Criteria

1. Age between 21 and 65 years of age
2. Must meet DSM-IV TR diagnostic criteria for: Major Depressive Disorder, Bipolar I or II Depressed, Generalized Anxiety Disorder, Social Phobia, Panic Disorder, or Post Traumatic Stress Disorder
3. Snaith-Hamilton Pleasure Scale (SHAPS) score ≥ 20
4. Reliable and willing to be available for the duration of the study
5. Willing and able to give written informed consent to participate
6. Able to understand and comply with instructions
7. If female of childbearing potential, must agree to use dual methods of contraception and be willing and able to continue contraception for 6 weeks after the last dose of study drug. Females using oral contraception must have started using it at least 2 months prior to the Baseline Visit
8. If male of childbearing potential, must have undergone surgical sterilization (such as a vasectomy) or agree to use a condom used with a spermicide during participation in the study and for 1 month afterward

4.3 Exclusion Criteria

1. Expected to require hospitalization during the course of the study
2. Current/history of a psychotic disorder, current manic or mixed episode, autism spectrum disorders, mental retardation
3. Met DSMIV-TR criteria for substance abuse within the last 3 months or substance dependence within the last 6 months, excluding caffeine and/or nicotine
4. History of unstable or untreated serious medical condition based on physician evaluation, medical history, and screening laboratory testing
5. Active suicidal intent or plan, or history of attempt within the past 3 months based on physician evaluation and Columbia Suicide Severity Rating Scale (C-SSRS)
6. Use of any antidepressant, antipsychotic, anxiolytic, anticonvulsant, mood stabilizing, muscle relaxant, centrally acting antihistaminergic, stimulant or insomnia medications (See Appendix 2) within 5 half-lives of baseline or at any time during after baseline
7. Use of any medication that is primarily metabolized by Cytochrome P450 2C8 within 14 days of baseline or at any time during the study. This includes: Cerivastatin, Paclitaxel, Repaglinide, Sorafenib, Rosiglitazone, Trimethoprim, Amodiaquine, Morphine, Amiodarone, Cabazitaxel, Carbemazepine, Chloroquine, Ibuprofen, Teprostinil, Torsemide.
8. Any contraindications to the magnetic resonance imaging procedures
9. Positive urine drug screen at any time during the study
10. Use of any investigational medication within 3 months prior to the start of this study or scheduled to receive an investigational drug other than the study drug during the course of this study
11. Known hypersensitivity to LY2456302
12. History of severe allergies or multiple adverse drug reactions
13. History of gastric disease (including peptic ulcer disease, gastritis, upper GI bleeding, or any GI precancerous condition), current clinically evident gastrointestinal complaints, or positive urea

breath test
14. Current use of a proton pump inhibitor or histamine 2 blocker, or a history of chronic NSAID use.
15. History of use of Salvia divinorum or use of Salvia divinorum at any time during the study.
16. Any other condition that in the opinion of the investigator would preclude participation in the study
17. Any smoking of cigarettes or use of other nicotine containing products within the last month or at any time during the study
18. Pregnant or lactating

5. RANDOMIZATION

IVRS Randomization will be carried out using the Simple Internal Randomization Engine (SIRE), which is a tool developed by the DCRI to randomize study patients. SIRE is fully integrated with the EDC database. A randomization list in hardcopy will also be kept under lock and key by the statistician as a back-up should the computer system be down. In case of system failure, the statistician will provide the individual dispensing the medication at a site with the medication allocation over the phone. It will also allow study physicians to obtain the randomization information from the statistician and procedures to break the blinding in cases of emergencies. All individuals having interactions with the subjects will remain blinded to treatment group assignment other than in cases of emergencies.

2. DURATION OF TREATMENT AND STUDY PARTICIPATION

Expected duration of study participation is up to 120 days, including up to 30 days of screening and Baseline, an 60-day treatment period, and a 30-day follow-up visit. Please see Table 1 (Milestones of Study) for additional information.

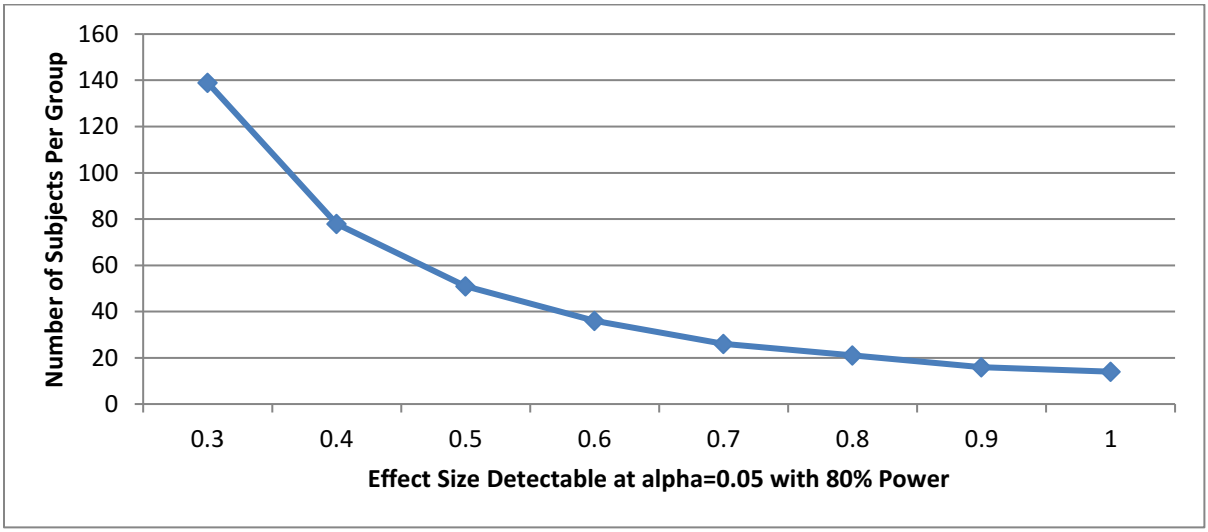
2. STATISTICAL ANALYSIS

7.1 Sample Size

A total of 90 subjects will be randomized: 45 subjects randomized to LY2456302 and 45 to placebo are included in the primary efficacy analysis. We conservatively anticipate that we will have incomplete data on up to 20% of subjects due to subject drop out or loss of data due to factors such as poor scan quality. As a result, we estimate that we could have complete data on as few as 72 subjects and as many as 90 subjects. In the Statistical Analysis section below, we outline how we will address the issue of missing data including carrying out analyses on the intent-to-treat (ITT) population and employing mixed effect models. If we assume the worst case scenario of 72 subjects, for a one tailed t-test at an

alpha value of 0.05, power is 80% to identify an effect size of 0.58. For a one tailed t-test at an alpha value of 0.10 power is 80% to identify an effect size of 0.50.

Our capacity to estimate the expected effect size on our primary outcome measure is limited by the studies that have been carried out with this measure to date. The most relevant study was carried out by Stoy and co-workers (2011) who evaluated 15 patients with major depression and 15 controls and administered open-label escitalopram to both groups for 6 weeks. However, it must be kept in mind that estimates of power based on this study are likely overly optimistic because this was an open-label treatment study and only included 15 depressed subjects. We can estimate the expected effect size for our study from the ventral striatal activation to reward anticipation subject group by time interaction observed in this study. The effect size for a greater increase in those with depression compared with controls is 0.88. We can also estimate effect size from the pre-to-post treatment difference in ventral striatal activation during reward anticipation and reward during the MID with fMRI within the depressed group which are 1.1 and 1.0 respectively. These effect sizes suggest that are likely to have more than sufficient power to detect a significant effect with our primary outcome measure in the proposed study at the alpha=0.05 level with 80% power.



7.2 Statistical Methods

Data Management: All data management activities, including establishing a trial eCRF, procedures for randomization and biomarker acquisition and tracking, will be done within the framework of DCRI and will conform to FDA GCP requirements.

Interim Analysis: As specified in the protocol, there will be no interim analysis carried out.

Primary Efficacy Analysis: We will employ "Intention-to-Treat" (ITT) principles. Statistical tests will be performed based on a one-sided test at the 5% level of significance. Supporting analyses will also be performed. An "as treated" analysis will be done per the actual treatment patients received. A "per protocol" analysis will restrict the analysis to participants who receive minimal exposure to the intervention, have a minimal number of longitudinal evaluations, and/or are free of major protocol violations. A "completer" analysis will only include participants who completed acute treatment without exiting or prematurely terminating from their assigned treatment. Because participants may be removed differentially across the treatment arms in these analyses, both approaches are vulnerable to differential selection bias and will be interpreted cautiously.

Point estimate and the corresponding confidence interval for the primary study outcome (fMRI ventral striatal activation during reward anticipation of reward during the MID) of the adjusted predicted score will be obtained. A mixed effects model analysis will be carried out for the primary outcome of the study, task-related fMRI activation in the ventral striatum during anticipation of reward occurring during the Monetary Incentive Delay Task. This analysis will test the hypothesis that LY2456302 will lead to a greater increase in ventral striatal activation during anticipation of reward than placebo.

Most of the study outcomes are observed repeatedly at well-defined time-points post-randomization, so that statistical methods for repeated measures data will be applied. This includes the linear model with structured covariance matrices and the mixed effects models as implemented in PROC MIXED in SAS. Site will also be included as an independent variable in order to account for variability among the study sites.

Secondary Efficacy Analysis : A mixed effects model analysis will also be carried out for the secondary outcomes of the study, SHAPS score and PRT-derived Reward Learning and Response Bias. These analyses will test the hypothesis that LY2456302 will: 1) decrease SHAPS score to a greater degree than PBO; and 2) increase PRT-derived reward learning and response bias to a greater degree than PBO.

Exploratory Analysis: Exploratory mixed effects model analyses will also be carried out with the exploratory outcomes of the study. This includes: ventral striatal fMRI activation during anticipation of loss during the MID Task; resting state delta EEG current density in the rostral anterior cingulate; resting state fMRI connectivity; self-rated affective responses to cues and feedback during the MID Task; EefRT total reward; VAS score; TEPS anticipatory and consummatory pleasure scores; HAM-D score; HAM-A score; CGI-S, CGI-I, and CPFQ score.

Covariates in Regression Models: The baseline value of the outcome, centered about its sample mean, will be included in each analysis. Otherwise, only age and sex will be entered as covariates.

Missing Values in Longitudinal Data: We will proactively monitor the amount of missing data, and ensure that we respond quickly to emerging problems. Statistically, missing data will be addressed through the use of mixed models analysis which will be carried out with PROC MIXED in SAS. We will carry out an assessment of the degree to which the structured covariance matrix in mixed effects models fits the data.

Other Confounders Arising Post-Randomization: Logistic regression analysis will be carried out to investigate: (a) adherence to the assigned study intervention, (b) co-administration of psychotropic medications, and (c) discontinuation from the study intervention, and we will apply logistic regression analysis to investigate these factors. First, we will determine whether these effects occur differentially across the treatment arms suggesting that a differential selection bias may have influenced the results. Then, we will investigate whether baseline characteristics are predictive of any behavior. This will include demographic characteristics, initial severity as measured by the baseline values of the outcome variables, and clinical characteristics such as diagnoses and medications taken at baseline.

Magnitude of the Clinical Effect: To evaluate the clinical significance of the impact of treatment on outcome, effect sizes (Hedge's g) will be calculated as (ME – MC) / SD pooled, where ME represents the adjusted mean of experimental treatment, MC represents the adjusted mean of the comparison treatment, and SD pooled represents pooling of the standard deviations from within both groups. For dichotomous outcomes, the number needed to treat (NNT) or harm (NNH)–defined as the number of subjects who need to be treated in order to bring about one additional good outcome (NNT) or harm (NNH)—will be calculated (± 95% CI) according to methods outlined by Sackett and colleague

7.3 Primary and Secondary Efficacy Assessments

The capacity of LY2456302 for engaging reward circuitry in those with mood and anxiety spectrum disorders will be assessed as follows

- The **Primary Outcome** for this study will be task-related fMRI ventral striatal (e.g., nucleus accumbens) activation occurring with reward and anticipation during the Monetary Incentive Delay (MID) Task

- The **Secondary Outcomes** will be:

    - An objective behavioral measure of anhedonia, the Probabilistic Reward Task (PRT).
    - A clinical self-report measure of anhedonia, the Snaith-Hamilton Pleasure Scale (SHAPS)

Monetary Incentive Delay Task-related fMRI

fMRI during the Monetary Incentive Delay (MID) Task will be obtained as the primary outcome in the proposed study in order to establish Proof of Concept in terms of a change in a neurobiological target. This neurobiological target will be the neural circuitry of the hedonic response, alterations of which we hypothesize underlie core clinical symptoms in patients with Mood and Anxiety Spectrum Disorders. Engagement of this neurobiological target will be evaluated with task-related fMRI assessments consisting of obtaining fMRI during the Monetary Incentive Delay Task (Wacker et al., 2009; Pizzagalli et

al., 2004, 2009; Knutson et al., 2008). This measure was chosen because it provides functional neural circuit-based indices of the hedonic response to stimuli. This is manifested in terms of the degree of activation of the ventral striatum. Evidence supporting the use of the Monetary Incentive Delay Task-related fMRI for this purpose is that depressed patients were found to have decreased ventral striatal activation to anticipated reward with this task (Knutson et al., 2008) and that this measure has been demonstrated to be sensitive to changes occurring with antidepressant/anxiolytic therapies (SSRI and SNRI) in a small open-label studies including those with major depression and healthy controls and a double-blind placebo-controlled study in healthy controls (Stoy et al., 2012; Ossewaarde et al., 2011).

This test will be obtained at baseline and at the end of double-blind treatment and will be carried out as previously described (Knutson et al., 2008).

Probabilistic reward task

The Probabilistic Reward Task (PRT) (adapted from Tripp & Alsop (1999)), was designed to objectively assess participants' propensity to modulate behavior as a function of reinforcement history. This task has been validated in multiple independent samples (e.g., Barr et al. 2008; Bogdan and Pizzagalli, 2006, 2009; Pizzagalli et al. 2005, 2007, 2008; Vrieze et al., 2012). Participants will complete two blocks of 100 trials, in which they will be asked to determine whether a briefly presented mouth on a cartoon face was 'long' or 'short', and report their decision by pressing one of two corresponding keys on a computer keyboard ('z' or '/'). Importantly, the brief presentation time (100 ms) and the minimal difference in length between the two target stimuli (11.5 vs. 13 mm) make it difficult for participants to perceptually distinguish which stimulus is presented. Moreover, an asymmetrical reinforcement ratio is implemented across the two blocks so that one of the two stimuli (the 'rich' stimulus) is consistently rewarded ("Correct!! You Won 5 Cents") three times more frequently than the 'lean' stimulus (30 vs. 10 times per block). Reinforcement allocation and key assignments will be counterbalanced across participants. Participants are instructed to respond as quickly and accurately as possible to maximize monetary rewards, and that not all correct responses will be followed by rewards. In healthy participants, such asymmetric reinforcement schedule has been found to induce a systematic preference (response bias) for choosing the stimulus paired with more frequent reward (Macmillan & Creelman, 2005).

Healthy controls are able to successfully modulate their behavior based on their experience, resulting in a significant response bias for the more frequently rewarded stimulus. In contrast, individuals with elevated depressive symptoms (Pizzagalli et al 2005) or MDD (Pizzagalli et al 2008c) show a blunted response bias, and overall reduced reward learning. Of note, reward learning negatively correlated with anhedonic symptoms and predicted them one month later (Bogdan and Pizzagalli 2006; Pizzagalli et al 2005). Moreover, trial-by-trial probability analyses revealed that MDD subjects were impaired at integrating reinforcements over time and expressing a response bias in the absence of immediate reward. This impairment correlated with anhedonic symptoms, even after considering anxiety and distress symptoms (Pizzagalli et al 2008c).

Data reduction and analyses. After removing trials with outlier reaction times (see Pizzagalli et al. 2005 for detail), response bias (log b) will be computed according to the following formula:

To avoid issues related to having a zero in one cell of the formula, 0.5 will be added to every cell of the detection matrix (Hautus, 1995). As evident from the formula, response bias reflects the participants' preference for the stimulus paired with more frequent rewards. Reward learning will be operationalized as the change in response bias from Block 1 to Block 2.

We will collect data at two timepoints which will each consist of two blocks of data for which our intent is to compute the change in response bias (RB) between these two blocks: RB = Response Bias (Block 2) – Response Bias (Block 1). Response Bias will be computed for each block (formula written above). We will collect the following 16 numbers:

Baseline:

i) Rich correct block 1; ii) Lean incorrect block 1; iii) Rich incorrect block 1; iv) Lean correct block 1; v) Rich correct block 2; vi) Lean incorrect block 2; vii) Rich incorrect block 2; viii) Lean correct block 2;

End of Double-Blind Treatment:

i) Rich correct block 1; ii) Lean incorrect block 1; iii) Rich incorrect block 1; iv) Lean correct block 1; v) Rich correct block 2; vi) Lean incorrect block 2; vii) Rich incorrect block 2; viii) Lean correct block 2;

The results of number of studies provide the rationale for using the PRT in this study and considering using the PRT to select subjects for entry into the trial. This includes a study identifying that PRT score predicts clinical outcome to naturalistic antidepressant treatment. In this study, 69 inpatients and 63 healthy controls performed the PRT at baseline (i.e., at intake for patients), and patients were administered the task again after 8 weeks of antidepressant treatment (Vrieze, Pizzagalli et al, in press). Relative to controls, MDD patients showed reduced reward learning ($F(2,280)=3.53$, $p=0.03$). Critically, this blunting was found only in patients with high anhedonia ($p=0.007$). Second, MDD subgroup (low vs. high anhedonia, as defined by the Snaith Hamilton Pleasure Scale (SHAPS) cutoff of 7) predicted reward learning when controlling for overall depression severity ($R2=0.13$, $p=0.001$). Of note, HDRS scores were not related to reward learning. Also SHAPS score uniquely predicted reward learning even when controlling for depression severity (HRSD scores) and anxiety comorbidity ($\beta=0.33$, $t=3.08$, $p=0.003$). Third, reduced reward learning at study entry increased the odds of a persisting diagnosis of MDD after 8 weeks of treatment (OR: 7.84, CI: 1.17-52.42, $p=0.03$).

The Snaith-Hamilton Pleasure Scale (SHAPS)

The Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995) is a well-validated 14-item questionnaire used to assess anhedonia. It asks participants to agree or disagree with statements of hedonic response in pleasurable situations (e.g., "I would enjoy my favorite television or radio program"). Four responses are possible: Strongly disagree, Disagree, Agree, or Strongly agree. Each item on the SHAPS is worded so that higher scores indicate greater pleasure capacity. A total score can be derived by summing the responses to each item. Items answered with "strongly agree" are coded as "1", while a "strongly disagree" response was assigned a score of "4." Therefore, scores on the SHAPS can range from 14 to 56, with higher scores corresponding to higher levels of anhedonia. The SHAPS covers four domains of hedonic experience: interest/pastimes, social interaction, sensory experience, and food/drink (Snaith et al., 1995). Participants completing the SHAPS are instructed to respond based on their ability to experience pleasure "in the last few days." This scale has shown adequate overall psychometric properties in clinical and student samples (Gilbert, Allan, Brough, Melley, & Miles, 2002; Snaith et al., 1995). The SHAPS convergent validity has been supported by its correlations with MADRS Hedonic Tone item, the Mood and Anxiety Symptom Questionnaire Anhedonic Depression subscale, and Positive and Negative Affect Schedule-Positive Affect subscale (Gilbert et al., 2002; Snaith et al., 1995). Its discriminant validity has been supported by its lack of association with MADRS Depressed Mood and Anxiety items (Snaith et al., 1995). The SHAPS has satisfactory test-retest validity in healthy participants over an interval of three weeks (intraclass correlation coefficient between test and retest: $r = .70$, $p < .001$; Franken, Rassin & Murris, 2007). Besides being well-validated, the SHAPS is of utility for our study because there is an established cutoff for clinical significance. Although this is also true for the Anhedonic Depression subscale of the Mood and Anxiety Symptoms Questionnaire (MASQ), we wanted a scale that assessed anhedonia and was not depression specific or specific to any other disorder given the goal of using it across diagnostic boundaries. ROC using MADRS anhedonia item score (cutoff was clinically significant level) as discriminator suggests that a SHAPS score of ≥ 20 is clinically significant anhedonia (Snaith et al., 1995). This was validated in 30 volunteers from the general population. It should be noted that the original ROC analysis was done with dichotomous ratings rather than the current 4 option rating system. The original finding was that 3 or more negative answers indicated clinical significance which corresponds to a score of at least 20 with the current rating system. One other important consideration that supports the use of the SHAPS in this study is that it is the only anhedonia measure that we are aware of that has been found to significantly improve with the administration of a treatment in at least one clinical trial (Di Giannantonio and Martinotti, 2012; Martinotti et al., 2011). In a study of alcohol dependent individuals, treatment with acetyl-l-carnitine led to statistically significantly greater improvement in the SHAPS than placebo by 10 days after initiating treatment (Martinotti et al., 2011). In an 8-week trial comparing the effects of venlfafaxine XR and agomelatine treatment in depressed patients, significant improvement from baseline on the SHAPS was observed in both groups with significantly greater improvement being found for the agomelatine treated patients (Di Giannantonio and Martinotti, 2012).

Finally, SHAPS scores among healthy participants have been related to reward-related activation within frontostriatal pathways (see e.g., Wacker et al., 2009), providing an additional reason for its inclusion in the current study.

The SHAPS will be collected at all study visits. It will be used to screen subjects for having anhedonia as part of inclusion/exclusion assessment. It will also be compared in subjects receiving LY2456302 and PBO in secondary analysis to assess the effects on a clinical self-rated measure of anhedonia.

7.4. Other Efficacy Assessments

Other efficacy assessments carried out in this study to be employed in exploratory analyses include ventral striatal fMRI activation during anticipation of loss during the MID Task; resting state delta EEG current density in the rostral anterior cingulate; resting state fMRI connectivity; self-rated affective responses to cues and feedback during the MID Task; EefRT total reward; VAS score; TEPS anticipatory and consummatory pleasure scores; HAM-D score; HAM-A score; CGI-S, CGI-I, and CPFQ score.

The VAS-Anhedonia, TEPS, and CPFQ are self-report instruments. The EefRT is a behavioral task and this task and the HAM-D, and HAM-A will be administered by appropriately trained and monitored raters. The training, assessment and maintenance of inter-rater reliability will be managed by the Duke Signal Detection Team. Clinical raters, neuropsychological technicians, and all staff involved in collection and analysis of clinical measures will be blinded to treatment assignment and to clinical status. They will have no interactions with subjects other than the administration of the specific tests they are assigned to administer. Raters and patients will complete best-guess forms so that the adequacy of the blind can be assessed. Best-guess forms will be used to formally assess the adequacy of the blind for patients and raters.

7.5. Exploratory Assessments

Exploratory Anhedonia Measures: To complement the SHAPS we include 3 secondary anhedonia measures: the Effort-Expenditure for Rewards Task (EefRT), the Visual Analogue Scale for Anhedonia (VAS-Anhedonia) and the Temporal Experience of Pleasure Scale (TEPS). These will be compared in subjects receiving LY2456302 and PBO in exploratory analysis.

The ***Effort-Expenditure for Rewards Task*** (EefRT; Treadway et al., 2009) is intended to assess the motivation to pursue rewards, one important dimension of reward-related function. It has been validated in a study of 60 individuals who were screened to have anhedonia with the SHAPS (Treadway et al., 2009). The EefRT was found to be correlated with the Beck Depression Inventory (BDI) anhedonia scale and the Chapman anhedonia scale. The EefRT task is a multi-trial game in which participants are given an opportunity on each trial to choose between two different task difficulty levels in order to obtain monetary rewards.

The ***VAS-Anhedonia*** is a standard VAS assessment of anhedonia severity which is included because it provides a global anhedonia indicator which takes very little time to obtain and which was found to be

sensitive to change with treatment in a prior placebo-controlled trial in alcohol dependent subjects (Martinotti et al., 2011). The test consists of making a rating on a 100 mm scale in response to the directive: "Make a mark on the line below that indicates how much pleasure you experience from food, sexual behavior, and meeting friends". At the left end of the scale is the anchor "No Pleasure" and at the right end of the scale is the anchor "Extreme Pleasure."

We also include the ***Temporal Experience of Pleasure Scale*** (TEPS) because it provides different information about reward-related function than the SHAPS and has been found to be correlated with activation in the key circuits of interest (nucleus accumbens and putamen) in Monetary Incentive Delay Task-related fMRI (Stanford et al., 2011). The TEPS is an 18-item self-report measurement of anticipatory (10 items) and consummatory (eight items) components of anhedonia which consists of a series of statements that must be rated according to how accurate they are for the individual (Gard et al., 2006). The scale differentiates the role of anticipatory pleasure ('wanting') from consummatory pleasure ('liking'). Both components are currently believed to be relevant to measuring anhedonia.

Other Exploratory Measures

The ***Hamilton Rating Scale for Depression*** *(HAM-D)* 17-item version (Hamilton, 1967) will be included in exploratory analysis to provide confirmatory support for changes in depression severity with treatment. This interviewer-administered semi-structured interview is one of the most widely used instruments in depression treatment studies.

The ***Hamilton Rating Scale for Anxiety*** *(HAM-A)* is a rating scale designed to measure the severity of anxiety symptoms (Hamilton, 1959). It is widely used in both clinical and research settings. The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). It has been demonstrated to acceptable reliability, validity and sensitivity to change (Maier, 1988). Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56, where <17 indicates mild severity, 18–24 mild to moderate severity and 25–30 moderate to severe. This instrument will be included in secondary analysis to provide confirmatory support for changes in anxiety severity with treatment.

The ***Cognitive and Physical Functioning Questionnaire*** *(CPFQ)* is a 7-item self-report instrument was intended to be a brief scale for measuring cognitive and executive dysfunction in patients with mood and anxiety disorders (Fava et al., 2009). This scale has been demonstrated to have strong internal consistency, good temporal stability and sensitivity to change with treatment (Fava et al., 2009). Intended to be a brief scale for measuring cognitive and executive dysfunction in patients with mood and anxiety disorders (Fava et al., 2009). This scale has been demonstrated to have strong internal consistency, good temporal stability and sensitivity to change with treatment (Fava et al., 2009).

The ***Clinical Global Impression – Severity*** *(CGI-S)* is a widely administered clinician rated global measure of subject overall illness severity. Subjects are rated on a 1-7 scale where 1 corresponds to "Normal, Not at All Ill", 2 is "Borderline Mentally Ill", the anchor for 3 is "Mildly Ill", the anchor for 4 is "Moderately Ill", 5 is "Markedly Ill", 6 is "Severely Ill", and 7 is "Among the Most Extremely Ill Patients". It will be administered at all subject visits.

The ***Clinical Global Impression – Improvement*** *(CGI-I)* is a widely administered clinician rated global measure of the degree of improvement from the initial assessment in subject overall illness severity.

Subjects are rated on a 1-7 scale where 1 corresponds to “Very Much Improved”, 2 is “Much Improved”, the anchor for 3 is “Minimally Improved”, the anchor for 4 is “No Change”, 5 is “Minimally Worse”, 6 is “Much Worse”, and 7 is “Very Much Worse”. It will be administered at all subject visits.

During the course of the trial subjects for whom the CGI-I is greater than 5 will be removed from the study and appropriate care given, for safety purposes.

7.6. Psychiatric Diagnostic Assessment

The psychiatric diagnostic assessment will consist of a clinical interview and administration of the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). The MINI is a brief, structured psychiatric interview administered to determine the presence of any neuropsychiatric disorders). It is a reliable and valid psychiatric diagnostic instrument. It will be used in place of other lengthier diagnostic tools (i.e., SCID-I) in order to decrease subject burden.

7.7. Safety/Adverse Effects Assessments

Safety assessments will be collected as secondary outcome measures for this Phase 2A study and will be conducted throughout the study at the protocol specified treatment visits. Specific safety assessments will include: Spontaneously reported adverse events (Aes) and the Columbia Suicide Severity Rating Scale (C-SSRS) (Posner, 2011). The C-SSRS will be administered at screening, baseline, and all assessment visits (See Table 2 Schedule of Assessments). Aes will be rated by the identifying investigator for relationship to study drug and severity. Unexpected Aes and all those rated as serious Aes will be reported to the relevant IRBs and the FAST-MAS PI, Dr. Krystal, who will communicate these to the study Data and Safety Monitoring Board (DSMB) and the FAST-MAS NIMH Program Officers. All Aes will be tabulated and provided to the DSMB on a regular basis for their review. Appropriate medical care will be provided to all those experiencing Aes. This may include referral to an appropriate practitioner outside of the study, transfer to an Emergency Room, or hospital admission. All subjects with Aes will be monitored regularly for the status of their AE until the AE is resolved.

7.8. Vital Signs/Laboratory Assessments

These assessments will include vital signs (height, weight, blood pressure, and pulse), beta-HCG test, urine drug screen, laboratory assessments (Complete blood count with differential, Electrolytes, Metabolic Panel [including liver function tests], Thyroid Function Tests, Urinalysis), and ECG. Tests for assessment of gastric adverse events include: gastrin, pepsinogen I/II, intrinsic factor, antiparietal antibodies, and vitamin B12 levels. Height will be assessed at baseline only. Otherwise vital signs will be obtained at all treatment visits. Beta-HCG, urine drug screen, and height will be obtained only at baseline. The laboratory assessments will occur at baseline and all assessment visits. ECG testing will occur 1,2,3 minutes after initial dosing and then at all assessment visits (See Schedule of Assessments). These tests will be reviewed within 24 hours by the site PI or Co-investigator. Where clinically significant findings are noted, appropriate medical intervention will be recommended as indicated.

Appendix A. General Milestones of Study	**Study Months**
Contract Execution and Study Startup	4.0
First Subject Enrolled	12
Last Subject Enrolled	
Last Subject Completes Treatment and F/u	3.0*
Database Lock and Sites Closed	1.0
Statistical Analysis Complete	2.0
Manuscript (or Final Clinical Study Report) Complete	2.0

*First patient first visit to last patient last visit = 15 months

Appendix B. Schedule of Assessments, Outcome Measures, Labs, and Procedures	**Screening**	**Baseline**	**Follow up**	**Double-Blind Treatment Period**				**Follow Up**
Visit	**Screening**	**A0**	**Phone**	**A1**	**A2**	**A3**	**A4**	**1 Month**
Weeks from Baseline	**Up to -4**	**0**	**1**	**2**	**4**	**6**	**8**	**12**
Informed Consent	**X**							
Physical Exam / Medical History / Demographics	**X**	**X**		**X**	**X**	**X**	**X**	
Treatment History	**X**	**X**		**X**	**X**	**X**	**X**	**X**
Mini-International Neuropsychiatric Interview (MINI)	**X**						**X**	
Clinical Interview/Interval History	**X**	**X**		**X**	**X**	**X**	**X**	
ECG	**X**	**X**		**X**	**X**	**X**	**X**	
Urine drug screen	**X**							
HCG	**X**							
Labs*	**X**	**X**		**X**	**X**	**X**	**X**	
Urea Breath Test for H. Pylori	**X**							
Medication Adherence				**X**	**X**	**X**	**X**	
fMRI with Monetary Incentive Delay Task, Resting State Connectivity		**X**					**X**	
Snaith-Hamilton Pleasure Scale (SHAPS)	**X**	**X**		**X**	**X**	**X**	**X**	**X**
Probabilistic Reward Task (PRT)		**X**					**X**	
Effort Expenditure for Rewards Task (EefRT)		**X**					**X**	
Quantitative EEG (QEEG)		**X**					**X**	
Temporal Experience of Pleasure Scale	**X**	**X**		**X**	**X**	**X**	**X**	**X**
Visual Analogue Scale for Anhedonia	**X**	**X**		**X**	**X**	**X**	**X**	**X**
HAM-D		**X**					**X**	
HAM-A		**X**					**X**	
Cognitive and Physical Functioning Questionnaire (CPFQ)		**X**					**X**	
Vital signs	**X**	**X**		**X**	**X**	**X**	**X**	**X**
Columbia Suicide Severity Rating Scale (CSSRS)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Blood Collection for Rutgers		**X**					**X**	
Blood Collection for Gastric Adverse Events**		**X**			**X**		**X**	
Blood Sample for Drug Blood Level Testing				**X**	**X**	**X**	**X**	
Adverse Effects Assessment with Patient Reported Inventory of Side-Effects (PRISE)		**X**		**X**	**X**	**X**	**X**	**X**

Clinical Global Impression-Severity (CGI-S)		X		X	X	X	X	X
Clinical Global Impression-Improvement (CGI-S)		X		X	X	X	X	X
Randomization		X						
Mock MRI Scanning Session	X							

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Appendix C. TABLE SHELLS

Table 1a. Demographics
Intent-to-Treat

	Placebo	LY	Total
Age			
21-35			
36-50			
51-65			
Gender			
Male			
Female			
Race/Ethnicity			
Caucasian			
African American			
Asian			
American Indian/Alaskan Native			
Native Hawaiian Or Other Pacific Islander			
Hispanic Origin			
Non-Hispanic Origin			
More than one race			
Unknown or not reported			

Table 1b. Demographics
As Treated

	Placebo	LY	Total
Age			
21-35			
36-50			
51-65			
Gender			
Male			
Female			
Race/Ethnicity			
Caucasian			
African American			
Asian			
American Indian/Alaskan Native			
Native Hawaiian Or Other Pacific Islander			
Hispanic Origin			
Non-Hispanic Origin			
More than one race			
Unknown or not reported			

Table 1c. Demographics

Per Protocol

	Placebo	LY	Total
Age			
21-35			
36-50			
51-65			
Gender			
Male			
Female			
Race/Ethnicity			
Caucasian			
African American			
Asian			
American Indian/Alaskan Native			
Native Hawaiian Or Other Pacific Islander			
Hispanic Origin			
Non-Hispanic Origin			
More than one race			
Unknown or not reported			

Table 1d. Demographics

Study Completers

	Placebo	LY	Total
Age			
21-35			
36-50			
51-65			
Gender			
Male			
Female			
Race/Ethnicity			
Caucasian			
African American			
Asian			
American Indian/Alaskan Native			
Native Hawaiian Or Other Pacific Islander			
Hispanic Origin			
Non-Hispanic Origin			
More than one race			
Unknown or not reported			

Table 2. Pre- to Post-Treatment Changes in fMRI Activation during Anticipation of Reward Primary Outcome

Outcome	Cases	Fixed Effect	Estimate	Standard Error	DF	95 Confidence Interval (Lower, Higher)	P-Value
fMRI Activation	ITT	Timept Treatment Timept* Treatment					
	As Treated	Timept Treatment Timept* Treatment					
	Per Protocol	Timept Treatment Timept* Treatment					
	Completers	Timept Treatment Timept* Treatment					

Table 3. Pre- to Post-Treatment Changes in SHAPS Secondary Outcome

Outcome	Cases	Fixed Effect	Estimate	Standard Error	DF	95 Confidence Interval (Lower, Higher)	P-Value
Snaith Hamilton Pleasure Scale (Clinical Anhedonia Measure)	ITT	Timept Treatment Timept* Treatment					
	As Treated	Timept Treatment Timept* Treatment					
	Per Protocol	Timept Treatment Timept* Treatment					
	Completers	Timept Treatment Timept* Treatment					

Table 4. Pre- to Post-Treatment Changes in PRT Secondary Outcome

Outcome	Cases	Fixed Effect	Estimate	Standard Error	DF	95 Confidence Interval (Lower, Higher)	P-Value
Probabilistic Reward Task (Behavioral Anhedonia Measure)	ITT	Timept Treatment Timept* Treatment					
	As Treated	Timept Treatment Timept* Treatment					
	Per Protocol	Timept Treatment Timept* Treatment					
	Completers	Timept Treatment Timept* Treatment					

Table 5. Pre- to Post-Treatment Changes in fMRI Activation During Anticipation of Loss For Exploratory Outcome

Outcome	Cases	Fixed Effect	Estimate	Standard Error	DF	95 Confidence Interval (Lower, Higher)	P-Value
Ventral Striatal fMRI Activation During Anticipation of Loss During the MID Task	ITT	Timept Treatment Timept* Treatment					
	As Treated	Timept Treatment Timept* Treatment					
	Per Protocol	Timept Treatment Timept* Treatment					
	Completers	Timept Treatment Timept* Treatment					

Table 6. Pre- to Post-Treatment Changes in Resting State Delta EEG Current Density in the Rostral Anterior Cingulate
For Exploratory Outcome

Outcome	Cases	Fixed Effect	Estimate	Standard Error	DF	95 Confidence Interval (Lower, Higher)	P-Value
Resting State Delta EEG Current Density in the Rostral Anterior Cingulate	ITT	Timept Treatment Timept* Treatment					
	As Treated	Timept Treatment Timept* Treatment					
	Per Protocol	Timept Treatment Timept* Treatment					
	Completers	Timept Treatment Timept* Treatment					

Table 7. Pre- to Post-Treatment Changes in Resting State fMRI Connectivity For Exploratory Outcome

Outcome	Cases	Fixed Effect	Estimate	Standard Error	DF	95 Confidence Interval (Lower, Higher)	P-Value
Resting State fMRI Connectivity	ITT	Timept Treatment Timept* Treatment					
	As Treated	Timept Treatment Timept* Treatment					
	Per Protocol	Timept Treatment Timept* Treatment					
	Completers	Timept Treatment Timept* Treatment					

Table 8. Pre- to Post-Treatment Changes in Self-rated Affective Responses to Cues and Feedback During the MID Task
For Exploratory Outcome

Outcome	Cases	Fixed Effect	Estimate	Standard Error	DF	95 Confidence Interval (Lower, Higher)	P-Value
Self-rated Affective Responses to Cues and Feedback During the MID Task	ITT	Timept Treatment Timept* Treatment					
	As Treated	Timept Treatment Timept* Treatment					
	Per Protocol	Timept Treatment Timept* Treatment					
	Completers	Timept Treatment Timept* Treatment					

Table 9. Pre- to Post-Treatment Changes in The EEfRT For Exploratory Outcome

Outcome	Cases	Fixed Effect	Estimate	Standard Error	DF	95 Confidence Interval (Lower, Higher)	P-Value
The Effort-Expenditure for Rewards Task (EEfRT)	ITT	Timept Treatment Timept* Treatment					
	As Treated	Timept Treatment Timept* Treatment					
	Per Protocol	Timept Treatment Timept* Treatment					
	Completers	Timept Treatment Timept* Treatment					

Table 10. Pre- to Post-Treatment Changes in VAS For Exploratory Outcome

Outcome	Cases	Fixed Effect	Estimate	Standard Error	DF	95 Confidence Interval (Lower, Higher)	P-Value
The Visual Analogue Scale for Anhedonia	ITT	Timept Treatment Timept* Treatment					
	As Treated	Timept Treatment Timept* Treatment					
	Per Protocol	Timept Treatment Timept* Treatment					
	Completers	Timept Treatment Timept* Treatment					

Table 11. Pre- to Post-Treatment Changes in TEPS For Exploratory Outcome

Outcome	Cases	Fixed Effect	Estimate	Standard Error	DF	95 Confidence Interval (Lower, Higher)	P-Value
The Temporal Experience of Pleasure Scale	ITT	Timept Treatment Timept* Treatment					
	As Treated	Timept Treatment Timept* Treatment					
	Per Protocol	Timept Treatment Timept* Treatment					
	Completers	Timept Treatment Timept* Treatment					

Table 12. Pre- to Post-Treatment Changes in HAM-A For Exploratory Outcome

Outcome	Cases	Fixed Effect	Estimate	Standard Error	DF	95 Confidence Interval (Lower, Higher)	P-Value
The Hamilton Anxiety Rating Scale (HAM-A)	ITT	Timept Treatment Timept* Treatment					
	As Treated	Timept Treatment Timept* Treatment					
	Per Protocol	Timept Treatment Timept* Treatment					
	Completers	Timept Treatment Timept* Treatment					

Table 13. Pre- to Post-Treatment Changes in HAM-D For Exploratory Outcome

Outcome	Cases	Fixed Effect	Estimate	Standard Error	DF	95 Confidence Interval (Lower, Higher)	P-Value
The Hamilton Depression Rating Scale (HAM-D)	ITT	Timept Treatment Timept* Treatment					
	As Treated	Timept Treatment Timept* Treatment					
	Per Protocol	Timept Treatment Timept* Treatment					
	Completers	Timept Treatment Timept* Treatment					

Table 14. Pre- to Post-Treatment Changes in CGI-I For Exploratory Outcome

Outcome	Cases	Fixed Effect	Estimate	Standard Error	DF	95 Confidence Interval (Lower, Higher)	P-Value
Clinical Global Impression - Improvement (CGI-I)	ITT	Timept Treatment Timept* Treatment					
	As Treated	Timept Treatment Timept* Treatment					
	Per Protocol	Timept Treatment Timept* Treatment					
	Completers	Timept Treatment Timept* Treatment					

Table 15. Pre- to Post-Treatment Changes in CGI-S For Exploratory Outcome

Outcome	Cases	Fixed Effect	Estimate	Standard Error	DF	95 Confidence Interval (Lower, Higher)	P-Value
Clinical Global Impression - Severity (CGI-S)	ITT	Timept Treatment Timept* Treatment					
	As Treated	Timept Treatment Timept* Treatment					
	Per Protocol	Timept Treatment Timept* Treatment					
	Completers	Timept Treatment Timept* Treatment					

Table 16. Pre- to Post-Treatment Changes in CPFQ For Exploratory Outcome

Outcome	Cases	Fixed Effect	Estimate	Standard Error	DF	95 Confidence Interval (Lower, Higher)	P-Value
The Cognitive and Physical Functioning Questionnaire (CPFQ)	ITT	Timept Treatment Timept* Treatment					
	As Treated	Timept Treatment Timept* Treatment					
	Per Protocol	Timept Treatment Timept* Treatment					
	Completers	Timept Treatment Timept* Treatment					

Table 17a. Descriptive Statistics for All Outcomes and Assessments in the Final Analysis

Intent-to-Treat

Variable	Mean	SD	Range
fMRI Activation During Anticipation of Reward (Primary Outcome) **Baseline** **Week 8**			
Snaith-Hamilton Pleasure Scale (SHAPS-Secondary Outcome) **Baseline** **Week 2** **Week 4** **Week 6** **Week 8** **Month 1** **LOCF**			
Probabilistic Reward Task (PRT-Secondary Outcome) **Format the same with fMRI (see the first row)**			
fMRI Activation During Anticipation of Loss (Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Resting State Delta EEG Current Density in the Rostral Anterior Cingulate (Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Monetary Reward Task (Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Effort Expenditure for Rewards Task (EEfRT-Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Visual Analogue Scale for Anhedonia (VAS-Exploratory Outcome) **Format the same with SHAPS (see the second row)**			
Temporal Experience of Pleasure Scale (TEPS) **Format the same with SHAPS (see the second row)**			
HAM-A (Exploratory Outcome) **Format the same with fMRI (see the first row)**			

HAM-D (Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Clinical Global Impression-Improvement (CGI-I-Exploratory Outcome) **Format the same with SHAPS (see the second row)**			
Clinical Global Impression-Severity (CGI-S-Exploratory Outcome) **Format the same with SHAPS (see the second row)**			
Cognitive and Physical Functioning Questionnaire (CPFQ-Exploratory Outcome) **Format the same with fMRI (see the first row)**			

Table 17b. Descriptive Statistics for All Outcomes and Assessments in the Final Analysis

As Treated

Variable	Mean	SD	Range
fMRI Activation During Anticipation of Reward (Primary Outcome) **Baseline** **Week 8**			
Snaith-Hamilton Pleasure Scale (SHAPS-Secondary Outcome) **Baseline** **Week 2** **Week 4** **Week 6** **Week 8** **Month 1** **LOCF**			
Probabilistic Reward Task (PRT-Secondary Outcome) **Format the same with fMRI (see the first row)**			
fMRI Activation During Anticipation of Loss (Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Resting State Delta EEG Current Density in the Rostral Anterior Cingulate (Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Monetary Reward Task (Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Effort Expenditure for Rewards Task (EEfRT-Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Visual Analogue Scale for Anhedonia (VAS-Exploratory Outcome) **Format the same with SHAPS (see the second row)**			
Temporal Experience of Pleasure Scale (TEPS) **Format the same with SHAPS (see the second row)**			
HAM-A (Exploratory Outcome) **Format the same with fMRI (see the first row)**			

HAM-D (Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Clinical Global Impression-Improvement (CGI-I-Exploratory Outcome) **Format the same with SHAPS (see the second row)**			
Clinical Global Impression-Severity (CGI-S-Exploratory Outcome) **Format the same with SHAPS (see the second row)**			
Cognitive and Physical Functioning Questionnaire (CPFQ-Exploratory Outcome) **Format the same with fMRI (see the first row)**			

Table 17c. Descriptive Statistics for All Outcomes and Assessments in the Final Analysis

Per Protocol

Variable	Mean	SD	Range
fMRI Activation During Anticipation of Reward (Primary Outcome) **Baseline** **Week 8**			
Snaith-Hamilton Pleasure Scale (SHAPS-Secondary Outcome) **Baseline** **Week 2** **Week 4** **Week 6** **Week 8** **Month 1** **LOCF**			
Probabilistic Reward Task (PRT-Secondary Outcome) **Format the same with fMRI (see the first row)**			
fMRI Activation During Anticipation of Loss (Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Resting State Delta EEG Current Density in the Rostral Anterior Cingulate (Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Monetary Reward Task (Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Effort Expenditure for Rewards Task (EEfRT-Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Visual Analogue Scale for Anhedonia (VAS-Exploratory Outcome) **Format the same with SHAPS (see the second row)**			
Temporal Experience of Pleasure Scale (TEPS) **Format the same with SHAPS (see the second row)**			
HAM-A (Exploratory Outcome) **Format the same with fMRI (see the first row)**			

HAM-D (Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Clinical Global Impression-Improvement (CGI-I-Exploratory Outcome) **Format the same with SHAPS (see the second row)**			
Clinical Global Impression-Severity (CGI-S-Exploratory Outcome) **Format the same with SHAPS (see the second row)**			
Cognitive and Physical Functioning Questionnaire (CPFQ-Exploratory Outcome) **Format the same with fMRI (see the first row)**			

Table 17d. Descriptive Statistics for All Outcomes and Assessments in the Final Analysis

Completers

Variable	Mean	SD	Range
fMRI Activation During Anticipation of Reward (Primary Outcome) **Baseline** **Week 8**			
Snaith-Hamilton Pleasure Scale (SHAPS-Secondary Outcome) **Baseline** **Week 2** **Week 4** **Week 6** **Week 8** **Month 1** **LOCF**			
Probabilistic Reward Task (PRT-Secondary Outcome) **Format the same with fMRI (see the first row)**			
fMRI Activation During Anticipation of Loss (Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Resting State Delta EEG Current Density in the Rostral Anterior Cingulate (Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Monetary Reward Task (Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Effort Expenditure for Rewards Task (EEfRT-Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Visual Analogue Scale for Anhedonia (VAS-Exploratory Outcome) **Format the same with SHAPS (see the second row)**			
Temporal Experience of Pleasure Scale (TEPS) **Format the same with SHAPS (see the second row)**			
HAM-A (Exploratory Outcome) **Format the same with fMRI (see the first row)**			

HAM-D (Exploratory Outcome) **Format the same with fMRI (see the first row)**			
Clinical Global Impression-Improvement (CGI-I-Exploratory Outcome) **Format the same with SHAPS (see the second row)**			
Clinical Global Impression-Severity (CGI-S-Exploratory Outcome) **Format the same with SHAPS (see the second row)**			
Cognitive and Physical Functioning Questionnaire (CPFQ-Exploratory Outcome) **Format the same with fMRI (see the first row)**			

Appendix D. FIGURES

Attached below is an example for Figures (Template from Another Trial). The two curves will represent two treatments instead of the populations for this trial.

Note: for MINI, fMRI, PRT, EEfRT, QEEG, HAM-D and HAM-A and CPFQ, we will use bar graphs to compare the mean predicted probabilities pre to post treatment.

Figure 6G. CGI-I predicted Scores by Time Periods

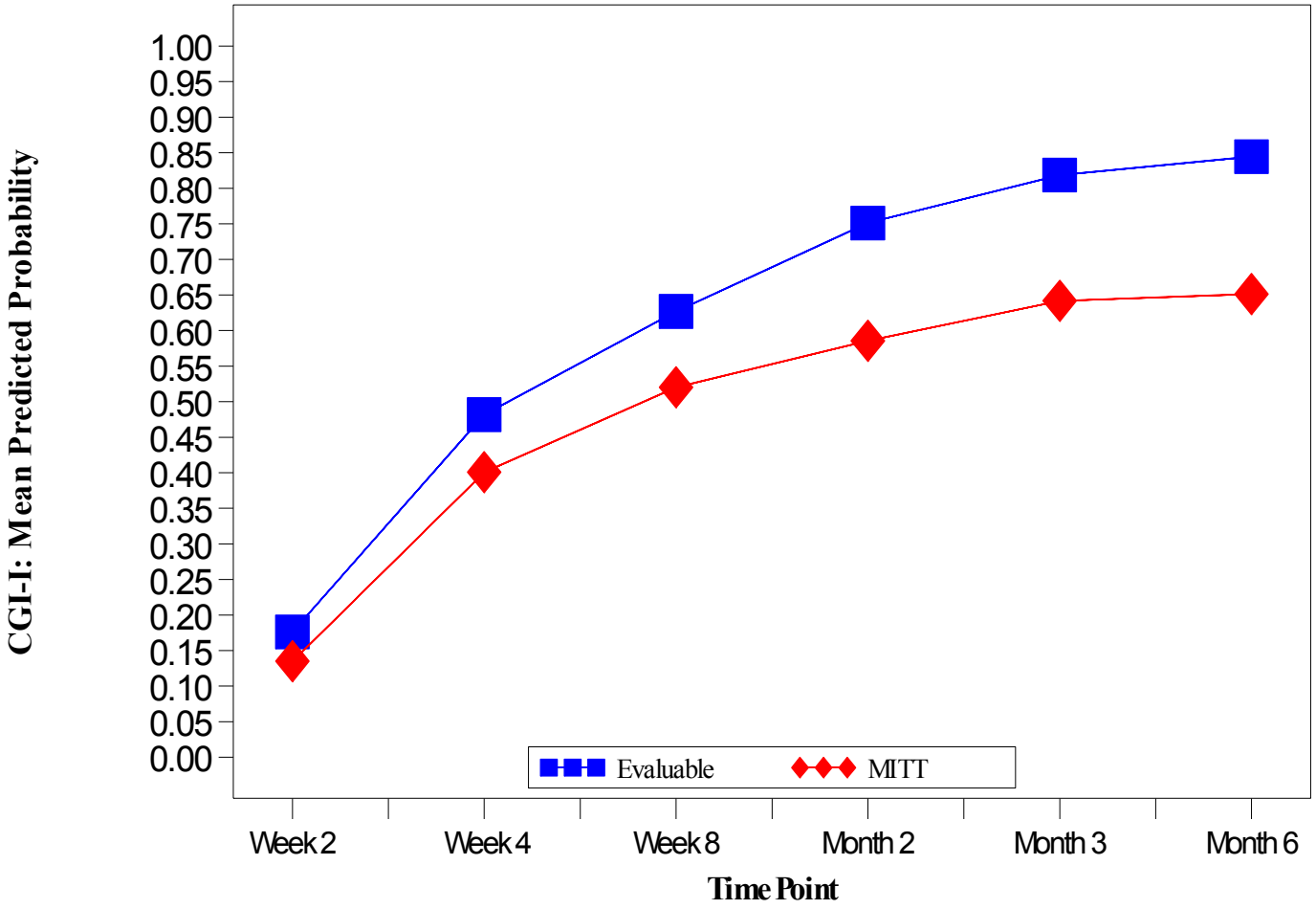

Figure 1a. Pre- to Post-Treatment Changes in fMRI Activation During Anticipation of Reward – Intent-to-Treat Population

X Axis Label: Time Points

Y Axis Label: fMRI: Mean Predicted Probability

Figure 1b. Pre- to Post-Treatment Changes in fMRI Activation During Anticipation of Reward – As Treated

X Axis Label: Time Points

Y Axis Label: fMRI: Mean Predicted Probability

Figure 1c. Pre- to Post-Treatment Changes in fMRI Activation During Anticipation of Reward – Per Protocol

X Axis Label: Time Points

Y Axis Label: fMRI: Mean Predicted Probability

Figure 1d. Pre- to Post-Treatment Changes in fMRI Activation During Anticipation of Reward – Study Completers

X Axis Label: Time Points

Y Axis Label: fMRI: Mean Predicted Probability

Figure 2a. Changes in Snaith-Hamilton Pleasure Scale (SHAPS) – Intent-to-Treat Population

X Axis Label: Time Points

Y Axis Label: SHAPS: Mean Predicted Probability

Figure 2b. Changes in Snaith-Hamilton Pleasure Scale (SHAPS) – As Treated

X Axis Label: Time Points

Y Axis Label: SHAPS: Mean Predicted Probability

Figure 2c. Changes in Snaith-Hamilton Pleasure Scale (SHAPS) – Per Protocol

X Axis Label: Time Points

Y Axis Label: SHAPS: Mean Predicted Probability

Figure 2d. Changes in Snaith-Hamilton Pleasure Scale (SHAPS) – Study Completers

X Axis Label: Time Points

Y Axis Label: SHAPS: Mean Predicted Probability

Figure 3a. Changes in Reward Learning and Response Bias (PRT) – Intent-to-Treat Population

X Axis Label: Time Points

Y Axis Label: PRT: Mean Predicted Probability

Figure 3b. Changes in Reward Learning and Response Bias (PRT) – As Treated

X Axis Label: Time Points

Y Axis Label: PRT: Mean Predicted Probability

Figure 3c. Changes in Reward Learning and Response Bias (PRT) – Per Protocol

X Axis Label: Time Points

Y Axis Label: PRT: Mean Predicted Probability

Figure 3d. Changes in Reward Learning and Response Bias (PRT) – Study Completers

X Axis Label: Time Points

Y Axis Label: PRT: Mean Predicted Probability

Figure 4a. Pre- to Post-Treatment Changes in fMRI Activation During Anticipation of Loss – Intent-to-Treat Population

X Axis Label: Time Points

Y Axis Label: fMRI: Mean Predicted Probability

Figure 4b. Pre- to Post-Treatment Changes in fMRI Activation During Anticipation of Loss – As Treated

X Axis Label: Time Points

Y Axis Label: fMRI: Mean Predicted Probability

Figure 4c. Pre- to Post-Treatment Changes in fMRI Activation During Anticipation of Loss – Per Protocol

X Axis Label: Time Points

Y Axis Label: fMRI: Mean Predicted Probability

Figure 4d. Pre- to Post-Treatment Changes in fMRI Activation During Anticipation of Loss – Study Completers

X Axis Label: Time Points

Y Axis Label: fMRI: Mean Predicted Probability

Figure 5a. Pre- to Post-Treatment Changes in Resting State Delta EEG Current Density – Intent-to-Treat Population

X Axis Label: Time Points

Y Axis Label: EEG: Mean Predicted Probability

Figure 5b. Pre- to Post-Treatment Changes in Resting State Delta EEG Current Density – As Treated

X Axis Label: Time Points

Y Axis Label: EEG: Mean Predicted Probability

Figure 5c. Pre- to Post-Treatment Changes in Resting State Delta EEG Current Density – Per Protocol

X Axis Label: Time Points

Y Axis Label: EEG: Mean Predicted Probability

Figure 5d. Pre- to Post-Treatment Changes in Resting State Delta EEG Current Density – Study Completers

X Axis Label: Time Points

Y Axis Label: EEG: Mean Predicted Probability

Figure 6a. Pre- to Post-Treatment Changes in Resting State fMRI Connectivity – Intent-to-Treat Population

X Axis Label: Time Points

Y Axis Label: fMRI: Mean Predicted Probability

Figure 6b. Pre- to Post-Treatment Changes in Resting State fMRI Connectivity – As Treated

X Axis Label: Time Points

Y Axis Label: fMRI: Mean Predicted Probability

Figure 6c. Pre- to Post-Treatment Changes in Resting State fMRI Connectivity – Per Protocol

X Axis Label: Time Points

Y Axis Label: fMRI: Mean Predicted Probability

Figure 6d. Pre- to Post-Treatment Changes in Resting State fMRI Connectivity – Study Completers

X Axis Label: Time Points

Y Axis Label: fMRI: Mean Predicted Probability

Figure 7a. Changes in Self-rated Affective Responses to Cues and Feedback During the MID Task – Intent-to-Treat Population

X Axis Label: Time Points

Y Axis Label: MRT: Mean Predicted Probability

Figure 7b. Changes in Self-rated Affective Responses to Cues and Feedback During the MID Task – As Treated

X Axis Label: Time Points

Y Axis Label: MRT: Mean Predicted Probability

Figure 7c. Changes in Self-rated Affective Responses to Cues and Feedback During the MID Task – Per Protocol

X Axis Label: Time Points

Y Axis Label: MRT: Mean Predicted Probability

Figure 7d. Changes in Self-rated Affective Responses to Cues and Feedback During the MID Task – Study Completers

X Axis Label: Time Points

Y Axis Label: MRT: Mean Predicted Probability

Figure 8a. Pre- to Post-Treatment Changes in EEfRT – Intent-to-Treat Population

X Axis Label: Time Points

Y Axis Label: EEfRT: Mean Predicted Probability

Figure 8b. Pre- to Post-Treatment Changes in EEfRT – As Treated

X Axis Label: Time Points

Y Axis Label: EEfRT: Mean Predicted Probability

Figure 8c. Pre- to Post-Treatment Changes in EEfRT – Per Protocol

X Axis Label: Time Points

Y Axis Label: EEfRT: Mean Predicted Probability

Figure 8d. Pre- to Post-Treatment Changes in EEfRT – Study Completers

X Axis Label: Time Points

Y Axis Label: EEfRT: Mean Predicted Probability

Figure 9a. Changes in Visual Analogue Scale for Anhedonia (VAS) – Intent-to-Treat Population

X Axis Label: Time Points

Y Axis Label: VAS: Mean Predicted Probability

Figure 9b. Changes in Visual Analogue Scale for Anhedonia (VAS) – As Treated

X Axis Label: Time Points

Y Axis Label: VAS: Mean Predicted Probability

Figure 9c. Changes in Visual Analogue Scale for Anhedonia (VAS) – Per Protocol

X Axis Label: Time Points

Y Axis Label: VAS: Mean Predicted Probability

Figure 9d. Changes in Visual Analogue Scale for Anhedonia (VAS) – Study Completers

X Axis Label: Time Points

Y Axis Label: VAS: Mean Predicted Probability

Figure 10a. Changes in Temporal Experience of Pleasure Scale (TEPS) – Intent-to-Treat Population

X Axis Label: Time Points

Y Axis Label: TEPS: Mean Predicted Probability

Figure 10b. Changes in Temporal Experience of Pleasure Scale (TEPS) – As Treated

X Axis Label: Time Points

Y Axis Label: TEPS: Mean Predicted Probability

Figure 10c. Changes in Temporal Experience of Pleasure Scale (TEPS) – Per Protocol

X Axis Label: Time Points

Y Axis Label: TEPS: Mean Predicted Probability

Figure 10d. Changes in Temporal Experience of Pleasure Scale (TEPS) – Study Completers

X Axis Label: Time Points

Y Axis Label: TEPS: Mean Predicted Probability

Figure 11a. Pre- to Post-Treatment Changes in Hamilton Rating Scale for Anxiety (HAM-A) – Intent-to-Treat Population

X Axis Label: Time Points

Y Axis Label: HAM-A: Mean Predicted Probability

Figure 11b. Pre- to Post-Treatment Changes in Hamilton Rating Scale for Anxiety (HAM-A) – As Treated

X Axis Label: Time Points

Y Axis Label: HAM-A: Mean Predicted Probability

Figure 11c. Pre- to Post-Treatment Changes in Hamilton Rating Scale for Anxiety (HAM-A) – Per Protocol

X Axis Label: Time Points

Y Axis Label: HAM-A: Mean Predicted Probability

Figure 11d. Pre- to Post-Treatment Changes in Hamilton Rating Scale for Anxiety (HAM-A) – Study Completers

X Axis Label: Time Points

Y Axis Label: HAM-A: Mean Predicted Probability

Figure 12a. Pre- to Post-Treatment Changes in Hamilton Rating Scale for Depression (HAM-D) – Intent-to-Treat Population

X Axis Label: Time Points

Y Axis Label: HAM-D: Mean Predicted Probability

Figure 12b. Pre- to Post-Treatment Changes in Hamilton Rating Scale for Depression (HAM-D) – As Treated

X Axis Label: Time Points

Y Axis Label: HAM-D: Mean Predicted Probability

Figure 12c. Pre- to Post-Treatment Changes in Hamilton Rating Scale for Depression (HAM-D) – Per Protocol

X Axis Label: Time Points

Y Axis Label: HAM-D: Mean Predicted Probability

Figure 12d. Pre- to Post-Treatment Changes in Hamilton Rating Scale for Depression (HAM-D) – Study Completers

X Axis Label: Time Points

Y Axis Label: HAM-D: Mean Predicted Probability

Figure 13a. Changes in Clinical Global Impression – Improvement (CGI-I) – Intent-to-Treat Population

X Axis Label: Time Points

Y Axis Label: CGI-I: Mean Predicted Probability

Figure 13b. Changes in Clinical Global Impression – Improvement (CGI-I)–As Treated

X Axis Label: Time Points

Y Axis Label: CGI-I: Mean Predicted Probability

Figure 13c. Changes in Clinical Global Impression – Improvement (CGI-I)–Per Protocol

X Axis Label: Time Points

Y Axis Label: CGI-I: Mean Predicted Probability

Figure 13d. Changes in Clinical Global Impression – Improvement (CGI-I)– Study Completers

X Axis Label: Time Points

Y Axis Label: CGI-I: Mean Predicted Probability

Figure 14a. Changes in Clinical Global Impression – Severity (CGI-S) – Intent-to-Treat Population

X Axis Label: Time Points

Y Axis Label: CGI-S: Mean Predicted Probability

Figure 14b. Changes in Clinical Global Impression –Severity (CGI-S)–As Treated

X Axis Label: Time Points

Y Axis Label: CGI-S: Mean Predicted Probability

Figure 14c. Changes in Clinical Global Impression – Severity (CGI-S)–Per Protocol

X Axis Label: Time Points

Y Axis Label: CGI-S: Mean Predicted Probability

Figure 14d. Changes in Clinical Global Impression – Severity (CGI-S)– Study Completers

X Axis Label: Time Points

Y Axis Label: CGI-S: Mean Predicted Probability

Figure 15a. Pre- to Post-Treatment Changes in Cognitive and Physical Functioning Questionnaire (CPFQ) – Intent-to-Treat Population

X Axis Label: Time Points

Y Axis Label: CPFQ: Mean Predicted Probability

Figure 15b. Pre- to Post-Treatment Changes in Cognitive and Physical Functioning Questionnaire (CPFQ) – As Treated

X Axis Label: Time Points

Y Axis Label: CPFQ: Mean Predicted Probability

Figure 15c. Pre- to Post-Treatment Changes in Cognitive and Physical Functioning Questionnaire (CPFQ) – Per Protocol

X Axis Label: Time Points

Y Axis Label: CPFQ: Mean Predicted Probability

Figure 15d. Pre- to Post-Treatment Changes in Cognitive and Physical Functioning Questionnaire (CPFQ) – Study Completers

X Axis Label: Time Points

Y Axis Label: CPFQ: Mean Predicted Probability