An 8-week Randomized Double-Blind Placebo-Controlled Multi-Site Study assessing Efficacy and Safety of MYDAYIS® (d-amphetamine / l-amphetamine) for Bipolar Depression

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Regulatory Sponsor: Mark A. Frye, M.D
Department of Psychiatry and Psychology
Mayo Clinic
200 1st St SW, Rochester, MN 55902
(507) 266-5100

Other Participating Site Co-Investigators: Susan L. McElroy, M.D. (site PI Lindner Center of Hope),

Mayo Clinic Site Co-Investigators: Nicolas A. Nunez, M.D., M.S.; Balwinder Singh, M.D.; Marin Veldic, M.D.; Katherine M. Moore, M.D.; Jennifer L. Vande Voort, M.D.; Paul E. Croarkin, D.O., M.S; Hannah K. Betcher, M.D.; Aysegul Ozerdem, M.D., Ph.D.; Manuel Gardea Resendez, M.D.; Ashok Seshadri, M.D.; Joshua Baruth, M.D., Ph.D.; Alfredo Cuellar Barboza, M.D.; Scott Schmidt, D.O., Pravesh Sharma M.D.

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List of Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
AE	Adverse Event/Adverse Experience
ANOVA	Analysis of variance
BD	Bipolar depression
BD-I	Bipolar disorder type I
BD-II	Bipolar disorder type II
BiB-CQ	Bipolar Biobank Clinical Questionnaire
BiB-PQ	Bipolar Biobank Participant Questionnaire
CFR	Code of Federal Regulations
CGI-BP	Clinical Global Impression of Change – Bipolar version
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CRF	Case Report Form
COPDGene COVID-19	Chronic Obstructive Pulmonary Disease Gene study, Coronavirus Disease 2019 Survey
C-SSRS	Columbia-Suicide Severity Rating Scale
CUDIT-R	Cannabis Use Disorders Identification Test Revised
DAT	Dopamine transporter
DC	Dopaminergic compounds
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (Text Revision)
DSMB	Data and Safety Monitoring Board
DSST	Digit Symbol Substitution Test
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
GAD-7	General Anxiety Disorder 7-item scale
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
MADRS	Montgomery Asberg Depression Scale
MDD	Major depressive disorder
PHI	Protected Health Information
PI	Principal Investigator

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QIDS-C16	Quick Inventory of Depressive Symptomatology (Clinician)
QIDS-SR16	Quick Inventory of Depressive Symptomatology (Self-Report)
SAE	Serious Adverse Event/Serious Adverse Experience
SCID	Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
SNP	Single nucleotide polymorphisms
SOP	Standard Operating Procedure
TEM	Treatment emergent mania
UPIRTSO	Unanticipated Problems Involving Risk to Subjects or Others
VMAT	Vesicular Monoamine Transporters

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Study Summary

Title	An 8-week Randomized Double-Blind Placebo-Controlled Multi-Site Study assessing Efficacy and Safety of MYDAYIS® (d-amphetamine / l-amphetamine) for Bipolar Depression
Running Title	MYDAYIS® for bipolar depression
Protocol Number	19-001722
Phase	Phase II
Methodology	Randomized, parallel-group, double-blind, placebo-controlled, flexible-dose adjunctive trial of MYDAYIS® (mixed d-amphetamine and l-amphetamine) followed by an open label phase.
Overall Study Duration	Estimated duration will be of 18 weeks.
Subject Participation Duration	18 weeks
Single or Multi-Site	Multi-center study.
Objectives	Aim of this study is to assess the efficacy and safety of MYDAYIS® as an augmentation agent for bipolar depression.
Number of Subjects	540 patients

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Diagnosis and Main Inclusion Criteria	Male or female aged 18-65 years of age with a diagnosis of bipolar depression type I / type II currently experiencing a major depressive episode unresponsive to mood stabilizer/ antipsychotic therapy with or without concomitant antidepressant therapy.
Study Product, Dose, Route, Regimen	MYDAYIS®, Oral administration, dose regimen for Double blind phase and open label phase. Titration may be adjusted by the study physician based on side effects and/or early treatment response. 12.5 mg x 7 days 25 mg x 7 days 37.5 mg x 14 days 50 mg daily x 28 days
Duration of Administration	16 weeks
Reference therapy	Placebo
Statistical Methodology	Change in MADRS from baseline to 8 weeks will be compared between groups during the treatment period using a repeated measures mixed model.

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1 Introduction

This protocol is a Phase 2 multi-site study which aims to evaluate the safety and effectiveness of MYDAYIS® [1] as adjunctive therapy for adults with bipolar depression. Results from this study WILL NOT be used to contribute to an approval of MYDAYIS ® for this indication. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Depression is the predominant prevailing mood state of bipolar disorder and it is associated with substantial morbidity and mortality. However, in comparison to acute mania, bipolar depression is understudied both from the standpoint of its pathophysiology as well as clinical trials and treatment development. Given the lack of evidence-based guidelines, clinicians and participants enter a treatment phase with little guidance [2].

Currently, MYDAYIS ® (mixed d-amphetamine and l-amphetamine) is an FDA approved medicine for adolescents and adults with ADHD based on more than 1600 patients in a series of randomized, double-blind placebo-controlled multicenter studies [3-6].

Stimulant agents, such as MYDAYIS ® (d-amphetamine / l-amphetamine), have had limited investigation and are recommended in some consensus guidelines, but not all, as third or fourth line therapy for the treatment of patients with refractory depression associated with bipolar disorder [7-9,10]. Although data are limited, current evidence from a Cochrane systematic review has suggested that stimulant medication may have benefit for depression with good tolerability [11].

There are other dopamine compounds (DCs) of potential interest for bipolar depression. Previous data suggest that pramipexole, a partial D3/D2 dopamine agonist FDA approved for Parkinson's disease, modafinil/armodafinil, dopamine reuptake inhibitor FDA approved for daytime somnolence and fatigue associated with shift work disorder, and lisdexamfetamine, a dopamine reuptake inhibitor also facilitating the terminal release of dopamine and norepinephrine FDA approved for children with attention deficit hyperactivity disorder all have evidence in reducing symptoms of bipolar depression. Our group conducted a systematic review and meta-analysis of these dopaminergic compounds (DC) to evaluate the efficacy and safety of augmentation treatments pramipexole, lisdexamphetamine /methylphenidate, and ar/modafinil in major depressive disorder (MDD) and bipolar depression (BD). 21 randomized controlled trials (RCT) of which MDD (13 studies, N=1102, N=1028 placebo) and BD (8 studies, N=828, N=827 placebo) were analyzed. Augmentation with DC exhibited a significantly greater response and remission rate vs placebo (RR, 1.21; 95% CI, 1.12–1.31; P< 0.00001; RR, 1.26; 95% CI, 1.10–1.44; P=0.0005, respectively) with no differences between major depressive disorder and bipolar disorder (I2= 0%, P= 0.73; I2= 47.3%, P= 0.17). All-cause discontinuation did not differ between DC vs placebo (RR, 1.02; 95% CI, 0.90–1.16; P= 0.76) or between mood disorders (RR, 1.05; 95% CI, 0.89–1.25; P= 0.50). The meta-analytic data support the efficacy of DC as an

augmentation strategy in mood disorders without increasing rates of discontinuation (in preparation Nunez et al., 2019).

1.2 Investigational Agent

MYDAYIS ® (d-amphetamine / l-amphetamine) [1] is a CNS stimulant FDA approved and indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 13 years and older. The compound comprises mixed salts of the stimulant amphetamine with equal amounts (by weight) of four salts: dextroamphetamine sulfate and amphetamine sulfate, dextroamphetamine saccharate and amphetamine aspartate monohydrate. This results in a 3:1 mixture of dextro- to levoamphetamine base equivalent. Although, MYDAYIS ® (d-amphetamine / l-amphetamine) therapeutic action has not been totally elucidated, mechanistically it blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron, facilitates the release of these monoamines into the extraneuronal space, and reduces the metabolism of dopamine via the vesicular monoamine transporter (VMAT-2) in which dopamine is facilitated into the cytoplasm favoring its diffusion to the extraneuronal space.

Pharmacokinetic studies have suggested after the administration of MYDAYIS, the peak plasma concentrations occurred in about 8 hours in adults. The mean plasma elimination half-life ranges from about 10 –16 hours. Renal excretion is the primary route for elimination with a fraction of a dose being hepatically metabolized. Importantly, both hepatic and renal dysfunctions might alter the elimination of MYDAYIS with prolonged exposure.

Dosing of MYDAYIS will be with 12.5 and 25 mg capsules with maximum dosage at 50 mg. Titration may be adjusted by the study physician based on side effects and/or early treatment response.

This study will investigate the use of MYDAYIS in adults diagnosed with bipolar depression requesting an IND exemption.

Request agreement with our assessment of meeting the following exemption criterion:

1. Use is conducted in compliance with the requirements concerning the promotion and sale of drugs. – All entities involved will provide medication to those who have signed consent for participation into the study
2. Use is conducted in compliance with the requirements for IRB review and informed consent.
3. Use is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug. – All entities involved do not plan to pursue any new indication of this drug.
4. Use is not intended to support a significant change in the advertising for the product. – All entities involved do not plan to pursue any change in advertising of the product.
5. Use does not involve factors that significantly increase the risks (or decrease the acceptability of risks) of using the drug product, such as administration route, dosage level, subject population, disease state. Bipolar depressed patients are at risk for treatment emergent mania (TEM). However, our recent meta-analysis of dopamine compounds (Nunez et al., 2019 in preparation)

does not show a significant risk in comparison to placebo; thus, TEM may reflect course of illness risk. This study will require the presence of an antimanic agent (lithium valproate, antipsychotic) which will be an added safety feature for this study design. Finally, to streamline pharmacy refills, we have a longer titration phase to full dose 50 mg.
6. Use does not intend to invoke exemption from informed consent. – All subjects must sign an informed consent document to be eligible for participation.

1.3 Pre-clinical and Clinical Data to Date

The rationale for evaluating dopamine stimulant treatments in bipolar depression is based on key pathophysiological studies which have identified the following: a dopamine dysregulation syndrome with increased and decreased dopamine in mania and depression respectively; clinical observations that Parkinson's disease treatments (L-dopa, pramipexole, deep brain stimulation) can cause mania; increased rates of tardive dyskinesia in bipolar disorder (vs schizophrenia); and recognition that dopamine antagonists (ie, both antipsychotics and lithium / anticonvulsant mood stabilizers valproate and carbamazepine) decrease dopamine transmission.

Mechanistically, stimulants (eg, amphetamines and methylphenidate) have shown to increase dopamine concentrations by blocking DAT inhibiting dopamine reuptake [13]. Additionally, stimulant drugs disrupt the function of the VMAT2, which transports monoamine neurotransmitters from stores in the cytoplasm to synaptic vesicles [14] making it work on reverse thus increasing cytoplasmic dopamine levels leading to a non-impulse dependent release. Although, stimulants mechanism of action is not fully deciphered, all the compounds share the property to enhance dopaminergic prefrontal transmission with a greater or no effect on the nucleus accumbens such as it has been proposed for modafinil/armodafinil.

Different genetic polymorphisms have been described in the literature highlighting its influence in disease expression and inter-individual variation for drug response. For example, the dopamine transporter (DAT1-gene SLC6A3) and its corresponding variants (rs2652511, rs2975226, rs27072 and rs27048) [15-16] the vesicular monoamine transporters (VMAT1-gene SLC18A1/ VMAT2-gene SLC18A2) [17] and the dopamine receptor 4 (DDR4) [18-19] have been the candidate genes most studied and linked with treatment response for ADHD; these variants have not been studied in depression [20].

Interestingly, preclinical data have underscored the important role of DAT in dopamine regulation as DAT knockout mice (absence of the transporter) have shown a reduced response to methylphenidate [21]; thus, blocking DAT increases dopamine synaptic concentrations [22].

The DAT1 gene has been studied extensively in several mental illnesses with its genetic variations. In particular, variations of DAT1 have been linked with illnesses such as schizophrenia and psychotic disorders [23] and associated with different subtypes of BD by its important role in the dopaminergic system homeostasis [24-25]. Specifically, several markers were identified near the DAT1 locus on chromosome 5 in addition to the presence of a susceptibility locus for BD on chromosome 22 [26].

Previous clinical studies genotyped DAT1 single nucleotide polymorphisms (SNPs), evaluating its association with BD and further the identification of 20 additional SNPs in DAT1 for a total of 63 variants. Precisely, 8 newly identified SNPs and 14 previously identified SNPs were analyzed in two independent samples and 2 out of 8 new SNPs (I 13 +1457; p= 0.024 and I8 + 2086; p=0.036), were found to be moderately associated with bipolar disorder [27].

Interestingly, these molecular data support a genetic overlap of these regions that underscores a complex relationship between dopaminergic dysfunctions in both schizophrenia and bipolar disorder. Altogether, these previous studies are consistent with the presence of multiple genetic variations at the DAT1 level, which conveys a susceptibility to bipolar disorder and merits further analysis for targeted therapies.

Drug response on methylphenidate, described a decreased response in homozygous individuals for the 9-repeat allele (9R) and 10-repeat allele (10R) [28-30]. In a sub-analysis of naturalistic trials, Kambeitz and colleagues demonstrated that 10R homozygous patients exhibited less improvement than non 10R [31]; although, better responses were also reported for the homozygous 10R on methylphenidate [32]. Currently, there is some evidence for both of the frequent SLC6A3 alleles, the 10R and the 9R being associated with reduced response to methylphenidate, though a number of studies find no effect at all [31].

For the DDR4 gene, Froehlich et al., in a 4-week double blind methylphenidate response study of 89 adult subjects with ADHD, reported that lacking the 4-R allele was associated with less improvement across MPH doses compared with 4-R carriers (effect size= 0.45) [33]. Examining the Catechol-O-methyltransferase (COMT) gene, previous pharmacogenetics studies have suggested a significant association between the COMT VAL/VAL genotype and response to methylphenidate [34].

As mentioned in the previous section, MYDAYIS has been approved for adolescent and adult ADHD supported by 3 randomized controlled trials [3-6]. In a phase 3, randomized, placebo-controlled 7-week optimization study (N=274) which evaluated the efficacy, tolerability, and safety of 12.5 and 37.5 mg/day with a mean dose of 43.5mg/d (12.5-mg/day dose being evaluated to further elucidate the lower end of the dose response), there was significantly greater reduction from baseline to endpoint in mean ADHD-RS-IV (total score change -14.3 v - 6.3 placebo ; $p < .0001$) and CGI-Improvement (rated as improved 51.5% v 21.2 % placebo ; $p < .0001$). Insomnia was the most commonly reported treatment emergent side effect, followed by dry mouth, decreased appetite and weight, and headache [3].

This was further supported in a second study which randomized 411 adult participants with ADHD to 25, 50, and 75mg/d of MYDAYIS vs placebo during a 6-week period assessing efficacy, tolerability, and safety. All dosages produced a greater reduction in ADHD symptoms, measures by the ADHD-RS total score changes (−10.6 [−13.2, −8.0]; $p < .0001$) with no statistical evidence of a dose–response relationship for efficacy [5]. Another phase 3, randomized, double-blind, placebo-controlled trial was conducted on 275 ADHD adult participants aged between 18 and 55 years during 4 weeks. Patients were randomized to either MYDAYIS 12.5mg or 37.5mg with 236 participants completing the study. The primary endpoint of the study was defined based on the change from baseline in the ADHD-RS-IV total score compared to placebo. The secondary endpoint was clinical global impression of improvement

(CGI-I) score. Results demonstrated that patients treated with MYDAYIS 12.5mg and 37.5mg as a daily morning dose showed greater progress compared to placebo with similar safety profiles [6].

Therefore, considering the aforementioned, it is of utmost importance that we gain a better understanding of the pathophysiology of stimulants effects on mood disorders and their genetic variations that will allow us to provide personalized and targeted treatments.

1.4 Dose Rationale

The recommended starting dose of MYDAYIS® for adult use (18-60 years) is 12.5 mg once daily in the morning upon awakening. Dosage may be adjusted in increments of 12.5 mg no sooner than weekly, up to a maximum dose of 50 mg once daily based on the therapeutic needs and response of the patient. Doses above 50 mg daily have shown no additional clinically meaningful benefit.

1.5 Risks and Benefits

CNS stimulants, including MYDAYIS ®, other amphetamine-containing products, and methylphenidate, have been associated with certain risks and high potential for abuse and dependence. It is important to assess the risk of abuse of stimulants or prescription medication prior to prescribing and monitor for signs of abuse and dependence while on therapy. Sudden death, stroke, and myocardial infarction have also been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in pediatric patients with structural cardiac abnormalities and other serious heart problems while taking CNS stimulants at recommended doses for ADHD.

Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. MYDAYIS® may lower the convulsive threshold in patients with prior history of seizure, in patients with prior EEG abnormalities in the absence of seizures, and in patients without a history of seizures and no prior EEG evidence of seizures.

Most common adverse reactions in adult patients with ADHD (*incidence* ≥ *5%* and at a rate at least twice placebo) have been reported to be:

- insomnia
- decreased appetite and weight
- dry mouth
- increased heart rate
- anxiety

Additionally, the FDA warnings and precautions include:

- serious cardiovascular reactions
- blood pressure and heart rate increases
- psychiatric adverse reactions (ie, induction of mania, hypomania, or psychosis)
- long term suppression of growth
- peripheral vasculopathy (including Raynaud's phenomenon)
- seizures
- serotonin syndrome

In a study by Adel Gabriel (2010), ADHD patients tolerated the treatment of mixed amphetamine salt extended release (Adderall XR, Max-XR), and there were no significant cardiovascular changes at 12 weeks. There was decrease in mean weight at 12 weeks by 2.2 kg (P <.001) [35]. Larger controlled studies are needed to support the effectiveness of mixed amphetamine salts in patients with comorbid anxiety symptoms [35].

The efficacy, tolerability, and safety in adults with ADHD have been examined in several phase III studies concluding that doses higher than 50 mg per day did not demonstrate additional clinical benefit and are not recommended.

2 Study Objectives

1. Evaluate the efficacy of CNS stimulant d-amphetamine / l-amphetamine (MYDAYIS®) treatment for bipolar I / II depression.
2. Evaluate the safety of CNS stimulant d-amphetamine / l-amphetamine (MYDAYIS®) for bipolar I/II depression.
3. Evaluate targeted (ie, dopamine transporter) and non-targeted or unbiased [ie, genome-wide association study (GWAS)] biomarkers associated with CNS stimulant d-amphetamine / l-amphetamine (MYDAYIS ®) for both mood (ie, antidepressant) efficacy.
4. Evaluate maintenance of response of CNS stimulant d-amphetamine / l-amphetamine (MYDAYIS®) in an 8-week open label extension.

3 Study Design

3.1 General Description

The MYDAYIS® Study is an 8-week, randomized, double-blind, placebo-controlled, flexible-dose adjunctive trial of MYDAYIS® (mixed d-amphetamine and l-amphetamine) in the treatment of bipolar depression. The randomized, double-blind phase will be followed by an 8-week open-label extension trial of MYDAYIS® (mixed d-amphetamine and l-amphetamine). There will be four phases:

1. 1-4 week screening / pre-randomization period
2. 8-week double-blind treatment period

3. 8-week open label extension period
4. Post study visit – Up to 2 weeks after completing the 8-week open-label extension trial, or at any time-point earlier for premature study exit drug discontinuation. For participants who end the study early, 1 week after last visit.

Study visits will have a window of +/- 3 days.

All 3 FDA approved treatments for bipolar depression have had randomized, placebo-controlled studies followed by an open-label extension (36-39). Furthermore, this is a common methodology for drug development in major depression, mania, and schizophrenia. To maintain the scientific merit of the blind, patients will not be given the results of their blind phase treatment. This is important to reduce potential observer bias and focus on current randomization allocation, which can impact investigator and/or study coordinators completion of rating scales of outcome measures. As the blind will not be broken, we are unable to identify those subjects who were on active drug that then would undergo a discontinuation and subsequent titration of study drug. This is unavoidable given the study design of not breaking the blind. Discontinuation of stimulants has not been associated with adverse side effect profile in both the regulatory ADHD trials and previous work in bipolar depression [1, 12]. This would not be a full discontinuation as a MYDAYIS BLIND patient would be dosed at maximum 50 mg and then started at 12.5 mg during open label extension phase.

Furthermore, a recent meta-analysis conducted by our group (Nunez et al., under review), has shown safety and efficacy profiles for stimulants (ie, dopaminergic compounds) during a period that ranges between 6 to 16 weeks of treatment which covers out study timeline (please refer to section 1.1 for more details).

3.2 Number of Subjects

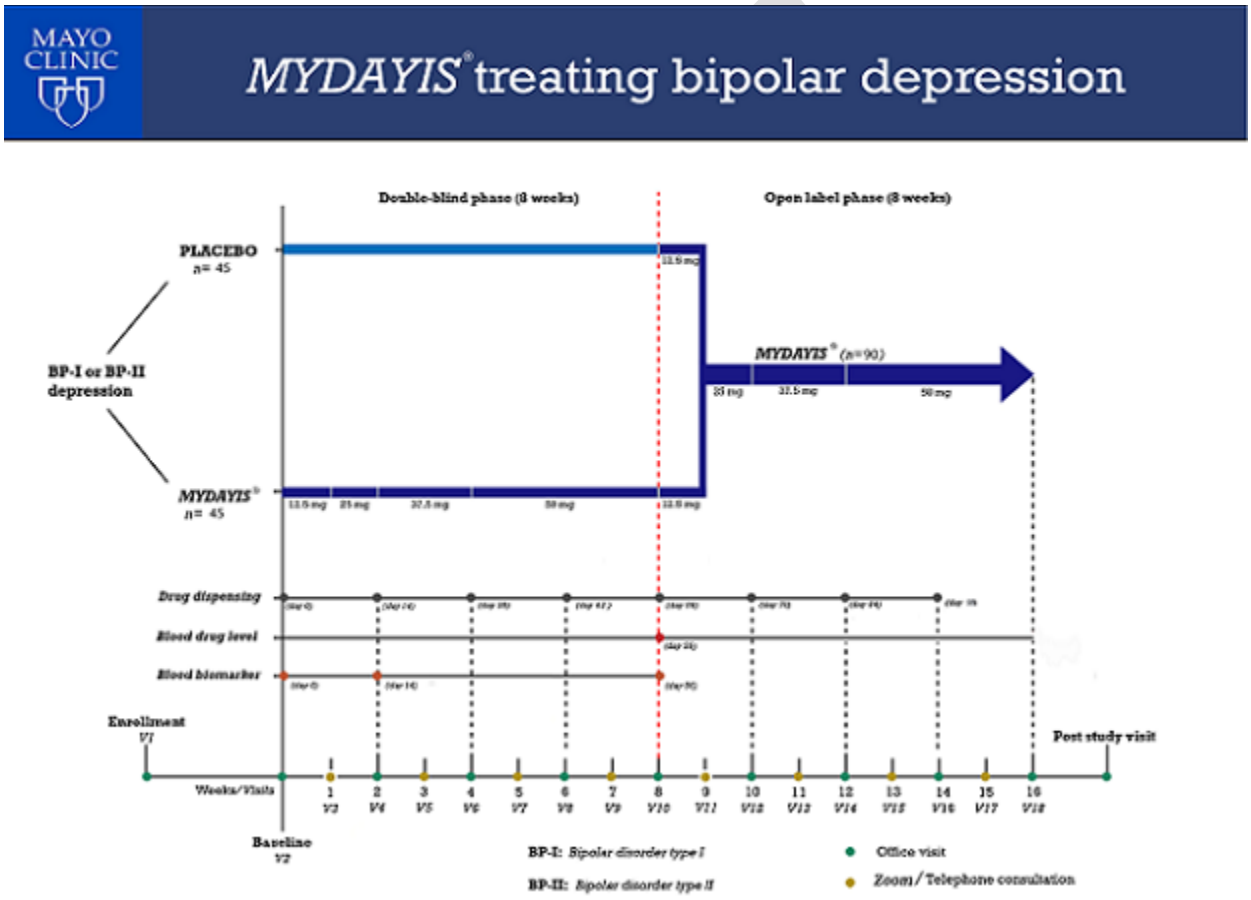
540 Bipolar I/II depressed adult patients, age 18-65, with or without symptoms of inattention and poor focus randomized to 8 weeks of adjunctive central nervous system (CNS) stimulant d-amphetamine / l-amphetamine (MYDAYIS®) [1] in comparison to adjunctive placebo.

3.3 Duration of Participation

Including screening / pre-randomization, study visits (both double-blind and open-label extension), and post study visit, the total study participation time is at least 18 weeks.

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Schematic diagram of study events



3.4 Primary Study Endpoints

Primary outcome measure will be change from baseline to endpoint or at last observation carried forward [LOCF] in the Montgomery-Asberg Depression Rating Scale (MADRS).

3.5 Secondary Study Endpoints

- Clinician and self-report symptoms of depression as measured by the Quick Inventory for Depressive Symptomatology (QIDS-C and QIDS-SR).
- Treatment remission (MADRS < 10).
- Self-report anxiety as measured by the General Anxiety Disorder 7-item scale (GAD-7).

- Treatment response (50% reduction in MADRS)
- Percentage of *much or very much* improved as measured by the Clinical Global Impression for Bipolar Disorder (CGI-BP)
- Reduction in sub-syndromal manic symptoms as measured by the Young Mania Rating Scale (YMRS)
- Self-report likelihood of falling asleep during normal daily situations as measured by the Epworth Sleepiness Scale (ESS)
- Self-report measure of fatigue as measured by the Fatigue Severity Scale (FSS)
- Self-report binge eating behavior as measured by the Binge Eating Scale (BES)
- Self-Report measure on the Morningness-Eveningness Questionnaire (MEQ).
- Self-Report measure on Rapid Eating and Activity Assessment for Patients (REAP)
- Improvement in cognition as measured by the Digit Symbol Substitution Test (DSST).
- Self-Report measure of COVID-19 positive status, symptoms, hospital care received, and recovery experience as measured by the Chronic Obstructive Pulmonary Disease Gene COVID-19 survey (COPDGene-COVID-19).
- Self-Report measure on how the COVID-19 pandemic has changed their lives as measured by the Coronavirus Impact Scale.

3.6 Primary Safety Assessments

Safety assessments include:

- Baseline ECG
- Physical exam and Vital signs completed by a physician on the team (PI or co-investigators).
- Laboratory testing (CBC, LFTs, blood chemistry, urine pregnancy test, urine drug screen, and potentially Lithium or Valproate levels, if appropriate
- Treatment emergent suicidal ideation quantified by any of the following:
    - ≥ 4 on MADRS item # 10
    - Response > 2 on QIDS-C or QIDS-SR question # 12
    - Yes response on Columbia-Suicide Severity Rating Scale (C-SSRS) Question # 3 a (ideation without plan or intent), Question #4 (ideation with intent, but no plan), or Question # 5 (ideation, intent, and plan)
- Treatment emergent mania operationalized as YMRS ≥ 20.

3.7 Identification of Source Data

The following source data will be directly recorded on the Case Report Form (CRF):

- Vital signs and physical examination.
- Events
- Patient Reported Outcomes
- Patient Completed Questionnaires

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The following source data will not be directly collected in the Case Report Form (CRF), but will be captured in supportive documentation (study source documents, EMR):

- Laboratory results and clinical interpretation of the values.
- ECG records and clinical significance of observations (when applicable)

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

1. Adults between 18 and 65 years of age
2. Bipolar I or II disorder as confirmed by structured clinical interview for DSM-IV-TR.
3. Subsyndromal depressive symptoms or major depressive episode unresponsive to steady and stable (ie, at least 2 weeks) mood stabilization (eg, lithium, valproate, lamotrigine, carbamazepine/oxcarbamazepine, and/or atypical antipsychotic therapy) and non-psychotropic medication.
4. Antidepressant therapy is allowed in the study as long as patients are also on a mood stabilizer. Patients will be enrolled provided that any needed modifications to the antidepressant would be made at least two weeks prior to randomization.
5. Patients receiving psychotherapy will be allowed to be randomized provided therapy frequency does not change during the 8-week blinded phase.
6. Symptom severity score on the Quick Inventory for Depressive Symptomatology – Clinician (QIDS-C16) ≥9, and the Clinical Global Impression for Bipolar Illness (CGI-BP) Depression Severity Scale ≥ 3.
7. Patients on stimulants for comorbid attention deficit disorder (ADHD) and/or binge eating disorder (BED) will be enrolled provided that the stimulant can be tapered and discontinued at least one week prior to randomization; symptom severity inclusion criteria 4.1.3 or presence of subsyndromal symptoms must be met again prior to randomization.
8. Patients with a prescribed opiate (eg. hydroxicodone) or other pain intervention for acute or chronic pain management will be allowed provided they: 1) use of a prescribed opiate or other pain intervention at a recommendation dose and established duration; 2) show no evidence of prescription misuse; 3) do not meet abuse or dependence criteria by SCID; 4) no known significant pharmacological interactions.
9. Ability to travel for the assessment visits.

4.2 Exclusion Criteria

1. Inability to provide written informed consent.
2. Inability to understand English.
3. Score less than 86% correct (ie, one wrong) on comprehension assessment that reviews study goals.
4. Clinically significant signs of acute suicidality from any of the following assessments:
    a. Response of > 2 on question #12 of QIDS-C or
    b. Response = 3 on the SCID Module A- #A19

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5. Medically serious suicide attempt within the past 6 months (medically serious defined as an ED evaluation and procedure and/or admit to inpatient unit such as internal medicine, cardiac, or ICU).
6. Concomitant treatment with monoamine oxidase inhibitors (MAOIs); also, within 14 days following discontinuation of treatment with a monoamine oxidase inhibitor.
7. Baseline Young Mania Rating Scale (YMRS) score ≥ 12.
8. Patients with active psychosis (measured by a score >4 on YMRS question #8) or a diagnosis of schizophrenia, schizoaffective disorder, delusional, or schizophreniform disorder identified by structured clinical interview for DSM-IV-TR.
9. Active abuse or dependence of alcohol, opiates, or cannabis (nicotine dependence will be an exception) by structured clinical interview for DSM-IV-TR; patients meeting full remission for at least 3 months can be randomized.
10. Positive toxicology screen for drugs of abuse (ie, cocaine, methamphetamine, illegal opiates).
11. Positive toxicology screen for cannabis and a cannabis use disorder by structured clinical interview for DSM-IV-TR. Participants who use cannabis for recreational or medicinal purposes and fail the toxicology screen can potentially be included in the study only if they take the CUDIT-R and score a 12 or less
12. Known lifetime history of cocaine or methamphetamine abuse or dependence identified by structured clinical interview for DSM-IV-TR.
13. Active stimulant prescription abuse or dependence by structured clinical interview for DSM-IV-TR; patients meeting full remission for at least 6 months can be randomized.
14. Known lifetime history of stimulant-induced mania.
15. Known hypersensitivity, such as angioedema or anaphylaxis, to amphetamines or other ingredients of MYDAYIS.
16. Clinically unstable medical disease.
17. Known history of a structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormality, coronary artery disease, stroke, or other serious cardiovascular problems.
18. ECG with clinically significant arrhythmias, conduction abnormalities, or voltage criteria met for left ventricular hypertrophy (unless cleared by cardiology consultation).
19. Uncontrolled hypertension (>160/100) or tachycardia (heart rate >110).
20. History of grand mal seizure; history of febrile seizure as infant permitted.
21. Established vasculopathy or history of Raynaud's phenomena.
22. Narrow angle glaucoma.
23. Chronic kidney disease (CKD) > stage IIIa (GFR 40-59).
24. Tourette syndrome.
25. Women who are pregnant, lactating or of child-bearing potential not using at least one adequate contraceptive measure (ie, hormonal contraception-birth control pills, intrauterine devices (IUD), tubal ligation or condoms during sexual intercourse).
26. Current positive test for SARS-CoV-2; those with previous COVID-19 illness and those who test positive for SARS-CoV-2 any time after starting study drug or placebo will be included.
27. Otherwise excluded for administrative reasons and/or clinician judgment.
28. Daily use of lorazepam (Ativan) at doses > 2 mg per day (or dose equivalent: clonazepam (Klonopin) > 1 mg, alprazolam (Xanax) > 1-2 mg, or diazepam (Valium) >20 mg) [58].

4.3 Subject Recruitment, Enrollment and Screening

Potential participants will be identified through routine clinical appointments, advertising, and existing lists/databases of individuals interested in being contacted about participation in research studies.

The recruitment of this study will be patients of Mayo Clinic, Rochester and Mayo Clinic Health System (MCHS), Austin and MCHS, Eau Claire. Mayo Clinic in Rochester will coordinate the recruitment, data collection, and analysis. For Mayo Clinic, Rochester, the main recruiting sources will be the Depression Center (Ge2A), Mood Disorders Unit (Ge3W), Adult Psychiatric Acute Care Unit (Ge2E), Primary Psychiatry and Psychology (GeMW), and Tertiary Psychiatry and Psychology (Mayo W11, IBH).

Patients may be referred from the Mayo Clinic Health System: La Crosse and Albert Lea.

We will also use Mayo Clinic Facebook and Twitter posts (with guidance from Research Recruitment Services), the Mayo Classifieds, and a Craigslist ad. We will work with local mental health organizations (eg, NAMI of SE MN), local organizations where people gather (eg, churches, barbershops), and the Mayo Clinic Center for Health Equity and Community Engagement Research to share the IRB-approved flyers and social media posts. In partnership with the Center for Health Equity and Community Engagement Research, we will translate our flyer into Spanish in order to get the word out in the local Hispanic and Latino community (still to only recruit those who are English speaking).

We will also be utilizing the Research Match (www.researchmatch.org) registry in order to obtain information about bipolar individuals who are interested in participating in research as an additional recruitment resource. Additionally, this study will be listed in www.clinicaltrials.gov.

ResearchMatch.org is a national electronic, Web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University. There is no cost for researchers at participating institutions in the ResearchMatch network to use ResearchMatch for the purposes of feasibility analysis or recruitment. The Vanderbilt IRB provides oversight for ResearchMatch as a recruitment tool and this has been documented within the ResearchMatch IRB Letter of Understanding (available upon request). However, individual requests to use ResearchMatch as a recruitment tool should be submitted to the participating institution's IRB. For more general information regarding ResearchMatch, please visit www.researchmatch.org.After being granted recruitment access, researchers will be able to search for appropriate matches amongst the non-identifiable ResearchMatch volunteer profiles in the system. Researchers may enter study inclusion/exclusion criteria in the ResearchMatch Search Builder, which will yield a list of potential matches to such criteria.

Researchers will send out IRB-approved content in the initial recruitment message to these potential matches (ResearchMatch volunteers) through ResearchMatch. This study's recruitment content will be inserted into the standard ResearchMatch electronic notification that informs

possible matched volunteers that a researcher has identified them as a potential match for their study. The secure ResearchMatch clearinghouse will route this standard notification that includes this specific study content (i.e., similar to the content available on a flyer or poster) to each of these potential ResearchMatch volunteer matches and they will have the option of replying yes, no, or not respond through a set of quick links available in this notification. **THIS MESSAGE WILL NOT INCLUDE THE STUDY'S DIRECT CONTACT INFORMATION** (e.g., EMAIL, PHONE) AS RESEARCHMATCH WILL MEASURE THE RESPONSE RATE THROUGH THE CLEARINGHOUSE'S QUICK LINKS MADE AVAILABLE IN THIS ELECTRONIC MESSAGE. These response rate metrics will be made available to researchers through their ResearchMatch dashboard as well as the Institutional Liaison dashboards. By responding yes, the volunteer has authorized ResearchMatch to release their contact information to the researcher(s) responsible for that study. This information will be made available on the researcher's ResearchMatch study dashboard. The researcher will be responsible for managing this contact information as called for by their IRB-approved study protocol.

University of Cincinnati affiliate--Lindner Center of HOPE (LCOH) SITE

University of Cincinnati (UC)

The University of Cincinnati (UC) College of Medicine, Department of Psychiatry at the UC College of Medicine was founded in 1932 and UC is the 14th largest recipient of NIH funding. Among departments of Psychiatry, UC has one of the largest psychopharmacology research programs in the United States dedicated to depression and bipolar disorder; UC has the necessary faculty and resources to support excellent clinical research. The faculty has a long-term successful record of sustained research support related to mood, eating, and impulse control disorders and pharmacological treatments.

Lindner Center of HOPE (LCOH)

LCOH is a nonprofit 91,820 square foot Mental Health facility affiliated with the University of Cincinnati and located in Mason, Ohio. LCOH provides comprehensive mental health, substance abuse, and co-occurring services. The Center was a founding member of the National Network of Depression Centers (NNDC), de facto recognition as a center of excellence in the treatment and research of mood disorders. The facility is located on 36 acres and is easily accessible to the tri-state area (Ohio, Kentucky and Indiana). LCOH has 48 inpatient beds with separate units for adolescents, adults and elderly patients. The annual capacity is 1,400 inpatients and 29,000 outpatients. The facility treats patients with public and private health insurance. Onsite assets include pharmacy, dining room, faith center, library, gymnasium, and exercise room. The Joint Commission accredits LCOH for Hospital and Behavioral Health Care, Licensed as a Private Psychiatric Hospital by Ohio Department of Mental Health and Certified for Mental Health Services by Ohio Department of Mental Health.

The LCOH Research Institute located onsite is dedicated to conducting clinical and outcomes research. The Research Institute has conducted numerous clinical trials of pharmacological treatments for mood, eating, and anxiety disorders, including many trials in bipolar depression.

The Research Institute is staffed by 4 Psychiatrists, 1 PhD, 4 Research Assistants, 1 Nurse Practitioner, 1 Statistician, and has dedicated Administrative support. The Research Institute has two exam rooms equipped with an electrocardiogram and laboratory space equipped with a -80 degree Celsius freezer to store blood samples, centrifuge, phlebotomy equipment and other supplies for routine medical examinations. Dr. McElroy is the Director of the Research Institute. The Clinical Staff at the LCOH Research Institute are trained in conducting numerous assessments including the Structured Clinical Interview –DSM IV –TR Axis I Disorders (SCID), Hamilton Rating Scale for Depression (Ham-D), Hamilton Anxiety Rating Scale (Ham-A), Inventory of Depressive Symptomatology (IDS), Young Mania Rating Scale (YMRS), Global Assessment of Functioning (GAF), and the Sheehan Disability Scale (SDS). The staff employed at the LCOH Research Institute has over 17 years' experience conducting research and recruiting study participants from the local environment (prior to LCOH opening the staff were part of the Clifton campus of the UC Department of Psychiatry).

Advertising: The LCOH Research Program has access to a full-time marketing staff, which, in turn coordinates television, radio and newspaper advertisements after appropriate approval by the UC IRB.

UC and LCOH also have excellent technical resources (eg, personal computers and software) for the analysis of data and preparation of manuscripts. Both PC and Macintosh computers are available and the Information Management staffs at LCOH are experienced in a variety of database programming languages including Stata, SAS, and SPSS. LCOH has integrated cutting-edge technology including an electronic medical record; wifi that integrates computers, telephones and voicemail; and state-of-the-art protection of patient-identified electronic data. The LCOH IT staff has expertise in web development and already manages the LCOH website (www.lindnercenter.org) in coordination with the marketing department.

The participants will be contacted by the Principal Investigator or study staff. Potential participants may be informed of the MYDAYIS® study during a routine clinical appointment. If a potential participant is currently hospitalized, permission to approach the individual will be obtained from the consultant providing psychiatric care to that individual. If a participant indicates interest in learning more about the study, a study Principal Investigator, Co-Investigator(s), or Coordinator will either talk with the participant in person or over the telephone to determine interest and eligibility. Potential participants may also come across one of the recruitment materials (listed below) and contact a Study Coordinator or Investigator directly to learn more about the project.

Potential participants identified from lists/databases of individuals interested in being contacted about future research studies they may qualify for may either be contacted via telephone (with an IRB-approved telephone script) or letter mailing (with an IRB-approved contact letter). The recruitment materials for this study include advertising posters and brochures posted in participant and employee waiting areas, physician referrals, and online listing in Mayo's clinical trials website. The research team will also request to retrieve diagnosis data from medical records at the Mayo Clinic to compile a list of participants with bipolar disorder type I or II. An invitation to participate letter will be sent to the list of participants. Eligibility will be

determined by the principal investigator or a psychiatrist who is a co-investigator by interview with the subject and by consultation of subject's medical.

Pre-screening procedures:

A potential participant will meet with a member of the team (Study Coordinator) to discuss details of the study and to answer any questions a potential participant may have. An IRB approved telephone script will be used for this purpose and telephone calls monitoring drug active participants throughout the length of the study as it has been illustrated above in the schematic diagram.

If a potential participant agrees to participate in the Study, they will then sign the IRB-approved informed consent form. Once informed consent is obtained, the study team will ensure information regarding the clinical trial and participant's role has been transmitted efficiently by having the participant complete the Comprehension Assessment (CA).

The study team member completing the consent process with the participant will review the responses provided by the participant. Any incorrect responses will be reviewed in detail until the participant understands the nature of the statement -- these reviews will be documented next to the appropriate items on the CA. The completed CA will be stored with the original copy of the participant's informed consent form. The participant will be given a copy of the consent and the CA.

Some research activities may occur after the initial participation process described above and the participant will be asked for their permission to be contacted in the future to obtain additional information for the study. These activities include annual computer linkages to a participant's medical record to ensure accuracy of the biobank database, requests to complete additional questionnaires, and requests for additional blood samples. All participants reserve the right to deny any requests for additional survey completion or sample collection.

Screening visit

Once informed consent is accepted and signed, initial structural diagnostic interview and depression severity ratings will be completed.

Once consented, the participant will be interviewed by a member of team (PI, Co-I, Study Coordinator) for the SCID, to confirm the diagnosis of bipolar I, II, current depressive episode according to DSM-IV-TR criteria. Once the SCID is complete, the participant will be asked to complete the following:

a. Quick Inventory of Depressive Symptomatology (QIDS-C)
b. Quick Inventory of Depressive Symptomatology (QIDS-SR)
c. Young Mania Rating Scale (YMRS)
d. Clinical Global Impression (CGI-BP)
e. Columbia-Suicide Severity Rating Scale (C-SSRS)

f. Bipolar Biobank Participant Questionnaire (BiB-PQ) and Bipolar Biobank Clinical Questionnaire (BiB-CQ)
g. Cannabis Use Disorders Identification Test-Revised (CUDIT-R) if applicable

If a participant fulfils all inclusion criteria and does not meet exclusion criteria mentioned previously or they are not on a mood stabilizer, they would need to be on a mood stabilizer and/or antipsychotic for at least 2 weeks provided by their primary provider of psychiatric care. Posteriorly, after these 2 weeks participants will be reassessed for study eligibility and remaining in the study if they still meet inclusion and do not meet any exclusion criteria.

After consent is obtained and eligibility has been confirmed (inclusion/exclusion criteria; SCID, questionnaire ratings and blood drawn), RAVE® randomization case report form (CRF) will be submitted.

Tracking and Retention

In order to achieve the aims of the study, significant effort will be made to insure high levels of retention throughout the study. Procedures that could be used to support high retention rates will include: (1) with the participants permission we will collect names and phone numbers of relatives or friends who know the contact information of the participants; (2) setting up a password protected electronic database with names, phone numbers, and projected times of proposed contacts for all participants; and (3) maintaining phone contact with participants throughout the study according to schedule telephone consultations and reminding participants in advance of study appointments; (4) +/- 3 day visit window. If a participant misses a visit or a Zoom or telephone call, an attempt to reschedule within the visit window must be made. If 3 consecutive visits are missed, the participant will be dropped from the study.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Drop-out Criteria

At each research study visit, assessment of depressive symptoms (QIDS), hypomanic/ manic symptoms (YMRS), and overall clinical impression (CGI-BP) will be completed.

Drop-out criteria will be defined as any of the following:

A) Hospitalization or any emergency visit for new onset of depression, mania, psychosis, or suicidality after starting participation in clinical trial. Patients will be re-assessed by study co-investigators or PI.
B) Worsening of depression (CGI-BP change from preceding phase of *much or very much worse*).
C) Treatment emergent mania defined as a YMRS>20 or CGI-BP change from preceding phase of *much or very much worse*.
D) Suicidal ideation with plan as defined by any of the following responses: Response > 4 on MADRS question # 10; Response ≥ 3 on QIDS-C or QIDS-SR question # 12; Yes response

on Columbia Suicide Severity Rating Scale (C-SSRS), Question #4 (ideation with intent, but no plan), or Question # 5 (ideation, intent, and plan).

E) Change in any maintenance psychotropic during the study trial.

F) Daily use of lorazepam (Ativan) at doses > 2 mg per day (or dose equivalent: clonazepam (Klonopin) > 1 mg, alprazolam (Xanax) > 1-2 mg, or diazepam (Valium) > 20 mg) [58].

G) Development of serotonin syndrome (mental status changes, autonomic instability, neuromuscular changes, gastrointestinal symptoms, seizures).

H) Intolerable side effects.

I) Other administrative criteria as determined by the research team such as poor adherence to clinical trial guidelines.

In accordance with the Declaration of Helsinki each patient is free to withdraw from the study at any time. The investigator also has the right to withdraw a patient from the study in the event of intercurrent illness, adverse events, pregnancy, or other reasons concerning the health or well-being of the patient, or in the case of lack of cooperation. Participants will be asked to complete a final visit for assessment and testing.

Special attention will be given to participants who develop suicidal ideation. Participants will be closely monitored at in person and Zoom or telephone visits to ensure medication compliance and participant safety. The SC will be supervised by the PI or co-investigators and notify if any subject endorses any active suicidal ideation or plan as well adverse events during the trial. Posteriorly, the PI or co-investigators will assess and monitor subject closely.

All questionnaires that involve questions related to depression and/or harm to self or others will be reviewed within 1 working day of receipt from the subject.

Subject Safety Management Plan

Subject Safety

a) Safety will be monitored by the Principal Investigator and study team.
b) Subjects will be assessed in person or by Zoom or telephone consults by the study investigators or an appropriately trained health professional at every visit and the evaluation will be documented.
c) Subjects will be monitored for adverse events (AEs) throughout every visit.
d) Subjects and families will be given 2 methods (clinic phone and EMR messaging) to contact the study team if adverse events occur between study visits.
e) Subjects will be evaluated for mood, suicidal ideation, and suicidal behavior as a part of the data collection process. Results will be reviewed on the same day by the study investigators or an appropriately trained health professional.

The participant will be asked to provide contact information, including an emergency contact. In an emergency (as determined by the PI and co-investigators) the study team will reach out to the emergency contact if the participant cannot be contacted.

During the consent process, subjects will be educated about the possibility of significant changes in mood, suicidal thinking, and/or behaviors during the study. These changes could include

worsening of mood symptoms, and/or suicidal thinking and behaviors such as psychotic symptoms. Subjects will be told to initiate contact with their study doctor, if they experience any significant mood or behavior changes including worsening suicidal ideation. Principal Investigator contact information is included in the consent/assent document and patient will be re-assessed by team physicians to evaluate participant's continuation in the study.

Management Plan for Suicidality

- If during the trial a subject has worsening of depressive symptomatology given by a CGI-BP score of much worse or very much worse, change of severity on the MADRS (ie, from moderate to severe) or an elevated score (ie, MADRS > 34) as well as presence of hypomanic or manic symptoms given by a YMRS score > 15, the subject will be evaluated by a study physician at the time of the visit and appropriate follow up will be arranged (Emergency department referral or scheduled visit with psychiatrist).
- If a subject endorses suicidal ideation, as outlined in the drop out criteria, determined by the investigator or study team physicians the subject will be evaluated by a study physician at the time of the visit to assess safety and continuation in the study. Further, appropriate follow up will be arranged (Emergency department referral or scheduled visit with psychiatrist) as necessary.
- If meeting drop out criteria, study participation will terminate, and the participant will be referred for further psychiatric care. If necessary, non-research follow up visits will be provided to facilitate care and referral.
- Investigators will notify the primary provider about the need for such referral. If the subject does not have a primary provider, the research consultant will provide a referral for psychiatric consultation.
- If a subject endorses suicidal ideation during Zoom or telephone visits by responding to questions from the C-SSRS: "Yes" response to questions 4, "Yes" response to question 5, or with a score of 4 or 5 on ideation items, the study coordinator will contact a study physician or co-investigator to return a call to the participant as soon as possible before the same day close of business. The investigator will assess safety, need of referral to emergency department, need for communicating with emergency contact, and ongoing study participation.

<u>New Psychotic or Manic Symptoms</u>

CNS stimulants, at recommended doses, may cause psychotic or manic symptoms, eg, hallucinations, delusional thinking, or mania [40]. In a pooled analysis of multiple short-term, placebo-controlled studies of MYDAYIS, psychotic or manic symptoms occurred in 0.1% of CNS stimulant-treated patients compared to 0% in placebo-treated patients [1].

If such symptoms occur, the patient will be evaluated by study team physicians or PI and consider discontinuing MYDAYIS. If the study team physicians or PI determine that it is in the participant's best interest, the PI may prescribe a benzodiazepine for temporary use.

The reason for and date of withdrawal from the study must be recorded on the CRF. If a patient withdraws from the study, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event or a clinically significant abnormal laboratory test result, monitoring will continue until the event has resolved or stabilized, until the patient is referred to the care of a local health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made. The specific event or test result(s) must be recorded on the CRF. All evaluations should be performed, according to the protocol, on the last day the patient takes study drug, or as soon as possible thereafter.

5 Study Drug

5.1 Description

The active ingredients in MYDAYIS® contain a mix amphetamine salt (MAS). The MAS include equal amounts of the neutral sulfate salts of dextroamphetamine and amphetamine, the dextro isomer of amphetamine saccharate and d,l-amphetamine aspartate monohydrate, with the enantiomer ratio of d-amphetamine and l-amphetamine being in a ratio of 3:1. Each capsule contains three types of drug-releasing beads, an immediate-release bead and two different types of delayed-release beads. The first delayed-release bead releases amphetamine at pH 5.5 and the other delayed-release bead releases amphetamine at pH 7.0.

The 12.5 and 25 mg capsules are intended for oral administration. The active ingredients are: dextroamphetamine sulfate and amphetamine sulfate, dextroamphetamine saccharate and amphetamine aspartate monohydrate. Inactive ingredients: hard gelatin capsules, ethylcellulose, hydroxypropyl methylcellulose, methacrylic acid copolymer, methyl acrylate, methyl methacrylate, opadry beige, sugar spheres, talc, and triethyl citrate. Gelatin capsules contain gelatin, titanium dioxide, yellow iron oxide and edible inks.

5.2 Treatment Regimen

Dosing schedule - Double blind phase
Titration may be adjusted by the study physician based on side effects and/or early treatment response.

Baseline, Visit 2 - Oral administration. 12.5 mg MYDAYIS matching placebo x 7 days
Week 1, Visit 3 - Oral administration. 25 mg MYDAYIS matching placebo x 7 days
Week 2, Visit 4 - Oral administration. 37.5 mg MYDAYIS matching placebo x 14 days
Week 4, Visit 6 - Oral administration 50 mg MYDAYIS matching placebo x 14 days
Week 6, Visit 8 - Oral administration 50 mg MYDAYIS matching placebo x 14 days

Dosing schedule - Open label extension phase

Blind to Open, Visit 10 - Oral administration. 12.5 mg MYDAYIS x 7 days
Week 1, Visit 11 - Oral administration. 25 mg MYDAYIS x 7 days
Week 2, Visit 12 - Oral administration. 37.5 mg MYDAYIS x 14 days
Week 4, Visit 14 - Oral administration. 50 mg MYDAYIS x 14 days

Week 6, Visit 16 - Oral administration. 50 mg MYDAYIS x 14 days

Lorazepam, no more than 2 mg QD PRN [or dose equivalent: clonazepam (Klonopin) > 1 mg, alprazolam (Xanax) > 1-2 mg, or diazepam (Valium) > 20 mg][58] will be allowed during the double blind and open label extension phases.

5.3 Method for Assigning Subjects to Treatment Groups

Study subjects will be randomized to receive MYDAYIS® or placebo on a 1:1 ratio according to computer-generated coding. Each pharmacy will have its own randomization list. Allocation concealment will be achieved by having the research pharmacy perform the randomization, package the study medication, and maintain the integrity of the blinded information throughout the study.

5.4 Preparation and Administration of Study Drug

MYDAYIS® will be in the form of a capsule (12.5 and/or 25 mg or matching placebo) and dispensed to the study subjects according to a predetermined randomization schedule. All dosing will be with 12.5 and/or 25 mg capsules and titration may be adjusted by the study physician based on side effects and/or early treatment response. Matched placebo capsules will be provided accordingly. MYDAYIS® will be administered orally with or without food. The following recommendations will be given:

- Swallow MYDAYIS® capsules whole, or
- The dose of a single capsule should not be divided.

5.5 Subject Compliance Monitoring

Each investigator will be responsible for monitoring patient compliance. Patients can be withdrawn from the study at any time if the investigator or the sponsor determines that the patient is not in compliance with the study protocol.

Subjects' compliance with the study drug will be evaluated by the Compliance Assessment scale (CA). The CA is a simple scale measuring compliance based on pill counts and clinical interviews. This scale is based on operationally defined degrees of compliance (full, partial, total non-compliance) [41]. The cutoff for data analysis is ≥90% compliance in relation to pill count and a clinical interview compliance score ≤ 2.

Additionally, we will confirm medication compliance by examining blood drug level at visits 10 and 18.

5.6 Prior and Concomitant Therapy

All psychotropic and non-psychotropic medications that the subjects are taking at study entry will be continued unchanged throughout the course of the study.

Once randomized an increase in the dose of baseline mood stabilizer, antipsychotic medication, or antidepressant medication or the addition of a new psychotropic medication (except for hypnotics) will result in subject termination from the study.

5.7 Masking/Blinding of Study

Study subjects will be randomized to receive MYDAYIS® or placebo on a 1:1 ratio according to computer-generated coding. Each pharmacy will have its own randomization list. Allocation concealment will be achieved by having the research pharmacy perform the randomization, package the study medication, and maintain the integrity of the blinded information throughout the study.

5.8 Receiving, Storage, Dispensing and Return

5.8.1 Receipt of Drug Supplies

Each pharmacy will acquire medication, create a placebo, and encapsulate both to match. Investigational Product(s) (IP) are received by study personnel acting on behalf of the investigator. Research pharmacy staff verify information on the packing slip matches the contents of the shipment. The following are verified by receiving personnel upon receipt of shipment: product identification, sponsor product label, quantity of items received, package size(s), lot numbers, expiration dates if available, product condition, and maintenance of storage conditions in transit. Any discrepancies in shipment are communicated immediately to study sponsor. Investigational products that do not contain an expiration date are deemed in date and acceptable to use until notice of expiration is received from sponsor or supplier. Research staff contacts sponsors and/or suppliers quarterly to determine if retest date or expiration is available. After shipment has been checked and verified, IP is immediately placed in appropriate storage conditions as indicated in study documentation.

5.8.2 Storage

Purchased drug will be stored at a controlled room temperature between 20 and 25 degrees protected from light (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) (See attachment for more details).

5.8.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug dispensed, drug returns, and drug remaining. Subjects will be informed about specific details of how to store MYDAYIS® (ie, locked cabinet).

This reconciliation will be logged on the drug reconciliation form and signed and dated by the study team.

Titration may be adjusted by the study physician based on side effects and/or early treatment response.

Study drug will be mailed directly to the Austin and Eau Claire participants (we will need to use the Outpatient Research Pharmacy for Austin and Eau Claire) and to Rochester participants unless they do not want that, in which case participants can pick it up from study staff.

We are aware that some participants may be uncomfortable with home delivery of their medication, so the following has been added to the ICF: If you agree to be in the study, you will have the study drug mailed directly to your home; if you prefer to pick it up in person, you would need to pick it up from the study team at the Saint Marys campus. If you participate in the study through MCHS – Austin or Eau Claire, you will have to get the study drug mailed to you.

5.8.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed, and dated. Any discrepancies noted will be documented and investigated, prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

Screening & Enrollment- Visit 1

1. Safety parameters: baseline ECG, vital signs, and physical exam; laboratory testing (CBC, LFTs, blood chemistry, urine pregnancy test, and drug screening; HbA1c and Lithium or Valproate levels if appropriate); treatment emergent suicidal ideation quantified by: response ≥ 3 on QIDS- SR or QIDS-C item # 12, or Columbia Suicide Severity Rating Scale (C-SSRS): "Yes" response to questions 4, "Yes" response to question 5; treatment emergent mania operationalized as YMRS ≥ 20 or hypomanic symptoms ≥ 12.
2. Structured Clinical Interview for DSM-IV-TR (SCID)
3. Quick Inventory of Depressive Symptomatology (QIDS-C)
4. Quick Inventory of Depressive Symptomatology (QIDS-SR)
5. Clinical Global Impression (CGI-BP)
6. Young Mania Rating Scale (YMRS)
7. Columbia-Suicide Severity Rating Scale (C-SSRS)
8. Bipolar Biobank Participant Questionnaire (BiB-PQ) and Bipolar Biobank Clinical Questionnaire (BiB-CQ)
9. Cannabis Use Disorders Identification Test Revised (CUDIT-R) if applicable

If the SCID was administered within the last year for another Mood Unit study, the results from the other Mood Unit study may be used. If the Bipolar Biobank Patient Questionnaire (BiB –PQ) or the Bipolar Biobank Clinical Questionnaire (BiB-CQ) were completed for another Mood Unit study two-weeks or less prior to the MoStGEN biobank enrollment, these two assessments can be

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used for the Mydayis study; if these two assessments were used in a Mood Unit study more than two weeks prior to Mydayis enrollment, they may need to be repeated.

Baseline visit - Visit 2-

1. Vital signs and weight
2. Physical exam if not performed at Screening/Enrollment visit
3. Drug dispensing
4. Blood for biomarkers
5. COVID-19 Status and Vaccination Questions (since last visit)

Behavioral scales completed include:

1. Montgomery Asberg Depression Scale (MADRS)
2. Quick Inventory of Depressive Symptomatology (QIDS-C)
3. Quick Inventory of Depressive Symptomatology (QIDS-SR)
4. Clinical Global Impression (CGI-BP)
5. Young Mania Rating Scale (YMRS)
6. Columbia-Suicide Severity Rating Scale (C-SSRS)
7. General Anxiety Disorder 7-item scale (GAD-7)
8. Epworth Sleepiness Scale (ESS)
9. Morningness-Eveningness Questionnaire (MEQ)
10. Fatigue Severity Scale (FSS)
11. Binge Eating Scale (BES)
12. Rapid Eating and Activity Assessment for Patients (REAP)
13. Digit Symbol Substitution Test (DSST)
14. COVID-19 Status and Vaccination Survey (Baseline)

If at any time during study participation, a participant becomes COVID-19 positive or experiences other illness that would keep them from an in-person visit within the ±3-day window, the visit will be changed to phone or Zoom. Accommodations include but are not limited to: vitals will not be taken for that visit and the self-report behavioral scales will be completed off-campus. Examples of how self-report data will be obtained include having a study staff ask the questions over the phone or a link to REDCap will be sent to the participant to have them electronically fill out the self-report ratings. Additionally, study drug or placebo can be provided to participants at the Rochester site in a Research Pharmacy Policy-approved manner.

The Coronavirus Impact Scale and COPDGene survey (as described in Section 3.5 on page 15) will be administered if a participant tests positive for COVID-19 during study participation. Participants will complete the surveys during the first visit (either in-person or via phone) after their positive COVID-19 test.

If at any time during study participation, a participant becomes hypomanic or experiences other safety circumstances, a phone/Zoom visit can be changed to become an in-person visit. Additionally, the study physicians or PI may decide to add an additional phone/Zoom or in-person

visit as another safety precaution. If at any time the study physicians or PI are concerned about a participant's health, clinical labs (eg, HbA1c, CBC, Blood Chemistry, AST, ALT, TSH,) could be run.

If at any time during the Double-Blind phase of the study, the study team feels like the participant's depressive symptoms have worsened yet do not include endorsing suicidality, it may be appropriate to review other treatment options (eg, other studies, clinical care, continuing to open label) with the participant. If it is in the participant's best interest and is clinically appropriate, the study physician may have the participant continue with the open phase of the study before completing all eight weeks of the Blind phase.

Visit 3- Week 1 of Blind Phase

*Zoom or Telephone consultation, or In-person visit *If in-person, vitals will be taken.*

1. Compliance Assessment
2. COVID-19 Status and Vaccination Questions (since last visit)

Behavioral scales completed include:

1. Montgomery Asberg Depression Scale (MADRS).
2. Quick Inventory of Depressive Symptomatology (QIDS-C)
3. Quick Inventory of Depressive Symptomatology (QIDS-SR)
4. Young Mania Rating Scale (YMRS)
5. Clinical Global Impression (CGI-BP)
6. Columbia-Suicide Severity Rating Scale (C-SSRS)

Visit 4- Week 2 of Blind Phase

1. Vital signs and weight
2. Drug dispensing
3. Blood for biomarkers
4. Compliance Assessment
5. COVID-19 Status and Vaccination Questions (since last visit)

Behavioral scales completed include:

1. Montgomery Asberg Depression Scale (MADRS)
2. Quick Inventory of Depressive Symptomatology (QIDS-C)
3. Quick Inventory of Depressive Symptomatology (QIDS-SR)
4. Clinical Global Impression (CGI-BP)
5. Young Mania Rating Scale (YMRS)
6. Columbia-Suicide Severity Rating Scale (C-SSRS)

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Visit 5- Week 3 of Blind Phase

Zoom or Telephone consultation

1. Young Mania Rating Scale (YMRS)
2. Columbia-Suicide Severity Rating Scale (C-SSRS)
3. Compliance Assessment
4. COVID-19 Status and Vaccination Questions (since last visit)

Visit 6- Week 4 of Blind Phase

1. Vital signs and weight
2. Drug dispensing
3. Compliance Assessment
4. COVID-19 Status and Vaccination Questions (since last visit)

Behavioral scales completed include:

1. Montgomery Asberg Depression Scale (MADRS)
2. Quick Inventory of Depressive Symptomatology (QIDS-C)
3. Quick Inventory of Depressive Symptomatology (QIDS-SR)
4. Clinical Global Impression (CGI-BP)
4. Young Mania Rating Scale (YMRS)
5. Columbia-Suicide Severity Rating Scale (C-SSRS)
6. Epworth Sleepiness Scale (ESS)
7. Fatigue Severity Scale (FSS)
8. Binge Eating Scale (BES)
9. Digit Symbol Substitution Test (DSST)

Visit 7- Week 5 of Blind Phase

Zoom or Telephone consultation

1. Young Mania Rating Scale (YMRS)
2. Columbia-Suicide Severity Rating Scale (C-SSRS)
3. Compliance Assessment
4. COVID-19 Status and Vaccination Questions (since last visit)

Visit 8- Week 6 of Blind Phase

1. Vital signs and weight
2. Drug dispensing
3. Compliance Assessment
4. COVID-19 Status and Vaccination Questions (since last visit)

Behavioral scales completed include:

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1. Montgomery Asberg Depression Scale (MADRS)
2. Quick Inventory of Depressive Symptomatology (QIDS-C)
3. Quick Inventory of Depressive Symptomatology (QIDS-SR)
4. Young Mania Rating Scale (YMRS)
5. Clinical Global Impression (CGI-BP)
6. Columbia-Suicide Severity Rating Scale (C-SSRS)

Visit 9- Week 7 of Blind Phase

Zoom or Telephone consultation

1. Young Mania Rating Scale (YMRS)
2. Columbia-Suicide Severity Rating Scale (C-SSRS)
3. Compliance Assessment
4. COVID-19 Status and Vaccination Questions (since last visit)

Visit 10 – End of Double-Blind Phase – Open Label extension phase starts.

1. Vital signs and weight
2. Drug dispensing
3. Blood for biomarkers
4. Blood drug levels
5. Medication Compliance Assessment
6. Physical exam
7. COVID-19 Status and Vaccination Questions (since last visit)

Behavioral scales completed include:

1. Montgomery Asberg Depression Scale (MADRS)
2. Quick Inventory of Depressive Symptomatology (QIDS-C)
3. Quick Inventory of Depressive Symptomatology (QIDS-SR)
4. Clinical Global Impression (CGI-BP)
5. Young Mania Rating Scale (YMRS)
6. Columbia-Suicide Severity Rating Scale (C-SSRS)
7. General Anxiety Disorder 7-item scale (GAD-7)
8. Epworth Sleepiness Scale (ESS)
9. Fatigue Severity Scale (FSS)
10. Binge Eating Scale (BES)
11. Rapid Eating and Activity Assessment for Patients (REAP)
12. Digit Symbol Substitution Test (DSST)
13. Cannabis Use Disorders Identification Test Revised (CUDIT-R) if applicable

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Visit 11- Week 1 Open label extension phase

*Zoom or Telephone consultation, or In-person visit *If in-person, vitals will be taken.*

1. Compliance Assessment
2. COVID-19 Status and Vaccination Questions (since last visit)

Behavioral scales completed include:

1. Montgomery Asberg Depression Scale (MADRS).
2. Quick Inventory of Depressive Symptomatology (QIDS-C).
3. Quick Inventory of Depressive Symptomatology (QIDS-SR)
4. Young Mania Rating Scale (YMRS)
5. Clinical Global Impression (CGI-BP)
6. Columbia-Suicide Severity Rating Scale (C-SSRS)

Visit 12- Week 2 Open label extension phase

1. Vital signs and weight
2. Drug dispensing
3. Compliance Assessment
4. COVID-19 Status and Vaccination Questions (since last visit)

Behavioral scales completed include:

1. Montgomery Asberg Depression Scale (MADRS).
2. Quick Inventory of Depressive Symptomatology (QIDS-C).
3. Quick Inventory of Depressive Symptomatology (QIDS-SR)
4. Clinical Global Impression (CGI-BP)
5. Young Mania Rating Scale (YMRS)
6. Columbia-Suicide Severity Rating Scale (C-SSRS)

Visit 13- Week 3 Open label extension phase

Zoom or Telephone consultation

1. Young Mania Rating Scale (YMRS)
2. Columbia-Suicide Severity Rating Scale (C-SSRS)
3. Compliance Assessment
4. COVID-19 Status and Vaccination Questions (since last visit)

Visit 14- Week 4 Open label phase

1. Vital signs and weight.
2. Drug dispensing
3. Compliance Assessment

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4. COVID-19 Status and Vaccination Questions (since last visit)

Behavioral scales completed include:

1. Montgomery Asberg Depression Scale (MADRS).
2. Quick Inventory of Depressive Symptomatology (QIDS-C).
3. Quick Inventory of Depressive Symptomatology (QIDS-SR)
4. Clinical Global Impression (CGI-BP)
5. Young Mania Rating Scale (YMRS)
6. Columbia-Suicide Severity Rating Scale (C-SSRS)
7. Epworth Sleepiness Scale (ESS)
8. Fatigue Severity Scale (FSS)
9. Binge Eating Scale (BES)
10. Digit Symbol Substitution Test (DSST)

Visit 15- Week 5 Open label extension phase

Zoom or Telephone consultation

1. Young Mania Rating Scale (YMRS)
2. Columbia-Suicide Severity Rating Scale (C-SSRS)
3. Compliance Assessment
4. COVID-19 Status and Vaccination Questions (since last visit)

Visit 16- Week 6 Open label extension phase

1. Vital signs and weight
2. Drug dispensing
3. Compliance Assessment
4. COVID-19 Status and Vaccination Questions (since last visit)

Behavioral scales completed include:

1. Montgomery Asberg Depression Scale (MADRS).
2. Quick Inventory of Depressive Symptomatology (QIDS-C).
3. Quick Inventory of Depressive Symptomatology (QIDS-SR)
4. Clinical Global Impression (CGI-BP)
5. Young Mania Rating Scale (YMRS)
6. Columbia-Suicide Severity Rating Scale (C-SSRS)

Visit 17- Week 7 Open label extension phase

Zoom or Telephone consultation

1. Young Mania Rating Scale (YMRS)

2. Columbia-Suicide Severity Rating Scale (C-SSRS)
3. Compliance Assessment.
4. COVID-19 Status and Vaccination Questions (since last visit)

Visit 18- Week 8 Open label extension phase

1. Vital signs and weight
2. Blood for biomarkers
3. Blood drug levels
4. Medication Compliance Assessment
5. Physical exam

Behavioral scales completed include:

1. Montgomery Asberg Depression Scale (MADRS)
2. Quick Inventory of Depressive Symptomatology (QIDS-C)
3. Quick Inventory of Depressive Symptomatology (QIDS-SR)
4. Clinical Global Impression (CGI-BP)
5. Young Mania Rating Scale (YMRS)
6. Columbia-Suicide Severity Rating Scale (C-SSRS)
7. Epworth Sleepiness Scale (ESS)
8. Fatigue Severity Scale (FSS)
9. Binge Eating Scale (BES)
10. Digit Symbol Substitution Test (DSST).
11. Cannabis Use Disorders Identification Test Revised (CUDIT-R) if applicable

Post-study visit

For those who complete the study, the Post-study visit will be occur after Visit 18. For those who leave the study early or who are withdrawn by the investigator or study team physician, the post-study visit will occur one week after leaving formal study participation. If labs for biomarkers or blood drug levels were due in a future visit and the patient-participant's study participation ended before that visit, the participant will be encouraged to do that blood draw. Additionally, if the participant is removed early from the study, the investigator or study team physician may use their discretion to order clinical labs, including Lithium or Valproate, as appropriate, and/or an ECG as a safety precaution. If the participant leaves the study early (dropped or withdrawn) and they did not recently have the Visit 10 physical exam, a brief physical exam will be performed. Vitals will be taken.

Behavioral scales completed include:

1. Montgomery Asberg Depression Scale (MADRS).
2. Quick Inventory of Depressive Symptomatology (QIDS-C).
3. Quick Inventory of Depressive Symptomatology (QIDS-SR)
4. Clinical Global Impression (CGI-BP)
5. Young Mania Rating Scale (YMRS)

6. Columbia-Suicide Severity Rating Scale (C-SSRS)

Biomarkers and drug levels

1. Baseline: Venipuncture will be performed using standard techniques. A total of 15 mL blood sample will be collected at baseline, taking into account laboratory tests and genetic studies.

The samples are detailed as follows:

1. a. Laboratory tests: A total of 15 mL will be collected for laboratory tests. One 10-mL EDTA tube (CBC, 10 mL total sample) and into one 5 mL no-additive serum tube (electrolyte panel, TSH, AST/ALT 5 mL total sample).

1. b. Genetic and biomarker predictors of response: Participants who are enrolled within a month to the MYDAYIS® Study, will share the same bio specimens for genetic and baseline biomarkers for predictors of response.

2. Subsequent visits:

2. a. Drug levels: At visit 10 and visit 18 or at study withdrawal, a total of 5mL will be collected for blood drug level of MYDAYIS®. (Plain Red top; centrifuge, aliquot serum, and send to Biospecimen Accessioning and Processing lab (BAP) for storage.) All blood drug samples will be analyzed at the end of the study after the Amphetamine level test has been developed.

2. b. Biomarkers: Blood samples will be drawn at Visit 2 (Baseline), Visit 4 (Blind Week 2), Visit 10 (Week 8—end of Blind-Beginning of Open), and Visit 18 (Open Week 16) for DNA extraction (EDTA purple top tubes), Epigenetic biomarkers (EDTA tubes), and blood drug levels (red top serum). A total of 115 mL blood sample will be collected throughout the study as summarized in the tables below:

	Enrollment	Visit 2	Visit 4	Visit 10	Visit 18	Total volume in study
Laboratory tests	15 ml					
Genomic/Biomarker		30 ml	30 ml	30 ml	30 ml	
Drug levels				5 ml	5 ml	
Total volume per visit	15 ml	30 ml	30 ml	35 ml	35 ml	145 ml

		# of tubes	Volume/tube	Total Volume
DNA (genotyping & sequencing)	EDTA	1	10ml	10ml

Epigenetics				
DNA Methylation	EDTA (plasma & buffy coat)	1	10ml	
Metabolomics	EDTA (plasma)	1	10ml	20ml
Drug level	Redtop (serum)	1	5ml	5ml

Each collaborating site will conduct the processing of samples and will store the samples at their site for later shipment to Mayo Clinic. Mayo Clinic sites' samples will be processed by BAP.

- DNA extraction at non-Mayo sites will be transferred into -80 degree appropriate plastic tube and placed in -80 degree freezer.
- DNA Methylation - EDTA tubes need to be kept on ice separated using a refrigerated centrifuge into plasma, buffy coat, and red blood cells. Plasma will be aliquoted into 200 ul aliquots and placed in the -80 degree freezer.
- Metabolomic platform would include both the amines and neuromodulators. EDTA tubes need to be kept on ice separated using a refrigerated centrifuge into plasma and buffy coat. Each being aliquoted into 300 ul aliquots and placed in the -80 degree freezer.
- Mydayis blood drug level – redtop serum tube will be centrifuged and serum will be aliquoted into .5ml aliquots and placed in the -80 degree freezer. Testing will be done at the end of the study.

Psychometrics Testing:

1. Structured Clinical Interview for DSM-IV (SCID) [42]; study coordinator rated. The SCID will be administered to all participants for screening purposes for entry into the study. This is a structured interview that allows for making diagnoses in accordance with DSM-IV. The interview takes approximately 30 minutes, depending on the pathology of the subject. If a SCID has been completed by study team within 1 year prior to enrollment and no change has occurred in mood/condition of participant, the previous SCID administered for other Mood Unit studies can be used as part of this study instead of duplication the diagnostic interview.
2. Quick Inventory for Depressive Symptomatology [43]; clinician (QIDS-C16) and self-report (QIDS –SR16). The 16-item Quick Inventory of Depressive Symptomatology (QIDS) is designed to assess the severity of depressive symptoms. This will be a screening measurement for symptom severity. Both the QIDS-C and QIDS-SR will be secondary outcome measures.
3. Montgomery Asberg Depression Rating Scale (MADRS); clinician and/or study coordinator rated. The MADRS is a 10-item observer rating scale assessing symptoms of depression [44]. The MADRS will be used for our primary outcome measure of baseline to endpoint change in depressive symptoms and for our secondary outcome measure of % participants who achieved remission defined as a MADRS < 10.
4. Young Mania Rating Scale (YMRS) [45] Clinician Rated: this is an 11-item observer rating scale assessing symptoms of mania. This scale measures a broad range of manic symptoms and has been shown to be sensitive to therapeutic effects. The YMRS will be used to assess the secondary outcome measure of baseline to endpoint change in subsyndromal manic

symptoms and as a safety measurement of treatment emergent hypomania (YMRS >12) or treatment emergent mania (YMRS ≥20).

5. Clinical Global Impression Scale for Bipolar Illness (CGI-BP) [46] clinician rated. The CGI, as modified for bipolar illness, allows for rating of degree of clinical improvement in depression, mania, and overall illness. Moreover, it addresses many of the specific criticisms leveled at the CGI relating to the types of ratings, technical and scaling problems, definition of time domain of the rating, and confounding of clinical response with tolerability and side effects. Section II of this instrument is a secondary outcome measure and will assess "change from preceding phase" of bipolar illness, rates of 1 (very much improved) or 2 (much improved) in the mania, depression and overall bipolar illness ratings will be considered the outcome measure of treatment response.
6. Columbia-Suicide Severity Rating Scale (C-SSRS) [47] clinician Rated. This 21-item interviewer administered rating scale that measures current intensity of suicidal ideation and will be measured at baseline and each visit. If there is a Yes response on Question #4 (ideation with intent, but no plan), or Question # 5 (ideation, intent, and plan), the participant will be withdrawn from the study.
7. Binge Eating Scale (BES); study coordinator rated. The BES is a 16-item questionnaire assessing the presence of certain binge eating behaviors which may be indicative of an eating disorder [48].
8. Rapid Eating and Activity Assessment for Patients (REAP- shortened version): The REAP is a brief survey of 16 questions examining dietary assessment (whole grains, calcium rich foods, fruits, vegetables, fat, saturated fat and cholesterol, sugary beverages and foods, sodium, alcoholic beverages, and physical activity to aid in clinical examination [49].
9. Epworth Sleepiness Scale (ESS) [50], subjective measurement of likelihood of falling asleep during normal daily situations scored on a 4-point scale from "would never" to "a high chance" (score ≥ 10 considered abnormal).
10. Morningness-Eveningness Questionnaire (MEQ) [51]: is a set of 19 questions that asks subject to consider their best rhythms and preferred clock time for sleep and engagement in various situations (ie, physical exercise, tests, work) assessing morning alertness, appetite, evening tiredness. Scores range from 16 to 86 with lower scores indicating even types and higher scores morning types.
11. Fatigue Severity Scale (FSS) [52] is a self- administered questionnaire of 9 items measuring the fatigue severity during the past week (abnormal score ≥ 4).
12. Digit Symbol Substitution Test (DSST) is a component of the Wechsler Adult Intelligence Scale [53] which specifically requires the integrity of executive function. The DSST assesses relative contributions of speed, memory, executive function and visual scanning being more sensitive to measure performance [54]. Participants are required to copy symbols that are paired with simple geometric shapes or numbers within a specific time for a total possible score of 0 to 133. Higher scores-correct number of symbols reflects greater objective cognitive functioning.
13. Compliance Assessment (CA). The CA is a simple scale measuring compliance based on pill counts and clinical interviews. This scale is based on operationally defined degrees of compliance (full, partial, total non-compliance) [41]. The cutoff for data analysis is ≥90% compliance in relation to pill count and a clinical interview compliance score ≤ 2.
14. Cannabis Use Disorders Identification Test Revised (CUDIT-R) [55]: is a brief 8-item screening instrument designed to identify potentially problematic or harmful recent cannabis

use. The maximum possible score is 40, with a cut-off score of 8 indicating 'hazardous' cannabis use, and a cut-off score of 12 or more indicating "possible cannabis use disorder" for which further intervention may be required.

15. COPDGene COVID-19 Survey [56]: An NIH approved questionnaire created by the COPDGene® Study, one of the largest studies on genetic factors of Chronic Obstructive Pulmonary Disease, which is intended to periodically monitor any illnesses related to COVID-19, previous test results and recovery status in cases of past infections. The approximate time for completing this survey is 10 minutes.
16. Coronavirus Impact Scale [57]: A scale that assesses the impact of the COVID-19 pandemic on economic, social and personal matters. It is a 12-item self-applied questionnaire that takes 10 minutes to complete.
17. COVID-19 Status and Vaccination Survey (Baseline): A clinician-applied brief questionnaire to inquire about the participant's past COVID-19 infection and vaccination status at study entry. This survey takes 5 minutes to complete.

** Answers to COVID-19 surveys will not impact the patient's eligibility for the MYDAYIS study. These surveys are intended to assess depressive illness trajectories and response to MYDAYIS in the context of SARS-CoV-2 serostatus.*

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Schedule of events of MYDAYIS ® trial

8-Week Randomized, Double-Blind, Placebo-controlled Treatment											8-Week Open Label								
Visit Title	**Enrollment**	**Baseline**	**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**	**W 13**	**W 14**	**W 15**	**W 16**	**Post Study Visit**
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19
Visit Type (Office=OV, Zoom-Telephone=ZTC)	OV	OV	ZTC	OV	ZTC	OV	ZTC	OV	ZTC	OV	ZTC	OV	ZTC	OV	ZTC	OV	ZTC	OV	OV
Visit Day	Day -14 to -7	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56	Day 63	Day 70	Day 77	Day 84	Day 91	Day 98	Day 105	Day 112	Day 119
RX Dose		12.5	25	37.5	37.5	50	50	50	50	12.5	25	37.5	37.5	50	50	50	50	0	0
Vital signs & Wt	X	X		X		X		X		X		X		X		X		X	
Physical exam	X									X								X	
ECG	X																		
Urine pregnancy	X																		
Toxicology urine	X																	X	
Lab testing (CBC, LFT, Blood chemistry)	X																		
Drug dispensing		X		X		X		X		X		X		X		X			
Blood -drug level										X								X	
Blood-biomarker		X		X						X								X	
SCID	X																		
COVID Status & Vaccination Survey (Baseline)		X																	
MADRS		X	X	X		X		X		X	X	X		X		X		X	X
QIDS-C	X	X	X	X		X		X		X	X	X		X		X		X	X
QIDS-SR	X	X	X	X		X		X		X	X	X		X		X		X	X
YMRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-BP	X	X	X	X		X		X		X	X	X		X		X		X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
GAD-7		X								X									
BiB-CQ/ PQ	X																		
DSST		X								X								X	
ESS		X				X				X				X				X	
MEQ		X																	
FSS		X				X				X				X				X	
BES		X				X				X				X				X	
REAP-S		X								X									
CUDIT-R if applicable	*X*									*X*								*X*	

8-Week Randomized, Double-Blind, Placebo-controlled Treatment											8-Week Open Label								
Visit Title	**Enrollment**	**Baseline**	**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**	**W 13**	**W 14**	**W 15**	**W 16**	**Post Study Visit**
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19
Visit Type (Office=OV, Zoom-Telephone=ZTC)	OV	OV	ZTC	OV	ZTC	OV	ZTC	OV	ZTC	OV	ZTC	OV	ZTC	OV	ZTC	OV	ZTC	OV	OV
Visit Day	Day -14 to -7	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56	Day 63	Day 70	Day 77	Day 84	Day 91	Day 98	Day 105	Day 112	Day 119
Compliance assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Coronavirus Impact Scale*																			
COPDGene*																			

*The Coronavirus Impact Scale and COPDGene COVID-19 survey will be administered if a participant tests positive for COVID-19 during study participation. They will complete the surveys the first visit (either in-person or via phone) after the diagnosis.

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7 Statistical Plan

7.1 Sample Size Determination

For our sample size calculation, we followed McElroy et al. 2014 Lisdexamfetamine bipolar depression trial [12]. They powered their study based on two prior pramipexole studies: Goldberg et al. 2004, effect size = 1.1 and Zarate et al., 2004, effect size = 1.4 respectively. Power calculation of the Lis-dexamphetamine trial was more conservative with an estimate effect of 0.85. Using a two-sample t-test, with a significance level of 0.05, and a power of 0.8, the required number in each group was found to be 23. Therefore, we expect to include a total sample size of 540 patients (270 subjects per site) to ensure that treatment group have at least 1 post-baseline assessment of MADRS.

7.2 Statistical Methods

Descriptive Statistics

Univariate descriptive statistics and frequency distributions will be calculated, as appropriate for all variables. Baseline values for demographic, clinical, and outcome variables (primary and secondary) will be tabulated for the treatment groups. For continuous variables, descriptive statistics (n, mean, standard deviation, standard error, median, minimum and maximum) will be provided for actual values and changes from baseline to each visit and endpoint by treatment group. For categorical variables, patient counts and percentages will be provided by treatment group. Fisher's exact test/ X^2 tests will be calculated for categorical variables and Wilcoxon's rank sum tests for continuous variables. Similar analyses will be conducted to examine potential site differences, using analysis of variance (ANOVA), Kruskal-Wallis tests, or X^2 tests.

Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) on the basis of predefined criteria will also be provided by treatment group.

In addition, the use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with study drug.

Efficacy analysis

The primary efficacy variable is the change from baseline to endpoint in the total score from the MADRS will be analyzed between groups during the treatment period using a mixed repeated measures model analysis of variance (ANOVA). Specifically, 8-week endpoints will be used for the analysis described. Models will be adjusted for baseline MADRS and covariates including site and other variables found significantly different between treatment groups, including but not limited to: age, gender, BP type, and BMI.

All analyses will be 2-tailed, at a significance level of 0.05, to control for type 1 error. We will use a model for the mean of the outcome variable that includes terms for treatment, time, and the treatment-by-time interaction. All categorical efficacy variables will be analyzed using a Cochran-Mantel-Haenszel (CMH) test using site and baseline medication as covariates.

SAS or R software will be used to carry out for all analyses. Precisely, we will use the SAS procedure MIXED. These mixed models allowed for random coefficients for the intercept and/or time variables, and/or correlated error terms (chosen from compound symmetric, first-order dependence and first-order autoregressive). The longitudinal analyses include all available observations from all participants. For secondary analyses we will use the last observation carried forward, and compute baseline-to-endpoint change scores for each measure by two-sample t-tests or Wilcoxon's rank sum tests were between the treatment groups. Fisher's exact test will be used to analyze the categorical response to treatment and adverse events.

Interim Analysis

No interim analysis is planned for this study.

7.3 Subject Population(s) for Analysis

The set of randomized patients includes all patients who were randomly assigned to a treatment group, regardless of whether or not a patient took any study drug.

The safety analysis set includes all patients who received 1 or more doses of study drug.

The full analysis set includes those in the safety analysis set who have at least 1 post-baseline MADRS efficacy assessment.

Handling of Missing Data

For all variables, only the observed data from the patients will be used in the statistical analyses (ie, there is no plan to estimate missing data).

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8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (ie, publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (ie, unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event

An untoward or undesirable experience associated with the use of a medical product (ie, drug, device, biologic) in a patient or research subject.

In pooled controlled trials of adult patients, 9% (54/626) of MYDAYIS® -treated patients discontinued due to adverse reactions compared to 2% (7/328) of placebo-treated patients. The most frequent adverse reactions leading to discontinuation (ie, leading to discontinuation in at least 1% of MYDAYIS® -treated patients and at a rate at least twice that of placebo) were insomnia (2%, n=15), blood pressure increased (2%, n=10), decreased appetite (1%, n=5), and headache (1%, n= 4)

The most common adverse reactions reported in adults were insomnia, decreased appetite, dry mouth, decreased weight, heart rate increased, and anxiety. The table below lists the adverse reactions that occurred ≥2% compared to placebo. The most common adverse reaction (insomnia) generally occurred early during treatment with MYDAYIS®

Body System	Adverse Reaction	MYDAYIS (N= 626)	Placebo (N= 328)
Nervous System			
	Anxiety	7% 2%	3% 1%

	Feeling Jittery Agitation Bruxism	2% 2%	0% 0%
Psychiatric disorders			
	Insomnia Depression	31% 3%	8% 0%
Metabolism and nutritional disorders			
	Decreased Appetite Weight Decreased	30% 9%	4% 0%
Gastrointestinal System			
	Dry Mouth Diarrhea	23% 3%	4% 1%
Cardiovascular System			
	Heart Rate Increased Palpitations	9% 4%	0% 2%
Genitourinary System			
	Dysmenorrhea Erectile Dysfunction	4% 2%	2% 1%

Serious Adverse Event

Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include:

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant disability or incapacity
- birth defect/anomaly and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data

For the purpose of this study, treatment-emergent mania (as defined previously) and treatment-emergent-worsening suicidality (as defined previously) will be treated as SAEs and then will follow the same procedures as any SAE with regard to reporting timelines.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

For this study, the study treatment follow-up period is defined as 7 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF) or in a separate adverse event worksheet. All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should be recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

The clinical course of each adverse event will be monitored at suitable intervals until resolved or stabilized, until the patient is referred to the care of a local health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made.

The onset and end dates, duration, action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded on the CRF. The relationship of each adverse event to study drug treatment and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

Relationship Index

The relationship of an AE to the Investigational Drug is a clinical decision by the sponsor-investigator (PI) based on all available information at the time of the completion of the CRF and is graded as follows:

1. Not related: a reaction for which sufficient information exists to indicate that the etiology is unrelated to the study drug; the subject did not receive the study medication or the temporal sequence of the AE onset relative to administration of the study medication is not reasonable or the event is clearly related to other factors such as the subject's clinical state, therapeutic intervention or concomitant therapy.

2. Unlikely: a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide plausible explanations.

3. Possible: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but which could also be explained by concurrent disease or other drugs or chemicals; information on drug withdrawals may be lacking are unclear.

4. Probable: a clinical event including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (de-challenge): re-challenge information is not required to fulfil this definition.

5. Definite: a reaction that follows a reasonable temporal sequence from administration of the drug, or in which the drug level has been established in body fluids or tissues, that follows a known or expected response pattern to the suspected drug, and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure (re-challenge).

Severity Index

The maximum intensity of an AE during a day should be graded according to the definitions below and recorded in detail as indicated on the CRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates.

1. Mild: No limitation of usual activities
2. Moderate: Some limitation of usual activities.
3. Severe: Inability to carry out usual activities

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriate action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

8.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

Information collected on the adverse event worksheet (and entered in the research database):

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention*):

- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5**)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The sponsor-investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

8.3.2 Sponsor-Investigator reporting: Notifying the FDA

The sponsor-investigator will report to the FDA and participating investigators all unexpected, serious suspected adverse reactions according to the required IND Safety Reporting timelines, formats and requirements.

Unexpected fatal or life threatening suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 7 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Other unexpected serious suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Any clinically important increase in the rate of serious suspected adverse reactions over those listed in the protocol or product insert will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

The sponsor-investigator must also notify the FDA (and sponsors must notify all participating investigators) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under § 312.32(c)(1)(i)-(iv).

Findings from other studies in human or animals that suggest a significant risk in humans exposed to the drug will be reported. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigators initial receipt of the information about the event.

8.4 Unmasking/ Unblinding Procedures

In the case of an emergency, if it is necessary to know what treatment a specific patient has received, the investigator may determine the patient's treatment by contacting the sponsor. In an extreme emergency, if the investigator is unable to contact the sponsor, the investigator may determine the patient's treatment without prior authorization. When this occurs, the investigator must contact one of the individuals identified in the clinical study personnel contact information section of this protocol immediately; the patient will be withdrawn from the study, and the event will be recorded on the study completion record. Proper documentation must be maintained when a treatment code is revealed.

8.5 Stopping Rules

When an adverse event has been identified, the study team will take appropriate action necessary to protect the study participant and/ or remove the subject from the study.

Subject Safety Management Plan

Subject Safety

a) Safety will be monitored by the Investigator and study team.
b) Subjects will be seen by the study investigators or an appropriately trained health professional at every visit and the evaluation will be documented.
c) Subjects will be monitored for adverse events (AEs) throughout every visit.
d) Subjects and families will be given 2 methods (clinic phone and EMR messaging) to contact the study team if adverse events occur between study visits.
e) Subjects will be evaluated for mood, suicidal ideation, and suicidal behavior as a part of the data collection process. Results will be reviewed on the same day by the study investigators or an appropriately trained health professional.

For the purpose of this study, treatment-emergent mania (as defined previously), treatment-emergent skin rash and treatment-emergent-worsening suicidality (as defined previously) will be treated as SAEs and then will follow the same procedures as any SAE with regards to reporting timelines.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.6.1 Safety Monitoring Board

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A Data and Safety Monitoring Board (DSMB) will be created to monitor study progress and address potential safety concerns. The DSMB will include two psychiatrists who are not involved in the study, two Mayo Clinic physicians not involved in the study and not members of the Department of Psychiatry and Psychology, and two outside members. The DSMB will be convened twice in the first year: at 6 months to review the protocol, consent, and initial review and at the end of year 1, to review recruitment numbers, dropouts, and adverse events. Thereafter the DSMB will meet each year of the study to review the same outcome measures. The DSMB will also meet on an ad-hoc basis as needed to address safety or other concerns should they arise.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be

printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

Data Management

The Statistics Team, which will be responsible for data management, biostatistics and bioinformatics support. The statistical team (Dr. Biernacka, Postdoc, MS Statistician, and Statistical Programmer) will meet weekly to plan and review ongoing data analyses.

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for:

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual, "Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717
3. Whichever is longer.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (eg, pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

In addition to individual site PIs monitoring study activity, designated study personnel from the sponsoring site Mayo Clinic will conduct on-site monitoring visits up to twice per year.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (eg, source

documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (eg, pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

This study is financed through benefactor funding secured through the Mayo Clinic Department of Development.

12.2 Conflict of Interest

No conflicts of interest at the moment.

Nothing specific to add here at this time (may need to edit later depending upon if the company provides us with the medication at little or no cost)

12.3 Subject Stipends or Payments

Participants will be provided study drugs for free. The participant will be paid $25.00 for the Enrollment visit, $40.00 for each office research visit in the blinded phase (total $265). The

participant will be paid $25.00 for each office research visit in the open label phase (total $150.00). Participants in Rochester will be provided parking vouchers for the in-person visits; parking is free in Austin, Eau Claire, and at Lindner.

13 Publication Plan

The principal investigator (PI) holds the primary responsibility for publication of the results and approval of the PI is required in order to share the information with a third party. The study will be registered with ClinicalTrials.gov (Link to protocol registration site for ClinicalTrials.gov: https://register.clinicaltrials.gov/) prior to the enrollment of the first subjects. All publications resulting from this project will be registered with a PMCID.

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